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A: Adenine is a purine base of nucleic acids. ►adenine

2,5-A (adenine) oligonucleotides: Adenine oligonucleotides are generated by 2,5-A synthethase from double-stranded RNA. These oligonucleotides activate RNase L, which attacks infecting viruses of vertebrates. If the two genes encoding these two enzymes are transformed into plants, they provide resistance against RNA viruses. ►host-pathogen relationship, ►ribonuclease L

Å (angström): A unit of length, 1/10 of 1 nm; 10^{-7} mm.

A6: *Agrobacterium tumefaciens* strain with a Ti plasmid coding for octopine production in the plant cell. ►*Agrobacterium*, ►opines, ►octopine

A20: A cytoplasmic Zn-finger protein that limits TNF-induced NF-κB responses. It reduces apoptosis. Its deficiency may increase inflammation and may result in death. ►TNF, ►NF-κB, ►apoptosis; Kumar-Sinha C et al 2002 J Biol Chem 277:575.

a: atto-, 10^{-18}, e.g., attomole/amole.

α: Average inbreeding coefficient, $\alpha = \Sigma p_i F_i$ where p_i is the relative frequency of inbred individuals with F_i coefficient of inbreeding. This value in most human populations is less than 0.001 while in isolated human groups it may exceed 0.02 or 0.04. ►inbreeding coefficient, ►error types

A Box: An internal control region of genes (5S ribosomal RNA and tRNA) transcribed by DNA-dependent RNA polymerase III; the consensus is 5′-TGGCNNAGTGG-3′. The tRNA genes also have an essential *intermediate segment* of about a dozen bases that has no consensus, yet its length is necessary for function. Nearby there is also another regulatory consensus, the B box 5′-GGTTCGAANNC-3′. The matrix attachment region (MAR) is also an A box (with a consensus of AATTAAA/CAAA). ►MAR; Borovjagin AV, Gerbi SA 2001 Mol Cell Biol 21:6210.

***A* Chromosome**: A member of the regular chromosome set in contrast to a B or supernumerary chromosome. ►B chromosome, ►accessory chromosome

α Complex: One of the alternate chromosome translocation complexes in *Oenothera*. ►β complex, ►translocation, ►*Oenothera*

A DNA: ►DNA

α Mating Type Factor of Yeast: Responsible for the secretion of the α factor (a pheromone), composed of 13 amino acids and it acts on *a* type cells. ►mating type determination in yeast

A Medium: For *E. coli*, g/L: K_2HPO_4 10.5, KH_2PO_4 4.5, $(NH_4)_2$ SO_4 1.0, Na-citrate.2 H_2O, 0.5 plus glucose 0.4%, thiamin 1 mg/L, $MgSO_4$ 1 mM, and an appropriate antibiotic. For different bacterial culture media. Winkler U et al 1976 Bacterial, phage and molecular genetics. An experimental course, Springer-Verlag, New York; ►culture media

α Particles: ►alpha particles

A Priori: A philosophical concept indicating that certain knowledge does not presuppose experience. In contrast, *a posteriori* concept is based on the acquisition of certain prior information.

A Rule: Adenylic acid is the preferred nucleotide for incorporation opposite to an abasic site of the DNA during repair. abasic sites, ►DNA repair; Otterlei M et al 2000 EMBO J 19:5542.

α Satellite: The centromeric DNA that is normally heterochromatic. However, it may have important role in controlling chromosome segregation and other centromere functions. The 171-bp tandemly repeated sequence has been found in all human centromeric area. It is connected by 17 bp (missing in the human, mouse and green monkey Y centromeres) with protein CENP-B, a common autoimmune antigen. All human centromeres and neocentromeres apparently include also CENP-A, a histone H3-like protein. Introduction of exogenous alphoid DNA into the cells may cause chromosomal instabilities. The CENP-B protein bears sequence similarity to the pogo transposases. ►centromere, ►neocentromere, ►satellite DNA, ►heterochromatin, ►segregation, ►meiosis, ►human artificial chromosome, ►microchromosome, ►hybrid dysgenesis; Buno I et al 2001 Genome 44:120.

A Site (decoding site): A compartment on the ribosome; at the beginning of the translation process the first codon, Met or fMet lands at the P site and the next amino acid is delivered to the A site. Then the elongation of the peptide chain proceeds. The decoding site of the 16S ribosomal RNA has the universally conserved |**A**1492 and |**A**1493 nucleotides as the location. (see Fig. A1). ►protein synthesis, ►ribosome, ►aminoacyl-tRNA synthetase; Rodnina MV, Wintermeyer W 2001 Annu Rev Biochem 70:415.

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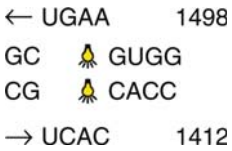

Figure A1. Decoding site

AAA Proteins: AAA Proteins are ATPases, enzymes cleaving off phosphates from ATP. They are equipped with Walker boxes. AAA domain proteins are molecular chaperones and have important roles in vesicular transport, organelle biogenesis, microtubule rearrangements, etc. Some of this group of enzymes is related to the prokaryotic RuvA proteins. The Mgs1 protein (maintenance of genome stability) of yeast has homologs in all prokaryotes and eukaryotes. Their defects contribute to increased mitotic recombination. ►ATP, ►ATPase, ►RuvABC, ►chaperone, ►Walker box, ►MD*l*1; Dalal S, Hanson PI 2001 Cell 104:5; Gadal O et al 2001 EMBO J 20:3695; Hishida T et al 2001 Proc Natl Acad Sci USA 98:8283; Sauer RT et al 2004 Cell 119:9; evolution and structure: Erzberger JP, Berger JM 2006 Annu Rev Biophys Biomol Struct 35:93.

AAAS: ►ALADIN

AAF: ►alpha accessory factor

α-Amanitin: A protein synthesis inhibitor fungal octapeptide. It blocks RNA pol II (0.1 μg/mL); RNA polymerase III is also blocked by it but at much higher concentrations (20 μg/mL), but pol I is insensitive to it even at 200 μg/mL. LD_{50} in albino mice is 0.1 mg/kg. ►RNA polymerase, ►pol, ►LD_{50}; Begun DJ, Whitley P 2000 Heredity 85:184.

AAR1: ►TUP1

Aarskog Syndrome (Aarskog-Scott syndrome, faciogenital dysplasia): A genetic disorder that is autosomal dominant, autosomal recessive, X-linked (Xq12) recessive short stature, hypertelorism (increased distance between organs or parts), scrotum (the testis bag) anomaly, pointed hairline (Widow's peak), broad upper lip, floppy ears, etc. The basic defect involves the RHO/RAC member of the RAS family of GTP-binding proteins. ►stature in humans, ►head/face/brain defects, ►RAS, ►faciogenital dysplasia, ►hypertelorism; Orrico A et al 2007 Am J Med Genet 143:58.

AATAAA: A consensus of 10–30 bp upstream from a CA dinucleotide at the site where cleavage, then polyadenylation of the mRNA commonly takes place. This consensus may also be a signal for transcription termination although normally, RNA polymerase II continues to work after passing it. ►polyadenylation signal, mRNA tail, ►transcription termination; Curuk MA et al 2001 Hemoglobin 25:255.

AATDB: *Arabidopsis thaliana* database provided general information on all aspects of the plant, including genes, scanned images of mutants, nucleotide sequences, genetic and physical map data, cosmid and YAC clones, bibliographical information. http://www.weeds.harvard.edu/index.html, or e-mail curator@ frodo.mgh.harvard.edu. ►AIMS, ►*Arabidopsis thaliana*, ►databases

AAUAAA: Consensus for polyadenylation of the mRNA. Apparently, the poly-A RNA polymerase enzyme and associated protein attach to this sequence before cleavage of the transcript and post-transcriptional polyadenylation take place. Yeast does not have this consensus. ►AATAAA consensus's role in polyadenylation

Ab: ►antibody

Ab Initio: Meaning from the beginning in Latin. For e.g., genes *ab initio* indicates the genes as first recognized by sequencing but the exact exon/intron structure had not been identified.

αβ T Cells: Represent the early stages of T cell development in the thymus and later recognize the major histocompatibility complex-bound peptide antigens resulting in the differentiation of B and T lymphocytes. The expression of the co-receptor CD4 and CD8 may involve the formation of the double negative $CD4^-$ $CD8^-$ to $CD4^+$ $CD8^+$ and the $CD4^-$ $CD8^+$ and the $CD4^+$ $CD8^-$, a process requiring the rearrangement of the α and β subunits of the T cell receptor, and the ligands existing within the thymocytes. At the same time, the T cells differentiate into the rather distinct CD4 T-helper cell and the CD8 T-killer cells. The CD4 expression in the mature T cells corresponds to their specificity toward class II and the CD8 expression toward the class I major histocompatibility complex (MHC) molecules. The differentiation into this two cell lineages is a selective process controlled by the relative strength and duration of the engagement with the T cell receptor (TCR). The HD (helper deficient) recessive mutation in mouse cause loss of CD4 T cell development because these cells were switched over to the CD8 T cell path. This HD locus encodes the zinc finger transcription factor Th-POK (T helper-inducing POZ/Krüppel), which under constitutive expression mediates the development toward the class I MHC molecules. Thus, Th-POK is a master regulator of T lymphocyte development (He X et al 2005 Nature [Lond] 433:826). ►lymphocytes, ►MHC, ►γδT cells, ►T cell, ►POZ, ►Krüppel

ABA (abscisic acid, 3-methyl-5-[1′-hydroxy-4′-oxo-2′-cyclyhexen-1′-yl]-cis-2,4-pentadienoic acid): A terpenoid, synthesized from mevalonate and xanthins, apparently through two pathways. It has multiple physiological functions in concert with other plant hormones, particularly with gibberellins and cytokinins, by regulating seed dormancy, germination, leaf abscission, stomatal opening, drought response, etc. Glucose-conjugated ABA is biologically not active. Activation of glycosidase, however, rapidly increases the active pool of ABA and the concomitant physiological responses to environmental cues (Lee KH et al 2006 Cell 126:1109). In the ABA signal transduction farnesyl transferase seems to be involved. Cyclic ADP-ribose, regulated by Ca^{2+}, seems to be another signaling molecule for ABA. Ca^{2+} ion channels are activated by H_2O_2 produced by the guard cells upon the induction of ABA and thus the stomatal opening/closing is controlled. Responses to ABA are regulated by ABRC (ABA response complex) in the genes that include an ACGT box and a variable coupling element. A G protein–coupled receptor interacts with the G protein subunit GPA1 to mediate all known ABA responses in *Arabidopsis* (Liu X et al 2007 Science 315:1712). The RNA-binding protein FCA, which plays a role in the control of flowering, is a receptor of abscisic acid (Razem FA et al 2006 Nature [Lond] 439:290). The Mg-chelatase H subunit is an ABA receptor (Shen Y-Y et al 2006 Nature [Lond] 443:823). Several *aba* genes have been cloned.

New evidence indicates that in human granulocytes ABA stimulates phagocytosis, production of reactive oxygen species and nitric oxide (NO) and chemotaxis through a signaling pathway sequentially involving a pertussis toxin (PTX)-sensitive G protein/receptor complex, protein kinase A activation, ADP-ribosyl cyclase phosphorylation, and consequent cyclic-ADP-ribose overproduction, leading to an increase of the intracellular Ca^{2+} concentration. Thus, it can be considered as a pro-inflammatory cytokine in humans (Bruzzone S et al 2007 Proc Natl Acad Sci USA 104:5759). ►abscisic acid, ►prenylation, ►farnesyl pyrophosphate, ►plant hormones, ►stoma, ►ion channels, ►glucosidase, ►chelation, ►G protein, ►pertussis toxin, ►protein kinase, ►ARF, ►cytokine; Lopez-Molina L et al 2001 Proc Natl Acad Sci USA 98:4782; Nambara E, Marion-Poll A 2005 Annu Rev Plant Biol 56:165.

Abasic Endonucleases (APE): APEs mediate base excision repair. Its deficiency in mouse leads to embryo lethality. Besides base excision, it is involved in acetylation-mediated gene regulatory function (Izumi T et al 2005 Proc Natl Acad Sci USA 102:5739). ►DNA repair, ►endonuclease, ►acetylation; Demple B, Harrison L 1994 Annu Rev Biochem 63:915.

Abasic Sites: Found in DNA where glycosylases (base exchange repair) have removed bases by cleaving the glycosylic bond. According to an estimate, approximately 100,000 abasic sites are generated per mammalian cell daily and their number increases by senescence. These sites may be intermediates in chemical mutagenesis and repair. DNA polymerases ζ and η can insert nucleotides opposite 8-oxoguanine (C) and O^6-methylguanine sites (C or T). The repair may not be highly efficient. ►glycosylases, ►DNA repair, ►A rule, ►oxidative damages, ►DNA polymerases, ►apurinic site; Haracska L et al 2001 J Biol Chem 276:6861; Guillet M, Boitaux S 2003 Mol Cell Biol 23:8386; Auerbach P et al 2005 Proc Natl Acad Sci USA 102:17711.

Abaxial: That which is not in the axis of body or of an organ.

ABC Excinuclease: A 260,000 M_r protein complex containing the subunits coded for by the *uvrA, uvrB* and *uvrC* genes of *E. coli.* UvrA is an adenosine triphosphatase and brings into position UvrB, which after attaching to the DNA cuts it at the 3′ position, and that provides the opportunity for UvrC to incise at the 5′ position. UvrD, a helicase releases the damaged oligomer along with UvrC. Following these events, DNA polymerase fills in the correct nucleotides. In yeast, the RAD1, 2, 3, 4, 10, and 14, carry out the same tasks as the ABC excinucleases of bacteria. In humans, the XPA (a damage recognition protein, comparable to UvrA), binds to the XPF-ERCC1 (excision repair cross-complementing protein) heterodimer and to the human single strand binding replication protein, HSSB. XPF (3′ cut) and XPG (5′ cut) are nucleases. The gap-filling polymerases are polδ and polε. XPB and XPD are helicase subunits of the TFIIH transcription factor. The excinuclease complex is released at the end of the process with the aid of the proliferating cell nuclear antigen (PCNA). This complex is capable of excision of cyclobutane pyrimidine dimers, 6-4 photoproducts (adjacent pyrimidines cross linked through C6-C^4), nucleotideadducts (molecules with added groups) formed by mutagenic agents. ►excision repair, ►adduct, ►DNA polymerases, ►DNA ligase, ►helicase, ►baseflipping, ►transcription factors, ►PCNA, ►cyclobutane, ►pyrimidine-pyrimidinone photoproduct; Zou Y et al 2001 Biochemistry 40:2923; Gu C et al 2006 Biochemistry 45:10739.

ABC Transporters (ATP-binding cassette transporters, 9q22-q31): ABC transporters constitute a large family of proteins, which hydrolyze ATP and mediate transfers through membranes. Altogether 56 ABC transporter genes are known and 38 of them are present in all vertebrates. These are now often called TAP. The ABC

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transporters have two membrane-spanning (MSD) and the dimeric ATP-nucleotide binding domains (NBD). MSDs may show greater variations, depending whether they operate as a pump or a conductance channel. The NBD subunits play the role of the engines of the transport and interact through their arm 1 with the two MSDs. The ABCA4/ABCR mutations may account for Stargardt disease (STGD1), fundus flavimaculatus (FFM, retinitis pigmentosa (RP) and cone-rod dystrophy (CRD), all recessive with somewhat overlapping retinal symptoms. ABC transporters may affect adrenoleukodystrophy, cystic fibrosis, retinal degeneration, hypercholesterolemia and cholestasis (see Fig. A2). By 2001, 48 ABC transporters belonging to 7 gene families have been identified. ►TAP, ►protein-conducting channel, ►TRAM, ►signal hypothesis, ►SRP, ►translocon, ►translocase, ►Stargardt disease, ►Tangier disease, ►pseudoxanthoma, ►Byler disease, ►high-density lipoprotein, ►multidrug resistance, ►multiple drug resistance, ►retinitis pigmentosa, ►cone dystrophy, ►dwarfism; Dean M et al 2001 Genome Res 11:1156; Neufeld EB et al 2001 J Biol Chem 276:27584; Chang G, Roth CB 2001 Science 293:1793 [this paper was retracted in (2006) because of software error]; Borst P, Elferink RO 2002 Annu Rev Biochem 71:537; Stacey G et al 2002 Trends Plant Sci 7:257; Dean M, Annilo T 2005 Annu Rev Genomics and Hum Genet 6:123; crystal structure of bacterial ABC transporter: Roger JP et al 2006 Nature [Lond] 443:180; structure with binding protein: Hollenstein K et al 2007 Nature [Lond] 446:213.

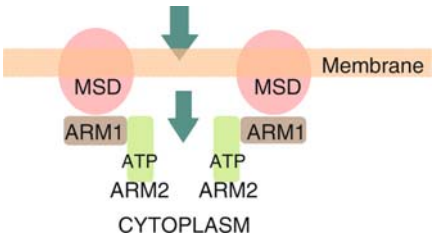

Figure A2. ABC transporter

ABCB: ►multidrug resistance

ABCD Model: An environmental matrix for the study of the performance of species (see Table A1).

Table A1. ABCD model

	Environment 1	Environment 2
Genotype 1	A	B
Genotype 2	C	D

Abdomen in *Drosophila*: The body segment between the thorax and telson. ►*Drosophila*

Abelson Murine Leukemia Virus Oncogene (*abl*): Mammalian homolog of the avian Rous sarcoma virus. It codes for a plasma membrane tyrosine kinase. When this enzyme acquires constitutive catalytic activity in the presence of the Philadelphia chromosome, it causes chronic myelogenous leukemia (CML) in humans. It is treated effectively by STI-571 tyrosine kinase inhibitor. ►oncogenes, ►Rous sarcoma, ►tyrosine kinase, ►leukemia, ►Gleevec, ►Philadelphia chromosome; Wang JY et al 1984 Cell 36:349; Shore SK et al 2002 Oncogene 21:8568.

Abembryonic: After fertilization, a blastomere is formed and its progeny generates the embryonic part of the blastocyst and another line of cells of the blastomere populates the space away from the embryo at the parietal trophectoderm, and the more superficial abembryonic cell mass away from the embryo. ►blastomere, ►blastocyst

Aberrant Genetic Ratios: Occur when the chromosomes carrying the wild type or mutant allele of a gene, respectively, have reduced transmission through meiosis or the viability of the gametes is diminished. Depending on the chromosomal location of the defect, either the one (wild type), or the other (recessive) allele may appear in excess of expectation of normal phenotypic ratios.

Aberration Chromosomal: ►chromosome breakage

Abetalipoproteinemia (microsomal triglyceride transfer protein deficiency, 4q22-q24): Abetalipoproteinemia involves very low levels of the very low density (VLDL), low density (LDL, apolipoprotein B, 2p24) and high density (HDL) of these lipoproteins (microsomal triglyceride transfer protein [MTP] defect). The rare recessive anomaly is accompanied by excretion of lipoproteins, malabsorption of fat, acanthocytosis (see Fig. A3) thorny type erythrocytes rather than the normal doughnut-shaped, retinitis pigmentosa (sclerosis (hardening), pigmentation and atrophy [wasting away] of the retina of the eye and irregular coordination of the nerves (ataxia). ►neuromuscular disease, ►beta-lipoproteins, ►hypobetalipoproteinemia, ►hyperlipoproteinemia

Figure A3. Abetalipoproteinemia

ABF-1: A nuclear transcriptional repressor belonging to the basic helix-loop-helix family. ►helix-loop-helix; Wong J et al 2001 DNA Cell Biol 20:465.

Abf (autonomously replicating sequence binding factor): Abf is involved in silencing of yeast mating types. Also it may bind to various promoters and thus may initiate replication or transcription. ►mating type determination in yeast, ►ARS, ►ORC, ►HML and HMR

ABH antigens: In humans, ABH antigens are secreted in the saliva and other glycoprotein-containing mucus in the presence of the *Se* (dominant allele, human chromosome 19q13.13), and the gene codes for the α2L-fucosyltransferase enzyme. The secreted glycoproteins, A and B are about 85% carbohydrate and about 15% protein. Approximately 75–80% of Caucasoids are secretors (homozygous or heterozygous for *Se*). The precursors of the antigens are Galactose(β1-3)*N*-acetyl-D-glucosamine-R and Gal (β1-4)*N*-acetyl-glucosamine-R (where R stands for the extension of the carbohydrate chain). Antigen H has the critical structure of that shown in figure (see Fig. A4). Antigenic determinant A is formed by *N*-acetylgalactosamine, and the B antigen by galactose addition at non-terminal position to the H antigen. Thus, the A, B and H antigens are different from each other by these carbohydrates and in some variants by the number of fucose molecules. The A and B alleles are codominant. The recessive O blood group lacks fucosidase activity that places a fucose, by an α1-2 linkage on a galactose. The Lewis blood group (Le [Les], 19q13.1-q13.11) is distinguished on the basis that its dominant allele Le places fucose in an α-1,4 linkage to the *N*-acetylglucosamine. Individuals that have no secretor activity but are Le belong to the Lewis blood group Le^a whereas when both Se and Le are expressed they represent the Le^b type. ►ABO blood group, ►Bombay blood type, ►fucosyl transferase, ►secretor; Domino SE et al 2001 J Biol Chem 276:23748.

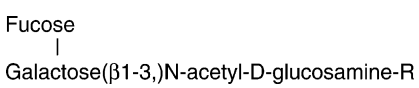

Figure A4. ABH antigens

Abilene (advanced networking for leading-edge research and education): Abilene is an advanced backbone network to connect aggregation points such as virtual laboratories, digital libraries and distance education at national and international scale. By the end of 2003, it is expected to communicate at 10 Gigabytes/ second. ►Internet2, ►BIRN; http://abilene.internet2.edu/.

Abiogenesis: Spontaneous generation of life, origin of living cells from organic material during the early history of the earth. spontaneous generation, ►origin of life; Trifonov EN, Berezovsky IN 2002 FEBS Lett 527:1.

ABL: ►abetalipoproteinemia

ABL (Abelson murine leukemia virus oncogene): Located to human chromosome 9q34.1 and mouse chromosome 2. When translocated to human chromosome 22 it may transcribe a fusion protein with an abnormal protein tyrosine kinase activity, which is probably the cause of chronic myeloid leukemia. Acute lymphocytic leukemia is also associated with a similar translocation, the Philadelphia chromosome, but it appears that tyrosine kinase activation is different from that of the fusion protein. The ABL gene has about 300-kb intron down-stream from the first exon. This intron appears to be the target of the translocations and causes acute lymphocytic leukemia. Insertion of DNA sequence into the *abl* gene of mouse results in several morphological alterations and death. Abl also controls differentiation, cell division, and stress responses. The SH3 domain negatively regulates Abl activity and deletion of SH3 makes it an oncogenic protein. Mutations in the SH3, or in the catalytic domain or and in the linker region between the SH3 and SH2 domains are also oncogenic. ABL deficiency in mice leads also to osteoporosis. ►oncogenes, ►ARG, ►Philadelphia chromosome, ►leukemia, ►SH2, ►SH3, ►osteoporosis; Maru Y 2001 Int J Hematol 73:308.

abl: B cell lymphoma (Abelson leukemia). Oncogene encoding a non-receptor protein tyrosine kinase. Ionizing radiation and alkylating agents activate this oncogene. In the Philadelphia chromosome the contact between BCR and ABL most commonly leads to myelogenous leukemia. In the absence of ABL the JNK/SAP kinases (Jun kinase) are not stimulated. ►leukemia, ►lymphoma, ►JUN, ►JNK/SAP, ►Philadelphia chromosome, ►BCR, ►tyrosine kinase

Ablation: Mechanical or chemical/toxin-mediated removal of cells or tissues of stem cells or plant meristems to study the role of those cells in differentiation and development. The purpose can also be achieved by obtaining genetic deletions in these areas, heterozygous for appropriate marker genes. The deletion of the dominant allele reveals the function of the recessives and permits tracing cell lineages on the basis of the visible sectors formed. Familial retina ablation may occur in animals as a hereditary abnormality. ►gene fusion, ►intercellular immunization, ►pseudodominance, ►deletion, ►cell lineages

ABM Paper: ►diazotized paper

A

ABO Blood Group: Represented by three major types of alleles (human chromosome 9q34) displaying codominance (see Table A2).

These blood types are extremely important because inappropriate mixing (in blood transfusion) results in agglutination that prevents the flow of blood through the veins and oxygen transfer, and it is potentially lethal. These antigens are actually carbohydrates (attached to polypeptides), and the genes A and B specify α-D-*N*-acetylgalactosaminyltransferase and α-D-galactosyltransferase enzymes, respectively. Gene O is not active as an enzyme. The A and B enzymes (M_r about 100,000) are dimeric and structurally similar to each other. The A and B molecules are identified as A and B antigens. Occasionally maternal antibodies against the A and B antigens may enter, through the placenta, the fetal blood stream and affect adversely the erythrocytes causing anemia and hyperbilirubinemia. In such cases medical treatment may be required. The ABO system has also a limited use in forensic medicine in paternity suites, in typing bloodstains, semen and saliva in criminal cases. Immunologically active forms may be recovered in old human remains and can also be used in archeological research. This blood group provided some correlative information in cancer research, e.g., in O individuals afflicted with carcinomas A antigen may be detected in 10–20% of the cases. The major clinical characteristics are as follows.

It appears, changes in glycosyltransferase activity are not uncommon in several types of tumors. The frequency of the various ABO alleles varies a great deal in the world population. It has been shown that the O blood type provided some protection against the most severe form of syphilis (*Treponema pallidum*) but somewhat higher susceptibility to diarrhea caused by some viral and bacterial infections. The B blood group may have afforded some protection against smallpox, plague and cholera.

Universally compatible red blood cells can be obtained by two bacterial glycosidase gene families that provide enzymes capable of efficient removal of A and B antigens at neutral pH with low consumption of recombinant enzymes. The crystal structure of a member of the -*N*-acetylgalactosaminidase family reveals an unusual catalytic mechanism involving NAD^+ (Liu QP et al 2007 Nature Biotechn 25:454). ►ABH antigen, ►Lewis blood group, ►blood groups, ►*Treponema pallidum*, ►forensic genetics; Race EE, Sanger R 1975 Blood groups in man, Blackwell, Oxford; Chester MA 2001 Transfus Med Rev 15:177; Patenaude SI et al 2002 Nature Struct Biol 9:685.

Aborigine: The first group of inhabitants, humans, animals or plants.

Abortion, Medical: Medical abortion is induced during the early period of pregnancy usually by antiprogestin (mifepristone) in combination with prostaglandins (in countries where approved), or by the less costly and not very effective misoprostol. Progestin is synthetic progesterone. In Western Europe, about 3.5/1000 pregnancies are medically terminated because of severe fetal anomalies. selective abortion, ►contraceptives, ►ensoulment, ►prostaglandins, ►mifepristone, ►progesterone, ►genetic screening, ►family planning, ►mortality

Abortion, Spontaneous: Spontaneous abortion is frequently caused by disease, stress, incompatibility genes or chromosomal aberrations. Various types of chromosomal defects were cytologically detected in 30–50% of the aborted fetuses. About 15–20% of the verified human pregnancies are aborted

Table A2. ABO blood group

Blood Group (Frequency in Caucasoids*)	Genotype	Antigens Formed	Antibodies Formed	Clumping With	Blood Type Acceptable for Transfusion
O (0.45)	i^Oi^O	neither	anti-A	A,B	O
			anti-B	AB	
A (0.44)	i^Ai^A or i^Ai^O	A	anti-B	B,AB	A,O
B (0.08)	i^Bi^B	B	anti-A	A,AB	B,O
	i^Bi^O				
AB (0.03)	i^Ai^B	A,B	neither	neither	A,B,O

*The frequency of these alleles varies in different populations. For the calculation of frequencies, see gene frequencies. Actually, the A type exists in A_1 A_2 forms; in about 1–2% of the A_2 and 25% of the A_2B individuals, anti-A_1 antigens occur.

spontaneously and an estimated 22% of the abortions occur before pregnancy is clinically detected (5 weeks after the last menstruation). For placentation, the main source of steroid, the corpus luteum is replaced by appropriate supply of estrogens and progestin. Pregnancies of increased maternal level of cortisol are more likely to become aborted spontaneously during the first 3 weeks after conception (Nepomnaschy PA et al 2006 Proc Natl Acad Sci USA 103:3938). Different molecular mechanisms may account for abortion. Th2 lymphocytes and IL-10 and TGF-β may suppress incompatible paternal antigens in the fetus. Th1 cytokines, IL-2, INF-γ, and TNF-α may contribute to abortion. Indolamine 2,3-dioxygenase (IDO) by catabolizing tryptophan may help in suppressing allospecific maternal T cells in the lining of the uterus (decidua). The special Vα14 natural killer T cells (NKT) when activated by α-galactosyl-ceramide or by glycosyl-phosphatidylinositols (the latter is present in blood parasites) may cause abortion. Perforin, TNF-α and INF-γ of the NKT cells may destroy the embryonic trophoblasts. Semi invariant natural killer cells (iNKT) recognize glycosphingolipids presented by monomorphic class I MHC-like glycoprotein molecules presented by CD1d (antigen-presenting molecules for T cells). In early gestation of mice a perforin like molecule and in later stages, a cytokine-dominated mechanism is responsible for pregnancy loss in a strain-dependent manner (Boyson JE et al 2006 Proc Natl Acad Sci USA 103:4580). ►selective abortion, ►trisomy, ►chromosomal rearrangements, ►chromosome breakage, ►Il-2, ►TNF, ►INF, ►T cells, ►perforin, ►CD1, ►allospecific, ►trophoblast, ►ceramides, ►inositines, ►miscarriage, ►family planning, ►corpus luteum, ►progestin, ►estradiol, ►cortisol; Hamerton JL 1971 Human cytogenetics, Academic Press, New York; Hallermann FB et al 2001 Eur J Hum Genet 9:539.

Abortive Infection: Occurs when bacteria are infected with a phage capsule that carries bacterial rather than phage DNA and thus cannot result in the liberation of phage particles. Abortive response by infection of mammalian cells may be caused by any deficiency of the interacting system. (Hosel M et al 2001 Virus Res 81:1).

Abortive Transduction: When the transduced DNA is not incorporated into the bacterial genome and in the absence of a replicational origin, it can be transmitted but cannot be propagated. Therefore, the transduced fragment is contained in a decreasing proportion of the multiplied bacteria. ►transduction, ►transduction abortive; Stocker BAD et al 1953 J Gen Microbiol 9:410; Benson NR, Roth J 1997 Genetics 145:17.

Abraxane: A new type of anti-breast cancer drug consisting of taxol/paclitaxel, attached to blood serum protein as an injectable nanoparticle. Clinical trials indicate better effectiveness than taxol alone. ►taxol, ►nanotechnology, ►breast cancer

Abrin: Agglutinin, a toxic lectin and hemagglutinin extracted from the seed of the tropical leguminous plant jequirity (*Abrus precarius*). Abrins A, B, C, D are glycoproteins of two polypeptide chains. The small A chain is an inhibitor of aminoacyl-tRNA binding and has nothing to do with agglutination. Abrin is more toxic to a variety of cancer cells (ascites, sarcomas) than to normal cells. ►aminoacyl tRNA synthetase, ►lectins, ►hemagglutinin, ►RIP; Wu AM et al 2001 Life Sci 69:2027.

ABRINE: *N*-methyl-L-tryptophan (α-methylamino-β-[3-indole]propionic acid). An inflammatory drug; unrelated to abrin. (See Richou R et al 1966 C R Acad Sci Hebd D [Paris] 263:308).

Abscisic Acid: It is a plant hormone regulating a variety physiological processes, including modification of the action of other plant hormones (see Fig. A5). Originally, it was detected as a substance involved in the abscission of leaves. ►ABA, ►plant hormones, ►stoma; Hugouvieux V et al 2001 Cell 106:477; Finkelstein RR 2002 Plant cell 14:S15.

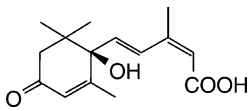

Figure A5. Abscisic acid

Abscission Zone: The thin-walled tissue layer (low in lignin and suberin) formed at the base of the plant organs before abscission (falling off) takes place. ►abscisic acid

Absinthe: A green liqueur, containing thujone, and it is a GABA antagonist. ►GABA

Absolute Dating: Determines the age of archeological objects by using either radiometry (using the rate of decay of radioactive isotopes), or electron spin resonance (measures age of crystals from a few thousand to 300,000 years), or thermoluminescence (Heated objects release light and energy. When they are heated again the time elapsed since they were heated last can be estimated). (Renne PR et al 2000 Sci Progr 83:107).

Absolute Linkage: There is no recombination between (among) the genes in a chromosome. ►recombination, ►linkage

A

Absolute Risk Increase/Decrease: Change in risk when from an old therapy the patient is subjected to a new one compared to the risk without the treatment.

Absolute Weight: The mass of 1000 seeds or kernels after appropriate cleaning.

Absorption: Uptake of compounds through cell membranes or through the intestines into the bloodstream.

Absorption Spectrum: The characteristic absorption peaks of a compound at various wavelengths of light, e.g., guanine has maximal absorption at about 278 nm at pH 9 but its maximum at pH 6.8 is at ca. 245 nm ultraviolet light; chlorophyll-a has an absorption maximum in benzene at ca. 680 and 420 nm visible light, whereas chlorophyll-b maxima are at ca. 660 and 460 nm, respectively. These characteristics vary according to the pH and the solvents used and are determined by spectrophotometers.

Abundance: Average number of molecules in cells.

Abundant mRNAs: A small number of RNAs that occur with great numbers in the cells. ►mRNA

Abzymes: Monoclonal antibodies with enzyme-like properties. If these antibodies can recognize the transition state analogs of enzyme-substrate reactions, they might have enzymatic properties. These abzymes would have numerous chemical and pharmaceutical applications. monoclonal antibody, ►antibody, ►catalytic antibody, ►transition state; Takahashi N et al 2001 Nature Biotechnol 19:563.

Ac—Ds (*Activator-Dissociator*): The first transposable element system recognized on the basis of its genetic behavior in maize. It contains 4563 bp and bordered by 11 bp imperfect, inverted repeats. The independently discovered *Mp* (*Modulator* of *p1* [pericarp color]) is the same transposon. *Ac* is an autonomous element and can move by its own transposase function. The *Ac/Mp* element makes a 3.5 kb transcript, initiated at several sites upstream, and a 2,421 base mRNA. A defective (deleted) version of it, *Ds* (*Dissociator*), is non-autonomous and requires the presence of *Ac* for transposition. *Ds* was originally discovered on the basis of frequent chromosome breakage associated with it. The *Ds* elements are quite varied in size but practically identical at the terminal sections to *Ac*. These elements have been identified first on the basis of mutation at known loci (*a, Adh, sh, wx, etc.,*) upon insertion and reversions when the inserted element is evicted (see Fig. A6).

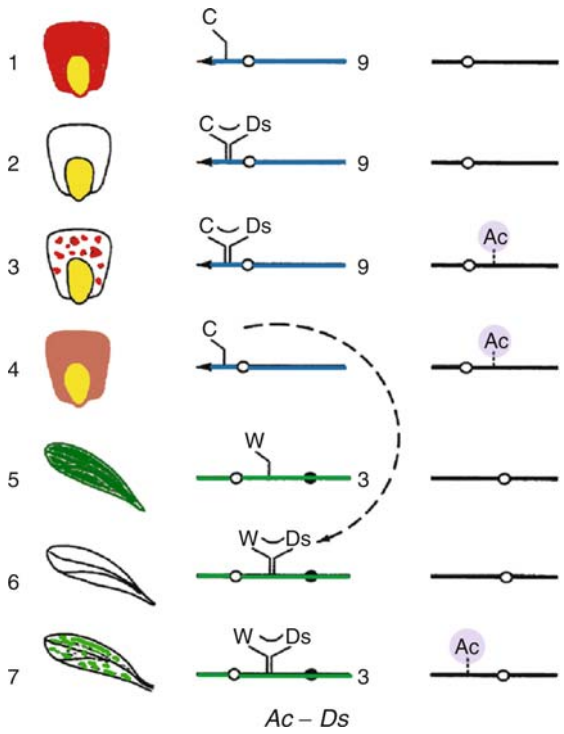

Figure A6. *Ac-Ds*. The possible phenotypic expression of genes in the presence of the *Ac-Ds* elements in maize. (1) The expression of the *C* allele in chromosome 9 in the absence of the transposable elements. (2) If *Ds* is introduced into the locus the function of *C* is disrupted and the kernel becomes colorless (2). If *Ac* (transposase) is introduced into any other location of the genome, it may cause the movement of the transposable element and colored spots appear (3). In case *Ds* is entirely dislodged from the germline, in the following generation full or partial function of the *C* gene is restored, depending whether the original site was completely restored or some modifications took place, and only diluted color appears (4). The *W* allele in chromosome 3 controls the development of green leaf color (5). If *Ds* moves into the gene it may disrupt its function and albinism is observed (6). In case *Ac* is introduced by crossing, *Ds* may move as indicated by the green stripes (7). Remember, *Ds* lacks transposase function although *Ac*, which carries the transposase, may move it

More recently it has been shown that many of the insertions do not lead to observable change in the expression of the genes or their effect is minimal and only sequencing of the target loci may then reveal their presence. The *Ac* element is transposed by a non-replicative manner and after meiosis only one of the sister-chromatids displays *Ac/Mp* at the original site (called *donor site*). In the other chromatid the element may be at another location (*recipient site*)

and the original location becomes "empty." The recipient sites are most commonly in the same chromosome and quite frequently within the vicinity of the donor site. The *Ds* element frequently initiates a series of events resulting in chromosomal breakage by the mechanism of *breakage-fusion-bridge cycles* and duplications between the original donor and recipient sites. The *Ds* element may move in an inverted manner to the vicinity of a locus and thus, the revertants may still contain a *Ds* element. In the control of transposition the 11-bp inverted terminal repeats and – in addition – sequences 0.05 to 0.18-kb have importance. The *Ac-Ds* target sites display 8-bp duplication, which remains even after the removal of the element. The empty target sites may show internal deletions and rearrangements. A transposase enzyme that can mobilize the *Ac* element, which codes for it, mediates the transposition but it may act on the *Ds* elements too (which are transposase-defective *Ac* elements). It appears that an increase in the number of some but not of other *Ac* elements results in proportionally smaller revertant sectors, and the genetic background, developmental specificities (e.g., somatic or germline tissues) and physiological factors may influence the timing and frequency of transposition. There is evidence in favor of methylation being one of the factor(s) affecting *Ac* expression. This family of transposable elements has additional members such *MITE* (miniature transposable element) that has the same termini but it is very short. The *Ds1* element is similar to *Ds* but it carries retrotransposons within its sequences. *Ac* has been successfully transferred to other species such as tobacco, *Arabidopsis* and yeast and it functions there similarly as in maize. The *Ac-Ds* system can operate also in zebrafish and mammalian cells (Emelyanov A et al 2006 Genetics 174:1095). ►controlling elements, ►transposable elements, ►hybrid dysgenesis, ►insertional mutation, ►transposase; Fedoroff NV 1989 Mobile DNA, In: Berg DE, Howe MM (eds) American Society of Microbiology, Washington, DC, pp. 377–411; Ros F, Kunze R 2001 Genetics 157:1723; AC distribution; Kolkman JM et al 2005 Genetics 169:981.

Acanthocytosis: ►abetalipoproteinemia, ►elliptocytosis; Wong P 2004 Med Hypotheses 62:966.

Acanthosis Nigricans: Hyperkeratosis and hyperpigmentation of the skin that may accompany the Crouzon syndrome and the Berardinelli-Seip syndrome. Interleukin IL-22 mediates interleukin IL23-induced dermal inflammation and acanthosis (Zheng Y et al 2007 Nature [Lond] 445:648). ►Crouzon syndrome, ►Donahue syndrome, ►achondroplasia, ►lipodystrophy, ►IL-22, ►IL-23, ►T cell

AcAP: An anticoagulant protein isolated from *Ancylostoma caninum* hookworm (see Fig. A7).

Figure A7. Hookworm

ACAT: ►sterol

Acatalasemia (CAT, 11p13): A rare dominant/semi-dominant/recessive trait involving the deficiency of the enzyme catalase. This enzyme has a protective role in the tissues by removing the H_2O_2. Symptoms include small painful ulcers around the neck, gangrenes in the mouth and atrophy of the gum and very low catalase activity in the blood and other tissues. The heterozygotes have intermediate levels of catalase activity. Acatalasemia may be classified into different groups according to the clinical symptoms, both in humans and in animals. The gene extends to 34 kb with 14 introns. It is closely linked to WAGR. ►Wilms tumor

Acatalasia: ►acatalasemia

ACC (1-aminocyclopropane-1-carboxylic acid): A precursor of the plant hormone ethylene. ►ethylene

Accelerator Mass Spectrometry (AMS): Quantifies isotopes such as C^{14}, H^3, Ca^{41}, Cl^{36}, Al^{26}, in biological, archeological, pharmacological, or other materials with attomole sensitivity and high precision. It can be used to study the tissue distribution, metabolism, pharmacokinetics, and radiological hazards of isotopes. It is also a potent tool for paleontological analysis and dating archeological remains. ►MALDI/TOF/MS

Acceptable Daily Intake: The safe dose of a chemical substance proven by experiment and it is generally divided by 100 for caution.

Acceptor Splicing Site: The junction between the right end of one exon and the left end of the next exon. ►introns, ►splicing

Acceptor Stem: A part of the tRNA, including the site (5′-CCA-3′) where amino acids are attached. aminoacyl-tRNA.

Access Time: The time interval between callings in a piece of information from a storage source to the actual delivery of that information to the caller. ►real time

A

Accessibility: Genetically determined ability of the genome to provide access for the V(D)J recombinase to rearrange the immunoglobulin genes. The accessibility depends on the increased activity of the loci, i.e., status of transcription, demethylation and increased DNase-sensitivity. ►V(J)D recombinase, ►RAG, ►immunoglobulins, ►CDR, ►RSS

Accession: A stable strain isolated or collected from natural habitat. ►provenance

Accession Number: In bioinformatics, accession number identifies permanently a particular molecular sequence submitted to a database. ►BankIt, ►Bioseq, ►gi, ►ASN.1. Accession number is used by various biological collections for the identification of specimens such as plants in a herbarium, differently acquired strains of organisms.

Accessory Cells (companion cells): Epidermal cells next to the guard cells around the plant stomata that appear different from the usual epidermal cells. In animals, they promote adaptive immunity although they are not directly involved in antigen recognition.

Accessory Chromosome: ►B chromosome

Accessory DNA: A product of DNA amplification in the cell. ►amplification

Accessory Gland: A relatively minor tissue aiding the function of a gland. ►epididymis

Accessory Pigments: Complement chlorophylls in absorbing light (carotenoids, xanthophyll, phycobilins).

Accessory Proteins: Accessory proteins such as transcription factors bind to upstream DNA elements for controlling transcription and other binding proteins that take part (not necessarily the main part) in a particular function. Accessory host proteins are also involved in the orientation or directionality of transposons. ►transcription factors, ►transposable elements, ►Transposons

Accessory Sexual Characters: The structures and organs of the genital tract including accessory glands and external genitalia, but not the gonads, which are the primary sexual characters. ►sex determination, ►gonad, ►sex phenotypic, ►secondary sexual character

Accommodation: ►decoding, ►ribosomal

Accuracy: The percentage of correct identification of carcinogens and non-carcinogens based on mutagenicity tests. The mutagenicity tests are much faster and less expensive than direct carcinogenicity assays but it is important to know how well these simpler tests reveal the carcinogenic (or non-carcinogenic) properties of the chemicals tested. Accuracy also means when a measurement conforms to a prediction based on physical-chemical properties of the structure of a protein. ►sensitivity, ►specificity of mutagen assays, ►predictivity, ►bioassays in genetic toxicology; Rédei GP et al 1984, Mutation, cancer and malformation, In: Chu EHY, Generoso WM (eds) Plenum, New York, p. 689.

Accuracy of DNA Replication: ►DNA replication error

ACE (angiotensin converting enzyme): ►angiotensin

ACE (affinity capillary electrophoresis): A procedure to test the binding strength of ligands.

Ace.mbly: Shotgun and directed sequencing evaluation program. ►shotgun sequencing, gene predictor.

ACEDB: *A Caenorhabditis elegans* (a nematode, useful for genetic analyses) database. ►*Caenorhabditis elegans*

Acenaphthene: A spindle fiber poison and thus polyploidization agent (see Fig. A8); it is also a fungicide and insecticide. ►polyploid, ►colchicine, ►spindle poison

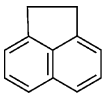

Figure A8. Acenaphthene

Acentric Fragment: The broken off piece of a chromosome that lacks centromere and therefore, its distribution to the poles during nuclear divisions is random and often lost. Acentric fragments are frequent consequences of irradiation of cells with X rays and other ionizing radiations (see Fig. A9). Chromosomal inversions may generate bridges (shown between the two poles) and three acentric chromosome fragments of substantial size that drift in the middle of the cell and are not distributed to the poles. ►centromere, ►chromosome morphology

Figure A9. Acentric fragment

Aceruloplasminemia (3q23-q24): Generally recessive deficiency of ceruloplasmin resulting in dementia, ataxia, diabet0065s, etc. Ceruloplasmin mediates the peroxidation of transferrin FeII to the FeIII form. ►ceruloplasmin, ►transferrin, ►iron metabolism; Hellman NE et al 2002 J Biol Chem 277:1375.

Acervulus: A disk-like conidia-bearing reproductive structure of fungi. ►conidia

Acesims (affinity capture-release electrospray mass spectrometry): Acesims uses biotinylated tags similarly to ICAT to capture conjugates in complex biological mixtures and to target specific enzymes that have role is metabolic defects such as disease. ►MALDI, ►ICAT, ►proteomics; Turecek F 2002 J Mass Spectrom 37:1.

Acetabularia: Single-celled green algae that may reach the size of 2–3 cm and may be differentiated into rhizoids, stem and cap. It can survive enucleation for several months. The rhizoids, containing the nucleus, may regenerate into complete plants; x ≈ 10. enucleate (see Fig. A10).

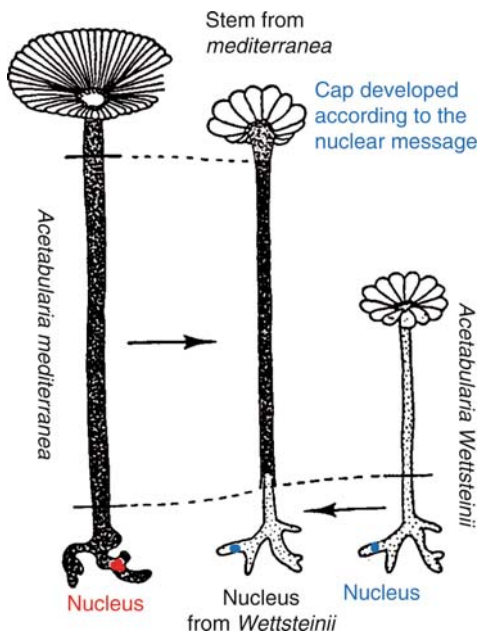

Figure A10. *Acetabularia* species are useful objects for developmental genetic studies and show dramatically the role of the cell nucleus. Grafting of the nucleus-containing section of the cell of *A. wettsteinii* to *A. mediterranea* caused *A. mediterranea* to develop a cap according to the instructions of the nucleus donor species. Experiment of J. Hämmerling in the 1940s. (Modified after Goldschmidt RB 1958 Theoretical Genetics. Univ. California Press. Berkeley, CA, USA)

Aceto-Carmine: ►stains

Acetonitrile (methyl cyanide): A highly poisonous liquid with ether-like odor, flash point 12.8 °C (beware of the vapors) a polar solvent used (among others) for the separation of oligonucleotides by reverse-phase chromatography on silica gels.

Aceto-Orcein: ►stains

Acetosyringone: (4-acetyl-2,6-dimethoxyphenol) and hydroxyacetosyringone are produced in plant cells (tobacco) and are one group of the compounds that induce the *vir* gene system of the *Agrobacterium* Ti plasmid. ►*Agrobacterium*, ►transformation [plants], ►virulence genes of *Agrobacterium*

Acetyl Coenzyme A: ►acetyl-CoA

Acetyl Group: Derived from acetic acid CH_3COOH; the R stands for different chemical groups (see Fig. A11). ►acyl group

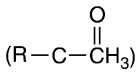

Figure A11. Acetyl group

Acetylation: Acetylation of histones opens the nucleosomal structure for transcription of the DNA. Acetylation of H3 and H4 histones may generate bromodomains for protein-protein interactions. Several non-histone proteins involved in the regulation of transcription are also acetylated. HMG proteins, nuclear import proteins and tubulins are also acetylated primarily at selected lysine sites. In the DNA-binding transcription factors (p53, E2F1, EKLF, GATA), the sites near to the binding domain is acetylated and this increases binding. Acetylation of some of the HMG-BOX proteins results in reduced binding to DNA. Acetylation of TCF may disrupt its binding to other proteins or acetylation may prevent binding together of some regulatory proteins. Acetylation may increase protein half-life (e.g., E2F1, α-tubulin) and may enhance protein targeting (e.g., p53). Signaling molecules may provide cues for acetylation. The roles of acetylation may bear similarity to that of kinases although the number of acetyltransferases is much much smaller than that of kinases. (See terms ►mentioned under separate entries, ►GCN5, ►histone acetyltransferases; Kouzarides T 2000 EMBO J 19:1176).

Acetyl-CoA (acetyl coenzyme A, ACoA): A heat-stable cofactor involved in the transfer of acetyl groups in many biological reactions (citric acid cycle, fatty acid metabolism, etc.). It has three major domains: the β-mercapto ethylamine unit, the pantothenate unit and adenylic acid. ►epinephrine, ►sirtuin (see Fig. A12).

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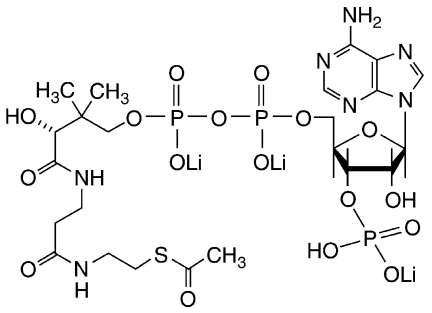

Figure A12. Acetyl coenzyme, Li salt

Acetyl-CoA Carboxylase Deficiency (ACAC): The recessive ACACA is in human chromosome 17q21. The cytosolic ACACA is primarily expressed in the liver and in adipose tissues. ACACB (12q24.1) is in the mitochondria and expressed mainly in the heart and muscles. ACAC causes multiple interferences with gluconeogenesis, fatty acid and the branched-chain amino acid metabolism. ACACB deficiency leads to continuous oxidation of fatty acids and reduced fat storage in mice. Acetyl-CoA carboxylase (also called ACCase) is a biotin-dependent enzyme in the pathway of long-chain fatty acids located in the cytosol and in the chloroplasts of plants. ACC1 deficiency is lethal for mouse embryos but ACC2-null mice are viable (Abu-Elhaiga L et al 2005 Proc Natl Acad Sci USA 102:12011). This enzyme is the target of oxyphenoxypropionate and cyclohexanedione herbicides. ►branched-chain amino acids, ►herbicides, ►obesity, ►fatty acids, ►obesity; Mao J et al 2003 Proc Natl Acad Sci USA 100:7515.

Acetylcholine (ACh, M_r 149): The acetylcholine receptor provides the connection between synapsing neurons and it is thus a signal transmitter. When acetylcholine binds to a receptor a Na^+/K^+ channel opens. The muscarinic acetylcholine receptors are activated by the fungal alkaloid, muscarine, whereas the nicotinic acetylcholine receptors are operating in the nerve and muscle cells. Acetylcholine receptors are diffusely distributed on the embryonic myotubes but become highly concentrated in a minute area in the post-synaptic membrane and they tether the synaptic cytoskeletal complex. ►ion channels, ►synapse, ►cytoskeleton, ►rapsyn, ►myotube, ►neuregulin, ►agrin, ►neurotransmitters, ►acetylcholine receptors, ►muscarinic acetylcholine receptors, ►myasthenia, ►memory, ►game theory, ►organophosphates; Smit AB et al 2001 Nature [Lond] 411:261; Miyazawa A et al 2003 Nature [Lond] 423:949.

Acetylcholine Receptors: Acetylcholine regulated cation (Na^+, K^+ and Ca^{2+}) channels between the motor neurons and the skeletal muscles. The receptor in the skeletal muscle contains five transmembrane polypeptides, encoded by four separate yet similar genes. When acetylcholine attaches to the receptor, a conformational change ensues resulting in a brief opening of the channel. They are easily isolated from the electric organs of some fishes. ►muscarinic acetylcholine receptors, ►nicotinic acetylcholine receptors, ►ion channels, ►agrin; Brejc K et al 2001 Nature [Lond] 411:269.

Acetylcholinesterase (ACHE): Encoded in human chromosome 3q25.2 by codominant alleles. It hydrolyzes acetylcholine into acetate and choline and it restores the polarized state in the postsynaptic nerve membranes. ACHE inhibitors are insecticides and drugs. Nerve gases are also ACHE inhibitors. ►acetylcholine, ►acetylcholine receptors, ►pseudocholinesterase deficiency, ►NTE, ►organophosphates

Acetylglutamate Synthetase Deficiency: A form of autosomal recessive hyperammonemia. ►hyperammonemia

Acetyltransferases: When first identified, it was believed that such enzymes acetylated histones but several enzymes became known later that acetylate other proteins and some that do not acetylate ►histones, ►histone acetyltransferases; Yang X-J 2004 Nucleic Acids Res 32:959.

ACF (ATP-utilizing chromatin assembly and remodeling factor): ►chromatin remodeling (Fyodorov D, Kadonaga JT 2002 Nature [Lond] 418:897).

aCGH: A microarray-based Comparative Genomic Hybridization (aCGH) technique used to identify and characterize DNA copy number variations across the genome. (See http://genome-www.stanford.edu/aCGH/; http://asterias.bioinfo.cnio.es/; ►microarray hybridization).

***Achaete-scute* Complex**: A complex X-chromosomal (1-0.0) locus of *Drosophila* regulating bristle formation and nerve differentiation. The posterior dorso-central bristles are usually missing and the hairs are also sparse in that area. The *achaete* phenotype is generally due to some type of chromosomal rearrangement or loss (see Fig. A13). ►complex locus

Figure A13. *Achaete-scute* complex. (From Bridges, C. & Brehme, K. Carnegie Inst. Washington 552: 12)

Achalasia-Addisonianism-Alacrima Syndrome (AAA, 12q13): Also known as triple A syndrome it is a complex glucocorticoid/adrenal/ deficiency causing failure of some muscles to relax, hypotension and weakness, failure in shedding tears normally and various nervous anomalies. The basic defect may involve a WD-repeat protein. Using a mutant of nucleoporin protein ALADIN^{I482S} it was shown that karyopherin-α/β-mediated import pathway was reduced and consequently DNA single-strand break repair (mediated by aprataxin protein) and ligase I activities were diminished leading to the symptoms of the disease (Hirano M et al 2006 Proc Natl Acad Sci USA 103:2298). ►WD-40; Handschug K et al 2001 Hum Mol Genet 10:283.

Acheiropodia: Recessive 7q36 developmental human anomaly (incidence ~0.000004) involving bilateral amputation of the extremities, hands and feet (see Fig. A14). The corresponding mouse locus is *Lmbr1*. It may be accompanied by polydactyly and can occur in both hands and feet.

Figure A14. Acheiropodia

Achene: A single-seed dry fruit.

Achiasmate: Nuclear division without the formation of chiasmata. Chiasma is generally a requisite for orderly segregation of the meiotic chromosome. In male *Drosophila* chiasma and crossing over are usually absent yet chromosomes segregate normally. Stromalin (member of the cohesin family) and *Modifier of Mdg4 in meiosis* (MNM), a member of the SMC family assure the normal process. ►meiosis, ►recombination, ►chiasma, ►distributive pairing, cohesin, ►SMC, ►Mdg; Thomas SE et al 2005 Cell 123:555.

Achilles' Heel Technique: A technique applicable to systems where there is abundant sequence information, and it permits the cleavage of only a small set of restriction sites. It works this way: DNA sequences around the site or set of sites are synthesized and added to the genomic DNA along with RecA, and a methylase. After deproteinization, a restriction enzyme is added. All the (methylated) restriction sites are protected from cleavage except those that were covered by the RecA-DNA complex. ►DNA sequencing, ►Rec, ►methylase, ►methylation of DNA, ►restriction enzyme; Szybalski W 1997 Curr Opin Biotechnol 8:75.

Achondrogenesis: Achondrogenesis has been described in two or more autosomal recessive forms involving deficiency in bone formation at the hip area and large head, short limbs, stillbirth or neonatal death. The phenotypes show variations and clear-cut differentiation of the symptoms is difficult. ►achondroplasia, ►hypochondroplasia, ►stature in humans, ►collagen

Achondroplasia (ACH): A rather common chromosome 4p16.3 dominant (homozygous perinatal lethal) type of human dwarfness that was observed (see Fig. A15), e.g., in Denmark at a frequency of 1.1×10^{-4}. Its mutation frequency (predominantly of paternal origin) was estimated to be within the range 4.3 to 7×10^{-5}.

The proximal bones in the limbs are most reduced. Large head with disproportionally small mid-face, abnormal hip and hands are characteristic. The heterozygotes are generally plagued by heart, respiratory and other problems. Hypochondroplasia appears to be allelic to achondroplasia. The so-called Swiss type achondroplasia is recessive and the afflicted individuals show reduced amount of leukocytes (lymphopenia) and agammaglobulinemia. Pseudoachondroplastic dysplasias (PSACH, spondyloepiphyseal dysplasia) are autosomal recessive (19p13.1) but some ambiguities were noted regarding the pattern of inheritance because of apparent gonadal mosaicism. PSACH is apparently due to defect in the cartilage matrix. The different forms do not have clear phenotypic distinctions within the group and from the dominant achondroplasia. Some of the skeletal reductions and defects are aggravated by face, eye defects, cleft palate and muscle weakness. Achondroplasia is caused by defects in lysosomal targeting of the fibroblast growth factor receptor 3 (FGFR-3), located

Figure A15. Autosomal dominant type achondroplasiac adolescent. (Courtesy of Dr. Rimoin DL Harbor General Hospital, Los Angeles, CA, and Dr. Judith Miles)

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in human chromosome 4p16.3. A recurrent missense mutation in a CpG doublet of the transmembrane domain of FGFR-3 caused an arginine substitution for glycine. Achondroplasia with developmental delay and acanthosis nigricans and thanatophoric dysplasia are also defective in fibroblast growth-factor receptor 3. Achondroplasiacs usually display normal intelligence. ►stature in humans, ►hypochondroplasia, ►pseudoachondroplasia, ►achondrogenesis, ►Ellis-van Creveld syndrome, ►agammaglobulinemia, ►cleft palate, ►fibroblast growth factor, ►dwarfism, ►receptor tyrosine kinase acanthosis nigricans, ►thanatophoric dysplasia; Cho JY et al 2004 Proc Natl Acad Sci USA 101:609.

Achromatic: Parts of the cell nucleus, which are not stained by nuclear stains. A microscope lens that does not refract light into different colors is achromatic.

Achromatopsia: Recessive inability to distinguish colors, low visual acuity and involuntary eye movements (nystagmus) is a rod monochromatism due to defects in the α-subunit or β-subunit of the cone cyclic nucleotide-gated cation channel (8q21-q22). This normally generates the light-evoked electrical responses of the cone receptors. Another locus 2q11-q12 with defect in the α-subunit of the cGMP gated ion channel debilitates the cone photoreceptor, and a third locus (Xp11.4) with cone dystrophy cause achromatopsia.

Acid-Base Catalysis: Acids and bases are common catalysts of organic reactions in proportion of the presence of H^+ or OH^- ions in the medium. Enzymes are particularly well-suited catalysts because they can carry out either acid or base, or simultaneously both acid and base catalysis. Ribozymes are also potential acid/base catalysts. ►transition state

Acid Blob: A sequence of acid amino acids (negatively charged), responsible for activation of a transcription factor. ►transcription factors; Almlof T et al 1995 J Biol Chem 270:17535.

Acid Fuchsin: A histological stain used to detect connective tissue and secretion granules (Mallory's acid fuchsin, orange G and aniline blue, and in the Van Gieson's solution of trinitrophenol staining of connective tissue of mammals). ►stains

Acid Maltase Deficiency: A type II glycogen storage disease involving defect(s) in α-1,4-glucosidase activity. The disease causes accumulation of glycogen in most tissues, including the heart. The first symptoms appear by 2 months after birth and by 5–6 months death results due cardiorespiratory (heart and lung) failures. Although it is classified as an autosomal recessive trait in humans (GAA, 17q25.2-q25.3), the heterozygotes may be distinguished clinically. ►glucosidase, ►Gaucher diseases, ►glycogen storage diseases

Acid Phosphatase: Cleaves phosphate linkages at low pH. Its levels are increased in most lysosomal storage diseases, particularly in Gaucher's diseases involving glucosyl ceramide lipidosis (defect in lipid metabolism involving cerebrosides, a complex of basic amino alcohols [sphingosine], fatty acids and glucose). Other diseases may also cause increase of acid phosphatase. In plants, only acid phosphatases are found in appreciable quantities. Yeast has at least 4 genes with acid phosphatase function; one of them is constitutive, others are repressed by inorganic phosphate. ACP1 is in human chromosome 2p25, ACP2 in 11p12-p11. ►alkaline phosphatase

Acid Reflux: Retrograde movement of stomach acid and bile to the throat and mouth. ►Barrett metaplasia

Acidic Dyes: Stain basic cellular residues.

Acidic Sugars: ►sialic acids

Acidocalcisomes: ►organelle

Acidosis: A reduction of buffering capacity of the body resulting in lower pH of fluids.

Acid-Sensing: Acid-sensing is mediated by proton-gated ion channels in the sensory neurons. ►ion channels

Acinar Cells: Exocrine cells, for e.g., mammary gland cells that secrete milk, lacrimal cells that secrete tears, etc. Acinar cells resemble sacs. ►exocrine

Acinus (apoptotic chromatin condensation inducer in the nucleus): Apparently the substrate of caspase-3 and this cleavage activates pyknosis in the cell nucleus. ►pyknosis, ►karyorrhexis, ►apoptosis, ►caspase, ►CAD; Seewaldt VL et al 2001 J Cell Biol 155:471.

Acinetobacter: Oxidase-negative, Gram-negative coccobacilli of widespread habitat but become infective primarily in hospitals affecting immune-compromised or wounded individuals. (Rahal JJ, Urban C 2000 Semin Resp Crit Care Med21(4):341). The bacteria are resistant to the majority of antibiotics and cause up to 40% death. ►nosocomial; Huys G et al 2005 J Med Microbiol 54(Pt 9):851.

ACIS (automated cellular image analysis): Detects rare cells (e.g., metastatic tumor cells occurring at a frequency of 10^{-6} to 10^{-7}) after immunocytochemical staining. Its efficacy far exceeds that of the manual detection. metastasis, ►FAST; Bauer KD et al 2000 Clin Cancer Res 6:3552.

AcMNPV (*Autographa californica* nuclear polyhedrosis virus): AcMNPV can be used for the construction

of insect and mammalian transformation vector. ►baculovirus, ►polyhedrosis virus

Acne: Inflammation of the sebaceous glands (that secrete oily stuff on the skin). It does not appear to be under strict genetic control, but rather caused by various environmental conditions, including bacterial infections, mechanical irritation, cosmetics, etc. It usually appears in puberty and disappears after but may leave behind permanent scars. Occasionally it occurs on infants. *Propionibacterium acnes* is one of the major causes of acne has a completely sequenced genome of 2,560,265 base pairs contains about (2333) genes and can cause several other diseases (Brüggemann H et al 2004 Science 305:671). ►skin diseases

Aconitase: An enzyme controlling the dehydration of citrate to cis-aconitate and the hydration of the latter to isocitrate. This enzyme has also an important role in the transport of iron. Iron-containing proteins regulate many processes in both prokaryotes and eukaryotes. In eukaryotic cells, the level of the storage protein ferritin increases when soluble iron level increases in the cytosol. The control of the process is mediated by a 30-nucleotide *iron-response element* to what aconitase binds and then blocks the downstream translation of RNA. Aconitase is an iron-binding protein, and the increasing level of iron within the cell dissociates it from the ferritin mRNA resulting in about two order of magnitude increase of ferritin by releasing the translation suppressor from the ferritin mRNA. The increased level of iron also decreases the stability of several mRNAs encoding the receptor that binds the iron-transporting transferritin and thereby reduces the amount of the receptor. Aconitase also binds to the 3′ untranslated tract of the transferrin receptor mRNA and enhances the production of the receptor, probably by stabilizing the mRNA. The human ACO1 gene is in chromosome 9p22-p14 and the mitochondrially located ACO2 is encoded in 22q11-q13. The mitochondrial aconitase, besides its metabolic function, contributes to the maintenance of mitochondrial DNA (Chen XJ et al 2005 Science 307:714). ferritin, ►translation repressor protein, ►IRE, ►rabbit reticulocyte in vitro translation system; Bulteau A-L et al 2004 Science 305:242.

α-CPM: (α-connecting peptide domain): Connects the α and β chains of the αβ T cell receptor but it is absent from the γδ T cell receptor. This domain is required for positive selection of T cells although negative selection may take place in its absence. ►T cell, ►T cell receptor, ►positive selection of lymphocytes

Acquired: Alteration that occurred during the lifetime of an individual. ►constitutional

Acquired Characters, Inheritance of: An ancient idea supposing that the minor and major environmental effects may cause long-lasting heritable changes in the genetic material. This view was proved incorrect by the advances of biology in the ninetieth century. However, poorly trained ideologues of Marxism, the followers of Mitchurin and Lysenko, revived it in the Soviet Union. Modern biologists, who claim the existence of environmentally inducible selective mutations, periodically resurrect it. Most of these recent experiments remain controversial because alternative explanations of the experimental data seem to be as good or even more satisfactory (see directed and local mutagenesis). Genetic transformation by plasmid vectors has been compared with inheritance of acquired characters. However, substantial differences exist between the two phenomena; in transformation, the actual transfer or loss of genetic material (DNA or RNA) has been demonstrated by standard molecular methods. In many cases, claims of inheritance of acquired characters in higher plants and animals have not been demonstrated. Landman (1993 BioScience 43:696) states "so far as I know, only changes in nucleic systems can be transmitted through the germline." Nevertheless, Landman (1991 Annu Rev Genet 25:1) lists a few apparent exceptions (unicorns in the garden, in the words of Frank Stahl) such as the cortical inheritance of *Paramecia* or the epigenetic changes in histone methylation or prions. Recently observed paramutation-like unorthodox cases of inheritance in plants and animals are rather unorthodox phenomena. These examples are in sharp contrast to those published during the soviet era, which do not meet the current scientific standards because the experiments did not use reliable controls and the genetic constitution of the material was either obscure or obviously contaminated.

Advantageous frameshift backmutations may take place, however, under selective conditions by recombination. The inheritance of acquired characters has also been attributed to a mechanism of canalization. The change in the environment permits selection of hidden variations in chaperones adapted to the environmental change. Even after the release of the stress, the selected new forms of the chaperones may persist and simulate inheritance of acquired characters. ►Lamarckism, ►Mitchurinism, ►Lysenkoism, ►soviet genetics, ►graft hybridization, ►transformation, ►recombination, ►frameshift, ►backmutation, ►chaperones, ►canalization, ►evolution, ►epimutation, ►paramutation, ►cortical inheritance, ►epigenesis, ►epigenetics, ►prions, ►transformation genetic; Zirkle C 1946 The Early History Of The Idea Of The Inheritance Of Acquired Characters And Pangenesis. American Philosophical Society, Philadelphia; Lindegren CC 1966 The Cold War In Biology, Planarian Press, Ann Arbor, Michigan.

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Acquired Immunity (adaptive immunity): The consequence of natural infection or vaccination or direct transfer of antibodies or lymphocytes from an appropriate donor. The acquired immunity is based on potential variations in the immunoglobulins in response to invading antigens. Somatic gene rearrangements lead to the generation of immune receptors in lymphocytes and the activated lymphocytes are clonally propagated. This immunity system consists of $CD4^+$ and $CD8^+$ T cells. T cells recognize antigens after being processed by the antigen presenting cells (dendritic cells, macrophages and B cells), which express MHC class II molecules. After the recognition, T helper cells (T_H-1 and T_H-2) differentiation begins. T_H-1 cells characteristically produce gamma interferon (INF-γ), which attacks intracellular invader microbes. For T_H-2 cells interleukin-4 (IL-4) is diagnostic. T_H-2 cells requires MHC class I molecules while T_H-1 cells depend on MHC class II. Both helper T cells utilize a variety of cytokines for the development of effector function, i.e., to be fully activated. In insects (*Drosophila*) the phagocytic plasmatocytes represent the cellular defense. In addition, the humoral reaction develops to microbial challenge by the secretion antimicrobial peptides into the hemolymph. ►innate immunity, ►immune system, ►immunity, ►vaccine, ►antimicrobial peptide; Crowe JE Jr et al 2001 J Immunol 167:3910; in vivo test model for human adaptive immunity in mice: Traggiai E et al 2004 Science 304:104; evolution of adaptive immunity: Cooper MD, Alder MN 2006 Cell 124:815.

Acquired Immunodeficiency Syndrome (AIDS): Caused apparently by the HIV-1 (HTLV-III) and HIV-2 (human immunodeficiency virus [lentivirus]), retroviruses. The general structure of the HIV-1 virus includes three major structural proteins: gag, pol and env, and several regulatory and accessory proteins: vif, vpr, vpu, vpt, tev/tnt (see Fig. A16).

The gag proteins serve as structural elements: 132 amino acid matrix [MA], 152–231 amino acid capsid [CA], 55 amino acid nucleocapsid [NC] and 51 amino acid p6 [vpr-binding protein]. The pol is processed into the dimer of two 99 amino acid protease [PR], reverse transcriptase [RT] is heterodimer of 560 and 440 residues, and the tetrameric, and the tetrameric integrase [IN] of 288-residue monomers. The reverse transcriptase generates the enzyme, which transcribes RNA into DNA and this viral copy can be inserted into the human chromosome and survive there for a long time as a provirus. The protease processes the polyproteins into the various enzymes of the virus and integrase facilitates the entry of the virion into the host cells. When HIV-1 traverses the inner nuclear envelope of the cell (macrophages) it contacts the emerin protein that facilitates viral integration into the

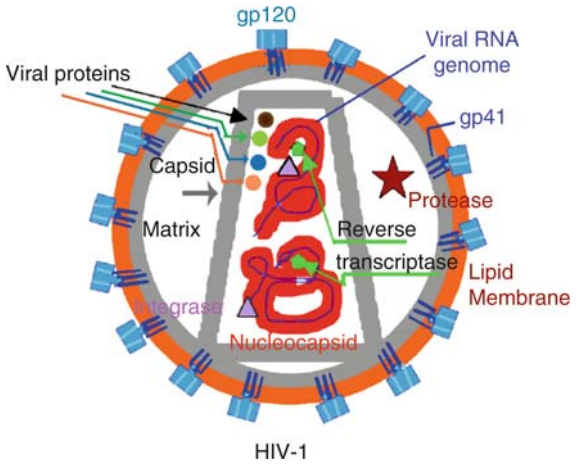

Figure A16. HIV-1. The schematic structure of the HIV-1 virus. The gp120-gp41 heterodimer associate in a trimer to form the spikes. This and the envelope determine antigenicity and immunogenicity (gp indicates envelope glycoproteins). Cryoelectron microscopy tomography revealed ~14 spikes per HIV-1 virions and ~73 spikes per particle of SIV. The surface gp120 of the trimeric SIV spike contains a primary mass with two secondary lobes. The transmembrane glycoprotein stalk of each trimer is composed of three independent legs projecting from the trimer head in tripod-like form (Zhu P et al 2006 Nature [Lond] 441:847)

chromatin (Jacque J-M, Stevenson M 2006 Nature [Lond] 441:641). The von Hippel–Lindau binding protein 1(VBP1), a subunit of the prefolding chaperone, is an integrase cellular binding protein that bridges interaction between integrase and the cullin2 (Cul2)-based von Hippel–Lindau (VHL) ubiquitin ligase. VBP1 and Cul2/VHL are required for proper HIV-1 expression at a step between integrase-dependent proviral integration into the host genome and transcription of viral genes. VBP1 and the Cul2/VHL ligase cooperate in the efficient polyubiquitylation of integrase and its subsequent proteasome-mediated degradation (Mousnier A et al 2007 Proc Natl Acad Sci USA 104:13615).

The *env* envelope protein includes a surface glycoprotein, gp120 [SU] and a transmembrane glycoprotein, gp41 [TM] that are processed from gp160 molecule. Protein gp120 facilitates binding the virus to the cell membrane and gp41 promotes fusion to the membrane. Human monoclonal antibody may block the virus by binding a critical region of gp41 epitope and may offer an approach of prevention of infection (Miller MD et al 2005 Proc Natl Acad Sci USA 102: 145759). The processing facilitates the interaction of the virus with the CD4 host cells and the CXCR4 and CCR co-receptors. The envelope protein vpr (14 kDa) accelerates replication

and infection. Vpr facilitates the transport of the viral core into the nucleus, stimulates the expression of viral genes and mediates cell cycle arrest at the G_2 stage (de Noronha CMC et al 2001 Science 294:1105).

Rev (19 kDa) is transcribed from two exons, regulates viral replication and its basic amino acid domain (nuclear export signal, NES) interacts with the Rev response element (RRE, within *env*) targeting the viral transcripts to the cell nucleus. Within the nucleus, the exportin-1/CRM1 protein represents a receptor for NES. Tat (14 kDa, two exons) is the primary regulator of the virus. Vpu (15–20-kDa) membrane protein attacks CD4 with the assistance of the proteasome degradation pathway. Nef (25–27 kDa) mediates the degradation of CD4 on the cell surface and promotes endocytosis through the clathrin-coated pits. Nef and Tat proteins may be produced before the integration of HIV into the chromosome. These two proteins activate quiescent T cells, a requisite for viral integration and replication. Activation of $CD4^+$ T lymphocytes and apoptosis that follows is an important sign of infection by HIV-1 and the Nef gene mediates this process through the T cell receptor-CD3 complex. The majority of other lentiviruses down-modulate this complex and less likely to give infection.

If Nef is inactivated AIDS progression slows down because T cells are not destroyed. Thus, it appears that human HIV-1 evolved by the loss of this function of Nef, resulting in immune evasion and AIDS (Schindler M et al 2006 Cell 125:1055).

Active genes are preferential targets of integration. (Schröder ARW et al 2002 Cell 110:521). Nef also inhibits the cellular protein ASK1, an apoptosis signaling serine/threonine kinase. That protects the infected cells from apoptosis although neighboring cells may die through bystander effect. Successful entry and productive infection requires the cooperation of the cellular protein cyclophilin A. In case cyclophilin is inhibited, HIV cannot infect neighboring cells even if HIV is within the originally infected cell. Similarly, by blocking the activity of MAPK, virulence of HIV is reduced. The viral Vif (virion infectivity factor) protein (23 kDa) is also required for the assembly of the viral coat proteins after infection (see Fig. A17). Vif also prevents deamination of cytidine into uracil by host APOBEC3 to avoid the damage to viral RNA (Priet S et al 2005 Mol Cell 17:479). Non-permissive host cells produce the CEM15 protein, which prevents viral infectivity of Vif-deficient HIV. CEM15 is absent from permissive cells and this permits infection by Vif-deficient virus (Pomerantz JR 2002 Nature [Lond] 418:594). For entry into the cell nucleus, the virion needs the nuclear localization signal (NLS) provided by the uncoated viral nucleoprotein pre-integration complex (PIC). Viral protein Vpr interacts with PIC and thus assists nuclear localization of HIV. The virus is not transmitted through the germline. The *tat* gene functions only through the 5′ RNA hairpin TAR (transactivation response element, 59 nucleotides) present within the repeat region (R) of the 5′ LTR. The 5′LTR includes also the basal core promoter, the core enhancer and a modulatory region. The eukaryotic eIF2 elongation initiation element recognizes TAR. The 5′ LTR serves also as the binding sites for a large number of host transcription factors (Pereira LA et al 2000 Nucleic Acid Res. 28:663). The Tat (14 kDa) primarily regulates the elongation of the transcript, generated by host RNA polymerase II. Pol II starts working at the 5′ LTR. The Tak-associated kinase (TAK) complex phosphorylates the COOH end (CTD) of transcriptase pol II. The phosphorylation is the job of Cdk9 (formerly called (PITALRE). Cdk9 is bound to Tat by cyclin T (CycT) and enhances the specificity of Cdk9 to 5′-TAR. The TATA box is situated −24 to −28 positions from the GGT initiator codon. Further upstream in the enhancer region are the binding sites for the USF (upstream enhancer), Ets-1 (thymocyte-enriched protein), LEF (lymphocyte-specific high-mobility group protein), NK-κB (nuclear factor κ binding protein) and Sp1 (a mammalian transcription factor) binding proteins within the region −166 to −45 in the 5′-LTR. Around the transcription initiation site are the overlapping SSR (initiator) and IST (initiator of short transcripts) sequences. The virus does not have known genetic repair system and displays great antigenic variability; therefore, it is difficult to develop an effective vaccine against it (Rossio JL et al 1998 J Virol 72:7992; Gaschen B et al 2002 Science 296:2354; cardiolipin).

The Nef protein protects the infected primary cells from cytotoxic T cells. The viral coding RNA genome

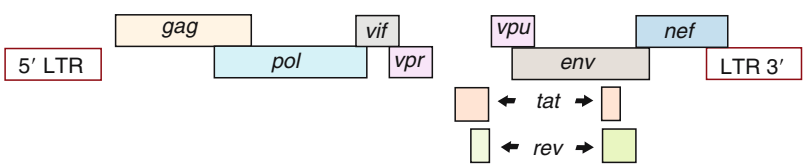

Figure A17. Genetic organization of HIV-1

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is about 9 kb. HIV1 and lentiviruses are suitable for the construction of transformation vectors that may integrate into non-dividing cells. Two of the viral proteins interact with nuclear import and mediate the active transport of the HIV pre-integration complex into the nucleus through the nuclear pores. The infection begins when the virus penetrates the cell membrane and its own lipid membrane fuses with the cell membrane and the viral core is released into the cell. Inside the cell, the viral reverse transcriptase synthesizes DNA copies of its RNA genome, and this DNA provirus integrates into the host genome with the aid of its terminal repeats, characteristic also for all types of insertion elements yet HIV is not transmitted through the germline. The HIV contains genes for proteins and their regulation. HIV does not have a lytic phase so it does not kill the cells directly. Instead, it assembles its particles in the cytoplasm and then infects other cells.

Upon infection by the HIV, monocytes, macrophages, endothelial cells and fibroblasts overproduce IL-1, IL-6 and TNFα. The anti-inflammatory IL-1ra and IL-10 are also hyperproduced. The latter ones inhibit the synthesis of the inflammatory lymphokines and IL-12. Soluble tumor necrosis factor receptors (sTNFR) hinder the binding of TNF to the cell membrane receptors. *Staphylococcus*-stimulated monocytes produce an order of magnitude less IL-12. After HIV infection $CD4^+$ T cells lower the output of IL-2. Since IL-2 stimulates several players of the immune system, the immune response decreases. The dysregulation of cytokine balance results in a deficiency of cell-mediated immunity. The delayed-type hypersensitivity reaction (DTH) cannot control then the intracellular microorganisms. The main cause of the immunological failures is the defect in the $CD4^+$ T cells, in the antigen presenting cells and the destruction of the $CD4^+$ T cells although several billion $CD4^+$ T cells are produced every day after the infection. A portion of the AIDS patients—upon induction by a gp41 peptide—express the natural cytotoxicity receptor, NKp44 and consequently the natural killer cells deplete the CD4 T cells and increase HIV load (Vieillard V et al 2005 Proc Natl Acad Sci USA 102:10981). The killer cell immunoglobulin-like receptor (KIR) family members similar to other NK cell receptors are expressed on T cells as well as on NK cells. Activating *KIR3DS1* allele in combination with *Bw4-80I,* associates with protection against HIV disease progression, as well as against opportunistic infections in HIV^+ individuals. *KIR3DL1* and *HLA-B Bw4* combination effectively increases the protective effect of NK (killer T cell) against HIV (Martin MP et al 2007 Nature Genet 39:733).

The primary targets are the helper T lymphocytes carrying the CD4 receptors. The immune system is debilitated when impairing these cells and that is the primary cause of the disease. In the endoplasmic reticulum of the infected cell 845–870 amino acid protein precursors of the viral envelope are formed. After the addition of asparagine-linked mannose chains, the glycoprotein gp160 precursor is synthesized. The trimeric gp160 is carried to the Golgi apparatus where through proteolysis the gp120 envelope protein and gp41 transmembrane proteins are formed.

Targeting the gp41 carboxy-terminus by a small protein, called 5-Helix, inhibits the entry of HIV-1 into the cell. A 20-residue peptide, called virus-inhibitory peptide (VIRIP) similar to the C-proximal region of α1 antitrypsin protease inhibitor interferes HIV-1 entry by targeting gp41 envelope protein of the virus. A few amino acid replacements in this natural peptide may increase its potency by two orders of magnitude (Münch J et al 2007 Cell 129:263). The binding of CD4 on the lymphocytes, monocytes, dendritic cells and brain microglia by the gp120 viral surface protein results in a conformational change in gp120. These changes may make available binding sites for chemokine receptors (primarily CCR5 and ligand CXCR4) to secure the necessary second receptors for the viral entry into the cell. Sulfated tyrosines of the CCR5 co-receptor play an important role in binding the gp-120 viral glycoprotein and HIV-1 infection (Choe H et al 2003 Cell 114:161). Mutation in CCR5 (CCR5Δ32) reduces the chance of HIV infection and disease progression (Agrawal L et al 2004 J Virol 78:2277). A chemically modified RANTES through inhibition of CCR5 provides protection against vaginal infection of simian/human immunodeficiency virus (Lederman MM et al 2004 Science 306:485). Polymorphism of these receptors and the stromal-derived factor (SDF-1) may either accelerate or retard the progression of the disease. Organ culture method permitted the identification of HIV infection sites in the vaginal and cervical mucosa and the virion binding can be reduced by pre-treatment with antibodies against β1 integron (Maher D et al 2005 Proc Natl Acad Sci USA 102:11504). Another approach would be populating the vaginal, cervical or rectal mucosa with bacteria secreting antiviral peptide. Such initiatives indicate that such a procedure might be effective (Rao S et al 2005 Proc Natl Acad Sci USA 102:11993).

The feline immunodeficiency virus uses directly the chemokine receptors and the V3 loop of the variable region is the most important for binding of the chemokine receptors. The constant regions in between the V regions are folded into the core of the glycoprotein. A so-called bridging sheet that binds to CD4 connects the outer and inner domains of the core. Mutations in the core area may influence infectivity and may serve as target for medical attack on the virus.

The CD4 induced antibodies (CD4i and its 17b epitope) may block the binding of the gp120—CD4 complexes to the chemokine receptors. The crystal structure of the V3-containing core of gp120 is known (Huang C-c et al 2005 Science 310:1025).

For neutralizing HIV probably the CD4BS epitopes, directed to the gp120 inner core are most significant. The 2G12 antibody recognizes the outer domain of gp120. The antigenic surface of gp120 is largely shielded from humoral immune responses by the glycosylation and other barriers. Conformational changes in gp120 provide additional structural means for the evasion of the immune reactions.

Avoidance of infection through body fluids (blood, semen, saliva, etc.) is the only effective defense until a clinically effective immunization or cure can be developed.

Human monoclonal neutralizing antibody b12 recognizes a conformational epitope that overlaps with the CD-4-binding site of the HIV-1 gp120 (see Fig. A18). In animals, b12 has a broad specificity.

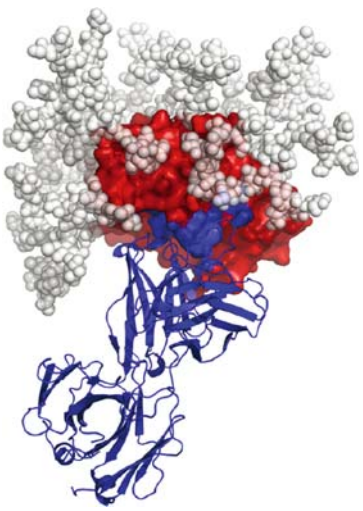

Figure A18. The b12 antibody (blue) to the HIV-1 exterior glycoprotein (red). The sugar (gray) occludes most of the gp120 surface from recognition. The blue surface (the epitope) marks where the receptor CD4 binds overlapping the b12 recognition site. (Courtesy of Peter D. Kwong and Jonathan Stuckey, Vaccine Research Center, NIAID/NIH)

Unfortunately b12-like antibodies are rarely produced in infected and vaccinated human subjects, indicating that the b12 epitope is poorly immunogenic for gp120–gp41 proteins. The gp120 viral glycoprotein has great ability to evade the human immune system.

The crystal structure of a constructed and stabilized gp120 molecule, which stays in the CD4-bound conformation even in the absence of CD4 was tested regarding antibody binding. The broadly acting antibody b12 in complex with this gp120 molecules was stabilized to various extents in the CD4-bound conformation and revealed the functionally conserved surface that allows for initial CD4 attachment, but also provides an atomic-level description of the b12 epitope, which serves as a key target for humoral neutralization of HIV-1. Thus, a site of vulnerability was revealed that shows promise for antibody targeting HIV-1 (Zhu T et al 2007 Nature 445:732; see structure diagram). Another type of vaccine using gp140R2 immunogen induced antibodies that achieved 50% to 80% neutralization of diverse HIV-1 subtypes (B and C and others) tested on rabbits. The effectiveness of gp120R2 induced antibodies was less good. The rare R2 type was selected because it had unusual CD4-independent phenotype and the exceptionally broad neutralizing response in the infected donor. Neutralization was IgG-mediated and HIV-1-specific. These results demonstrate that induction of truly broad-spectrum neutralizing antibodies is an achievable goal in HIV-1 vaccine development (Zhang PF et al 2007 Proc Natl Acad Sci USA 104:10193).

Generally, the first sign of the disease is the susceptibility to *Pneumocystis carinii,* an opportunistic fungal pathogen causing influenza-like symptoms. This happens because the AIDS patients have only 200 CD4 helper cells per mL of blood versus 800 in normals. The other, most critical, diagnostic feature of AIDS is the development of Kaposi's sarcoma, a disease causing bluish eruptions all over the body that becomes cancerous. In tissue culture, the infected and uninfected cells fuse into syncytia and this and immunological methods are used as laboratory diagnostic procedures for the infections. AIDS, one of the most dreaded diseases of the twentieth century is now being battled with the most advanced techniques of molecular genetics; yet no effective cure has been devised till year 2008.

Although the majority of the specialists in medical virology and molecular biology maintain the view that the causative agent of the disease is HIV, some reject this assumption and others look at the mechanism with some reservations. They find likely or conceivable that AIDS is the result of the synergistic action of viral and other requisites such as the use of drugs (antibiotics, etc.), some types of autoimmune predisposition, and thus has multifactorial origin.

The AIDS disease has infected >21 million people worldwide and their numbers are increasing daily by 8,500–14,000 individuals. There are now three main groups of HIV-1: (i) M type, which is the most widely spread, (ii) the O group in Cameroon, Gabon and equatorial Guinea and a new (iii) N type found in (1998) in Cameroon, Africa. There are also 10 known

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subtypes of the virus. The three main types appear to have originated independently from the chimpanzee virus SIVcpz. The HIV-2 strains seem to be originated in West Africa from the simian virus strain SIVsm of the sooty mangabeys (*Cercocoebus atys*). Adaptation to infectious forms of the virus required mutation as well as recombination. There are at least 10 host genes involved in the degree of susceptibility (Heeney JL et al 2006 Science 313:462).

A whole-genome study identified polymorphisms that explain nearly 15% of the variation among individuals in viral load during the asymptomatic set-point period of infection. One of these is found within an endogenous retroviral element and is associated with major histocompatibility allele human leukocyte antigen (HLA)–B*5701, whereas a second is located near the HLA-C gene. An additional analysis of the time to HIV disease progression implicated two genes, one of which encodes an RNA polymerase I subunit (Fellay J et al 2007 Science 317:944).

The suggestions that the AIDS epidemics originated through SIV contamination of the early polio vaccines do not seem to have scientific basis.

The pharmaceutical industry is developing various drugs to combat the disease. None of the drugs so far provides a full cure or prevention, yet definite progress is made. The first and best-known chemicals (AZT) attack the viral replication system; protease inhibitors are aimed at the assembly process of the viral coat protein in order to prevent multiplication of HIV (Prejdova J et al 2004 Curr Drug Targets Infect Disord 4(2):137). The virus depends on cutting and processing of host cellular protein and uses protease to this end. Unfortunately, the protease inhibitors may cause very unpleasant side effects and HIV may develop resistance against the drugs by inhibiting primarily the mitochondrial DNA polymerase γ and possibly other DNA polymerases (Feng JY et al 2001 J Biol Chem 276:23832). None of the current drugs actually kills and/or removes the virus; instead only limit its functions. Halting the treatment may lead the virus to re-emerge from its hiding place in the lymph nodes. Other potential drug targets may be the cells' entry sites and CXCRE4 and CCRS receptors. According to some estimates HIV may produce >10 billion virions daily. Since its genome contains 10^4 nucleotides, the virus can readily test all possible mutational combinations. The estimated number of mutations/replication/nucleotide is 3×10^{-5}. The generation time is about 2.5 days. Drug resistance is based primarily on new mutation rather than on transmission of resistant virus. In addition, recombination facilitates the production of new variants. The combination of two nucleoside-analogs and protease inhibitor may reduce the level of the viral RNA copies from 20,000 and 1,000,000 copies/mL plasma below detectability (i.e., below 200 to 400 copies/mL). These figures are concerned with viral levels in the blood. The newer techniques may detect even 20 virions/cell and reveal that the best medication available in (2001) cannot completely deplete the virus from the body. The lymph nodes and other sanctuaries may regenerate the virus after the discontinuation of the therapy. Additional problems may arise from the irreversibility of the tissue (thymus) damage. HIV-1 replication requires the REV oncogene cofactor and eukaryotic peptide elongation factor EIF-5A. Some mutations in the elongation factor retained the ability to bind to the HIV-1 REV response element: REV complex, and were expressed in human cells. When such T lymphocytes were infected with replication-competent virus, replication was inhibited. RNA decoys of the Tat and Rev genes may mimic the viral TAR and RRE RNAs but are non-functional yet sequester HIV-1 regulatory functions needed for the viral replication and gene expression. RNA polymerase III synthesizes these decoys and the transcript is a tRNA-TAR chimera. The decoys may, however, tie up some cellular molecules that could interfere with TAR and RRE. Type III RNAses Dicer and Drosha, responsible for miRNA processing, inhibited virus replication both in peripheral blood mononuclear cells from HIV-1–infected donors and in latently infected cells. In turn, HIV-1 actively suppressed the expression of the polycistronic miRNA cluster miR-17/92. This suppression was found to be required for efficient viral replication and was dependent on the histone acetyltransferase Tat cofactor PCAF (Triboulet R et al 2007 Science 315:1579).

Antisense/ribozyme RNAs against various (TAR, U5, *tat, rev, pol, vpu, gag, env*) transcripts have also been explored. Double-stranded 54-mer oligodeoxynucleotide (ODN), which consists of an antisense strand targeting the highly conserved polypurine tract of HIV, and a second strand, compatible with triple-helix formation, interferes with viral replication. Upon treatment of HIV-infected cells with ODN early after infection no viral nucleic acids, syncytia or p24 viral antigen expression was observed (Moelling K et al 2006 FEBS Lett 580:3545). ODN prematurely activates RNase H and thus inhibits the synthesis of the 2nd strand of retroviruses.

RNAi has been shown to be an effective inhibitor of HIV replication. Unfortunately, the virus can mutate at the siRNA recognition sites and escape the inhibition by producing an alternative secondary structure of the target (Westerhout EM et al 2005 Nucleic Acids Res 33:796). The viral Tat protein can abrogate the cellular RNA-silencing defense by subverting the Dicer enzyme (Bennasser Y et al 2005 Immunity 22:607).

The latent provirus, integrated into the cells, may possibly be eliminated from the body by induced apoptosis of the cells harboring the provirus. CD4 protein, conjugated with ricin or *Pseudomonas* exotoxin, may home on the gp120 viral surface proteins and may destroy the infected cells. For the incapacitation of the HIV virus self-inactivating E-vectors, removing the encapsidation signal (Ψ, psi) from the 5′ LTR have been designed. Vectors containing the Cre/LoxP system are also capable of deleting the packaging signal (Ψ) and replacing it with a desired sequence. An emerging novel approach would be to employ substrate-linked protein evolution of a tailored recombinase that recognizes an asymmetric sequence within an HIV-1 LTR. This type of recombinase efficiently excised integrated HIV proviral DNA from the genome of infected cells. This approach is different from others because it would actually remove HIV from the infected human genome. Preliminary data are promising yet it is not clinically applicable (Sarkar I et al 2007 Science 316:1912). Other current research attempts are focusing on the immune system to prevent infection. Although several interpretations are available, it is still uncertain why the period required for the development of full scale AIDS requires such a different length of latency after the initial infection. It had been assumed that the immune system is weakened by the ever-increasing viral diversity. Others believe that an immune dysregulation is responsible for the outbreak. Others suggest that the cellular immune system against AIDS be directed to both conserved and variable epitopes. It is assumed that the cytotoxic T lymphocytes alone cannot eliminate the virus and there is a need to achieve a balance between the viral load and the $CD4^+$ T lymphocytes. After a period, the increasing variations in the HIV-1 population deplete and foul up the immune system. In the so-called non-progressor individuals, AIDS may not develop for more than 10 or even 20 years after the infection (HIV-exposed persistently seronegatives [HEPS]). There are high levels of $CD8^+$ $CD38^-$ cytotoxic lymphocytes, high peripheral blood $CD8^+$ major histocompatibility class I-restricted anti-HIV cytotoxic lymphocytes in the cells of such a person, and those stay at an even level. There is also a strong $CD8^+$ non-MHC-restricted HIV suppressor activity and high level of antibody against HIV. Most untreated HIV-1-infected individuals have continuous viral replication and ultimately progress to AIDS. However, a rare subpopulation of HIV-infected patients spontaneously controls viral replication for long periods in the absence of treatment. These individuals, called HIV controllers (HIC), are characterized by undetectable plasma HIV-1 RNA. Some of these are infected by replication-incompetent viruses yet these individuals display a potent immune response to HIV-1. The controllers generally exhibit a strong $CD8^+$ T cell specific response and high frequencies of HIV-specific $CD8^+$ T cells despite very low levels of viral antigens. These HIC cells express the activation marker HLA-DR but not CD38. The HIV-specific $CD8^+$ T cells from HIC are thus qualitatively different from those of progressors. Some HLA-B haplotypes (e.g., B27 and B57) are over represented in HIC suggesting an important role of class I-restricted $CD8^+$ T cells and multi-epitopic and *de novo* $CD8^+$ T cell responses are associated with suppression of viremia despite cytotoxic T lymphocyte escape mutations (Saez-Cirión, A et al 2007 Proc Natl Acad Sci USA 104:6776).

The window of opportunity to clear HIV and prevent long-term, established infection might close permanently once a pool of latently infected cells is in place. This aspect of HIV infection puts it in sharp contrast with almost all other viral infections, in which the initial rounds of viral replication do not establish a permanent reservoir of infection. For this reason, HIV poses a greater challenge to the classic vaccination paradigm in which prevention of clinically relevant infection ultimately leads to the eradication of the microbe, even though initial rounds of viral replication may occur (Johnston MI, Faucci AS 2007 New England J Med 356:2073).

Any vaccine developed against HIV should stimulate $CD4^+$ and/or $CD8^+$ cytotoxic T lymphocytes. Several vaccines are under clinical trials. These are based on various viral vectors (Canary pox virus, replication defective adenovirus, adeno-associated virus) carrying some HIV-1 protein genes. The viral spikes carry gp120 and gp41 glycoproteins and facilitate viral entry of the host cells. The host cell produces an N-linked glycan on its membrane surface and this protects HIV from recognition by the host immune system. Some spike proteins evade detection by host antibodies. The spike protein gp120 can fuse to $CD4^+$ before the host antibody could recognize and neutralize the viral spikes. In addition, the virus has great natural diversity and all these factors combined make vaccine development difficult. In vaccine development, two functions of the virus must be targeted: preventing HIV from finding cellular co-receptors and reducing the chance of effective fusion between the virus and the host. Antibody b12 can prevent CD4 binding or antibodies 2F5 and 4E10 can interfere with fusion. Various molecular designs are under development that creates new epitopes that elicit effective response by host paratopes. It is of consideration that the antibodies function not only in the circulation system but be expressed effectively at mucosal anatomical sites of the viral entry. $CD4^+$ memory T cells may reduce viremia upon challenging

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SIV-protein vaccinated monkeys during the initial phase of SIV infection and improves survival. The survival was associated with the preservation of memory $CD4^+$ T lymphocytes and this feature may guide the evaluation of AIDS vaccines in humans (Letvin NL et al 2006 Science 312:1530). There is no vaccine available in (2006) that would prevent the infection for sure or attenuate the progression of the diseases (Douek DC et al 2006 Cell 124:677).

In case of chronic HIV infection $CD8^+$ lymphocytes are impaired, display low cytokine production and reduced ability for proliferation. The cause of this is that the PD-1/PDCD1 (programmed death) and its ligand (PD-L/CD274) inhibit T cell function by antibodies to CD3 immunoglobulins. Blocking the engagement of PD-1 to PD-L1 restores lymphocyte function and reduces viral load in the cells (Trautmann L et al 2006 Nature Med 12:1198; Day CL et al 2006 Nature [Lond] 443:350). These new findings may improve the chances of fighting AIDS.

Studies indicate that in the non-progressors the gene coding for the chemokine receptors (of the non-syncytium inducing viral isolates [NSI]) CCR2 or CCR5 is mutated (contain deletion[s]), and thus it appears that CCR5 and 2 assist infection by HIV-1. These receptors are ligands for a group of CC-chemokines (CC, CXC) and MIPα and β and RANTES produced by $CD8^+$ T lymphocytes. These and siRNA are able to suppress HIV replication in vitro probably by competition for the CCR5 receptors (Quin X-F et al 2003 Proc Natl Acad Sci USA 100:183). Mutation in HIV may facilitate the use by other members of the chemokine receptor family, including CCR3 and CCR2. Mutations in CX_3CR1 reduce the binding to the chemokine fractalkine and enhance the progression toward the development of AIDS. In late-disease stage cases the chemokine CXCR4/SDF1 may be used for entry into the cell. The CCR5 receptors may be polymorphic. Homozygosity and heterozygosity for the mutant alleles of CCR5 of the cells also appear to convey reduced susceptibility to infection. The viral protein gp120 reduces the response to chemokines. The frequency of the mutant alleles in Caucasian populations is about 0.092 and thus, the predictable frequency of homozygosis ($0.092^2 \approx 0.0085$) is about 1%. This type of mutation seems to be much less common in African and Japanese populations. It is also likely that some non-progressors were infected with less aggressive HIV variants. The residual genetic constitution of the infected individual may also affect the course of the disease.

A (2005) study revealed that homozygosity for a mutation in the chemokine receptor CCR5 (synonym CKR5) and CCR2 protects against HIV infection and heterozygosity may be of some advantage. Segmental duplication in human chromosome 7q11-q21 may involve one or more copies of the (CCL3L1) chemokine ligand 3-like gene (synonym MIP-1α) and similar effects are conveyed by CCL4L1 (MIP-1β-like). CCL3L1 is a suppressor of HIV-1 and a co-ligand of CCR5. Individuals with low copy number of CCL3L1 had 69 to 97% higher risk of infection by HIV, and an increasing risk of rapid progression to AIDS and death. Interestingly, however, various African populations—with high rates of AIDS—displayed higher copy numbers (mean 5.95) of the gene than European and other populations (2.99). Similarly, chimpanzees had higher copy numbers (9.30). The absolute gene copy number was however, substantially confounded by the overall genetic constitution. Nevertheless, in the large and diverse populations examined 42% of the infections and about 30% of the accelerated progression was attributed to CCL3L1 and CCR5 (Gonzalez E et al 2005 Science 307:1434). HIV infection takes place through these receptors. The average rate of HIV transmission was 0.0082/coital acts within approximately 2.5 months after seroconversion of the index partner, 0.0015/coital acts within 6–15 months and 0.0028/coital act 6–25 months before the death of the index partner. Higher HIV load, genital ulcer disease, and younger age of the index partner were significantly associated with higher rates of transmission in African populations (Wawer MJ et al 2005 J Infect Dis 191:1403).

A homozygous mutant form of the chemokine SDF-1 gene, which codes for the principal ligand of a co-receptor of CXCR4 of the CD4 T cells of the HIV-1 virus, substantially restricts AIDS pathogenesis. It seems to offer better protection than the CCR5 and CCR2 chemokine receptor variants. Heterozygosity for the HLA class I loci A, B and C conveys longer survival after infection by HIV-1. The latest evidence indicates that HLA-B restricted HIV-1 more than two-fold through $CD8^+$ T lymphocytes than HLA-A (Kiepiela P et al 2004 Nature [Lond] 432:769). But the presence of alleles B*35 and Cw*04 potentiate rapid progression of the disease. Screening of the blood donations for possible HIV infection is based on the determination of the proportion of CD4/CD8 molecules. The normal ratio is about 2 and in infected blood it is below 1. It has been claimed that in infants, the HIV-1 infection may be transient but further analysis of these cases did not confirm the claims. None of the HIV vaccines tested so far provided protection. Attenuated live HIV with *nef* gene deletions appeared successful at first, but because of the high viral mutation rate, infective virus is recovered by time. In macaques the *nef*-defective SIV vaccine was protective. Compounds that inhibit the virus attachment to cells (CMPD167, C52L, BM-378806) applied to the vagina of rhesus monkeys

provided protection against simian-HIV-1 (SHIV-162P3) infection (Veazey RS et al 2005 Nature [Lond] 438:99). The HIV-1 virus can infect Old World monkeys but reverse transcription is blocked in these species. SIV and HIV infection involves the general destruction of 30 to 60% of memory CD^+ T cells and indicates the onset of immunodeficiency symptoms (Mattapallil JJ et al 2005 Nature [Lond] 434:1093). The host cytoplasmic body component TRIM5α appears to block uncoating of the retroviral capsid (Stremlau M et al 2004 Nature [Lond] 427:848). Recombinant envelope-protein-subunit vaccines also failed to elicit envelope-specific CTL or antibody-specific immune responses that could effectively neutralize HIV-1 in humans. Attempts to provide immunological protection against the V3 hypervariable loop of the viral envelope protein (essential for the viral gp120—CD4—chemokine interaction) is still being explored. Recombinant vaccinia virus carrying HIV protein fragments raised some hopes because similar constructs were effective in monkeys against SIV. Another possibility is to use engineered avian pox viral vectors, which have shown some promise (displaying some CTL activity), yet the immunogenicity generated may be too low. Unfortunately, in immuno-suppressed humans, serious side effects were encountered and the vaccines became impractical. BCG and other bacteria have also been considered as a potential vaccine vectors. DNA vaccines provide CTL activation and immune response but so far, the levels are very low to be effective. In rhesus monkeys infected with SIV lacking N-linked glycosylation at the 4th, 5th and 6th sites of the envelope protein reduced the immune evasion of the virus. Normally cytotoxic T lymphocytes (CTL) recognize the invading HIV by their surface Tat peptides. Unfortunately, through mutation this Tat peptide mutates very rapidly and becomes unrecognizable by CTLs. Immunization before infection by an appropriate Tat vaccine may provide a headway for CTL to gain control over the virus. Antisense RNA, complementary to the viral genome or to messenger RNA may also curtail viral functions by blocking transcription, translation or activation of RNase H. RNase H may significantly reduce the effectiveness of drugs inhibitory to viral replication (Nikolenko GN et al 2005 Proc Natl Acad Sci USA 102:2093)

Gene therapy using a suicide gene under the control of the HIV promoter may be activated by TAT and all the infected lymphocytes may be eliminated before the virus replication gets out of control (Caruso M et al 1995 Virology 206:495). RNA decoys that curtail replication of the virus have also been targeted at TAT. Transdominant Rev has also been used to limit productive infection (Escaich S et al 1995 Hum Gene Ther 6:625). Intrabodies were also explored as a protective measure (Marasco WA et al 1999 J Immunol Methods 231:223). siRNA may also inhibit HIV-1 infection (Novina CD et al 2002 Nature Med 8:681). New type of drugs attempts to block the entry of the virus (Moore JP, Doms RW 2003 Proc Natl Acad Sci USA 100:10598). The integrase inhibitor drug, naphthyl pyridine carboxamide (L-870812), blocks the integration of the viral nucleic acid into the chromosome. Other well-established drugs target the reverse transcriptase (Hogberg M et al 1999 J Med Chem 42:4150), or the protease (Lebon F, Ledecq M 2000 Curr Med Chem 7:455), or both. HIV-susceptible transgenic outbred Sprague–Dawley rats can be used as an animal model for rapid and predictive preclinical evaluation of the inhibitory potency and of the pharmacokinetic properties of antiviral compounds targeting early steps in the HIV replication cycle (Goffinet C et al 2007 Proc Natl Acad Sci USA 104:1015).

So far the most effective protection from AIDS is behavioral, the avoidance of exposure to the virus. Infection by the virus is the easiest through blood cells, plasma or cerebrospinal fluids. The semen transmits 10 to 50 times more viruses than the vaginal/cervical fluids. Injection of drug, contamination by tainted blood and sexual transmission are major risk factors in the disease worldwide (Piot P et al 2001 Nature [Lond] 410:968). In the USA, the major route of infection is male homosexual contacts whereas in Africa heterosexual copulation is the predominant means of spreading the disease. ►retroviruses, ►CD4, ►$CD8^+$, ►CD38, ►antibody, ►HLA, ►proteasome, ►clathrin, ►endocytosis, ►cyclophilin, ►MAPK, ►fusin, ►telomere, ►T cells, ►thymus, ►CTL, ►MIP-1α, ►NF-κB, ►Sp1, ►kissing loop, ►TBP, ►RANTES, ►AZT, ►TRIM5, ►Nevirapine, ►circumcision, ►SDF-1, ►TIBO, ►NF-κB, ►Sp1, ►HMG, ►enhancer, ►herpes, ►gene therapy, ►chemokines, ►CCR, ►CXCR, ►SIV, ►cyclam, ►primates, ►chimpanzee, ►hominidae, ►vaccinia virus, ►BCG, ►immune system, ►immunization genetic, ►antitrypsin, ►therapeutic vaccine, ►antibody neutralizing, ►antisense technologies, ►RNAi, ►seronegative, ►Kaposi sarcoma, ►HIV-1, ►integron, ►antisense technologies, ►peptide nucleic acid, ►RNAi, ►antivector cellular immunity, ►ribozyme, ►ricin, ►exotoxin, ►apoptosis, ►CD4, ►E vector, ►*Cre/LoxP*, ►liposome, ►raft, ►biolistic transformation, ►DC-SIGN, ►DNA flap, ►reverse transcript aseand protease sequences, ►retroviral restriction factors, ►*Pneumocystis carinii*, ►decoy RNA, ►numt, ►APOBEC3G, ►enfuvirtide, ►von Hippel-Lindau, ►cullin, ►ubiquitin, ►prefoldin; Science 288:2129 ff; Amara RR et al 2001 Science 292:69; Nature [Lond] 410: 963 ff; Poignard P et al 2001 Annu Rev Immunol 19:253; Englert Y et al

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2001 Hum Reprod 16:1309; Wu Y, Marsh JW 2001 Science 293:1503; Gallo RC, Montagnier L 2002 Science 298:1730; evolution; Rambaut A et al 2004 Nature Rev Genet 5:52; HIV issue of Science 313:467–490 2006, status of HIV vaccine potentials in 2007: Johnston MI, Faucci AS 2007 New England J Med 356:2073; HIV drug resistance: http://hivdb.stanford.edu; vaccine trials: www.iavi.org; Vanderbilt program: http://www.hivvaccineresearch.com/links.html; HIV Protein Interaction Database: http://www.ncbi.nlm.nih.gov/RefSeq/HIVInteractions/index.html; mutation selection: http://www.bioinformatics.ucla.edu/HIV/.

Acridine Dyes: Such as proflavin, acriflavine, acridine orange are potential frameshift mutagens by intercalating between the nucleotides of DNA. Some acridines act by photosensitization of the DNA. It has been used to cure bacteria from plasmids (by selective removal), and to induce respiration-deficient mitochondrial mutations in yeast. mtDNA, ►fluorochromes, ►curing of plasmids, ►frameshift

Acriflavine: ►acridine dyes; formula (see Fig. A19).

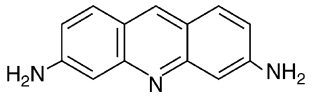

Figure A19. Acriflavin

Acrocentric Chromosome: Has a near terminal centromere and one arm is very short (see Fig. A20); acrocentric chromosomes may fuse or become translocated and may generate biarmed chromosomes. ►Robertsonian translocations

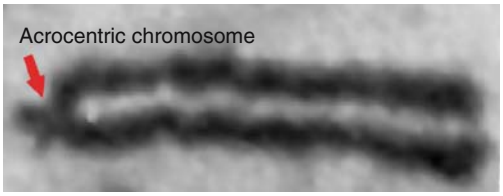

Figure A20. Acrocentric chromosome

Acrocephalosyndactyly: ►Apert syndrome; ►Pfeiffer syndrome

Acrodermatitis Enteropathica (8q24.3): A recessive blistering of the skin usually accompanied by lack of hairs on the head, eyebrows and eyelashes, and partial pancreatic hyperplasia and thymus hypoplasia. The deficiency in zinc-binding is characteristic and causes low levels of zinc and alkaline phosphatase (a zinc metalloenzyme) in the plasma. The treatment with zinc is very successful. ►alkaline phosphatase, ►zinc fingers, ►skin disease, ►Wilson disease, ►Menke disease, ►hemochromatosis, ►hyperkincemia; Wang K et al 2002 Am J Hum Genet 71:66.

Acrodysostosis: An autosomal dominant defect of bone development of paternal origin and increased occurrence by the age of the father.

Acromesomelic Dysplasia: A type of dwarfism based on shortening of the forearm and foreleg and other bones because of defect in the bone morphogenetic protein-1 gene (AMDM, 9p13-q12). The Hunter-Thompson dwarfism is based on a defect of the cartilage-derived morphogenetic protein-1 (CDMP1, 20q11.2). ►bone diseases

Acromegaly: Increased growth due to over-production of the pituitary hormone. (See for review: Melmed S 2006 New England J Med 355:2558).

Acropetal: The youngest leaf on the stem is at the tip of the stem of the plant.

Acrosomal Process: A spike-like actin structure on the head of the sperms of several animals and at its base is the acrosome, a sac of hydrolytic enzymes destined to facilitate the penetration through the gelatinous coat of the egg. Before acquiring competence for fertilization the spermatozoa must be activated by bicarbonate mediated soluble cAMP. The process is enhanced by progesterone, probably by acting on a $GABA_A$ receptor. In the starfish egg jelly *ARIS* (polysaccharide with repeating units of sulfated pentasaccharide), *Co-Aris* (steroid saponin) and *asterosap* (a variety of 34 amino acid peptides) are required for the acrosomal process. In sea urchins, FSP (sulfated fucose polymer) activates the acrosomal process. In mammalian egg, the three ZP (zona pellucida) proteins bind to the receptors on the sperm plasma membrane and stimulate the exocytosis of the acrosomal vesicle in the front part of the sperm. Activated sperm contains nitric oxide synthase and nitric oxide is important for fertilization. Phospholipase Cδ4 is also required for the process. ►acrosome, ►sperm, ►GABA, ►progesterone, ►fertilization, ►ICSI; Tulsiani DR, Abou-Haila A 2001 Zygote 9:51; Kang-Decker N et al 2001 Science 294:1531; acrosome structure: Schmid MF et al 2004 Nature [Lond] 431:104.

Acrosome: ►acrosomal process (see Fig. A21)

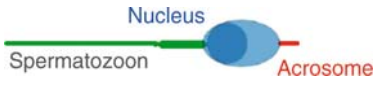

Figure A21. Acrosome

Acrosome Reaction: ►acrosomal process

Acrosyndesis: A spurious end-to-end pairing of the chromosomes during meiosis.

Acrylaldehyde: It is a toxic compound made from allyl alcohol by the enzyme alcohol dehydrogenase. Cells defective in this enzyme permit the selective survival on allyl alcohol as it is not converted to acrylaldehyde. ►mutant isolation, ►alcoholdehydrogenase

Acrylamide: In the presence of ammonium persulfate and TEMED (*N,N,N′,N′*-tetramethylenediamine) it is polymerized into chains with various length depending on the concentration used. In the presence of *N,N′*-methylenebisacrylamide it becomes crosslinked and pores are formed depending on the length of the chains and the degree of crosslinking. It can be used to separate nucleotides by electrophoresis from 2000 to 6 bp, depending on the pore size of the gels. Acrylamide is a potent neurotoxin and potential carcinogen. It can be absorbed through the skin. Although the polymerized form is considered nontoxic, it should be handled only with gloves because of the trace amounts of monomers. Acrylamide may be formed in small quantities in deep-fried starchy food. ►electrophoresis, ►gel electrophoresis; Mottram DS et al 2002 Nature [Lond] 419:448.

ACT: Activator of CREM (in the testis) by binding through a LIM domain. ►CREM, ►LIM

ACT: An Artemis based DNA sequence comparison viewer program. ►Artemis; http://www.sanger.ac.uk/Software.ACT/.

ACTH (adrenocorticotropin hormone): ACTH controls adrenocortical growth and steroidogenesis. The hypothalamus controls the ACTH releasing factor and in response to that, the anterior pituitary releases this hormone. ACTH is encoded in human chromosome 2. ►animal hormones, ►adrenocorticotropin, ►cAMP, ►steroid hormones, ►hormone-response elements, ►pituitary gland, ►brain, ►POMC

Actin: A protein of the cytoskeleton and the thin muscle fibers. Actin gene number varies in different organisms; yeast has only one, *Dictyostelium* 8, *Drosophila* 6, *Caenorhabditis* 4, humans about two dozen at dispersed locations. The cytoplasmic actins involved in cellular motility are similar in all eukaryotes. α-Actins are located in the smooth, skeletal and cardiac muscles. The smooth muscles have in addition γ -actin. In the cytoplasm of mammals and birds, there are β- and γ -actins. The amino acid sequence and composition of the actins is rather well conserved and differences exist mainly at the amino terminals. Actin genes have different numbers of introns and pseudogenes, permitting evolutionary inferences partly because the flanking sequences are much more variable than the genes. Some proteins bind actin in monomeric or filamentous form such as myosin (a contractile protein in muscles), α-actinin (involved in cross-linking actins). Profilin (mediates the formation of actinin bundles), fimbrin (cross-linking parallel actin filaments), filamin (promotes the gel-formation by actins), tropomyosin (strengthens actin filaments), spectrin (attaches filaments to plasma membranes), gelsolin (fragments filaments), etc. The natural products jasplakinolide and latranculin B have opposite effects on actin filaments (see Fig. A22), the former is stabilizing while the latter is destabilizing the filaments. ►cytoskeleton, ►podosome, ►myosin, ►filament, ►microfilament, ►microtubule, ►myofibril, ►tropomyosin, ►cofilin l, ►CDC42, ►mRNA migration, ►Wiskott-Aldrich syndrome, ►cardiomyopathy dilated, ►glomerulosclerosis, ►cytoskeleton, ►pollen, ►nemaline myopathy, ►pollen; Geeves

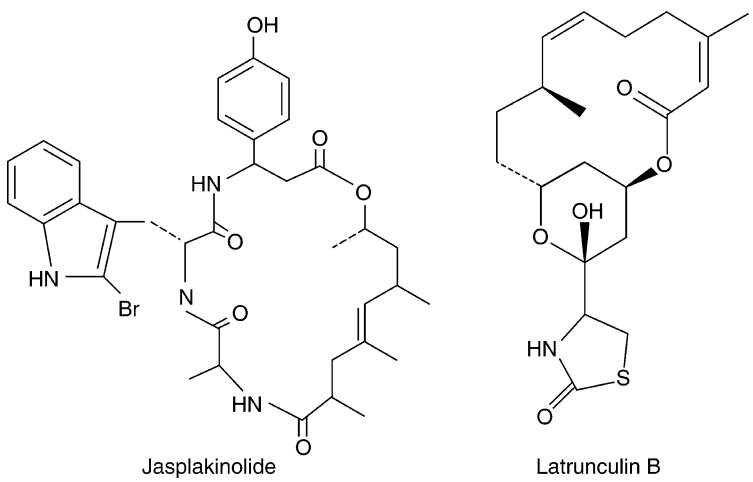

Figure A22. Jasplakinolide and Latrunculin B

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MA, Holmes KC 1999 Annu Rev Biochem 68:687; Higgs HN, Pollard TD 2001 Annu Rev Biochem 70:649; Quinlan ME et al 2005 Nature [Lond] 433:382.

Actin Contractile Ring: Formed prior to the separation of the dividing chromosomes and contracts after anaphase. It may be involved in the formation of the septum between the two cells. ►cell cycle

Actinin, α (M_r 120 K): Antiparallel peptide in muscle Z lines, focal adhesion and intermediate junction structures. Actinin α 2 (1q42-q43) and actinin α 3 (11q13-q14) are somewhat different, yet partially compensate for each other. Their function is required for fast (not the enduring) muscle function, and the frequency of the latter gene (R577X) is significantly higher in athletes who require high velocity muscle functions (sprint, judo, short distance cyclists, speed skaters). In 18% of healthy white population, the R577X is inactive because of homozygosity of a stop codon in the gene. The female sprint athletes also show higher frequencies, however, they are generally heterozygous for the 577RX allele (Yang N et al 2003 Am J Hum Genet 73:627). ►glomerulosclerosis, ►actin, ►CAM, ►junction complex

Actinomorphic: A structure (flower) in multiple symmetry patterns (see Fig. A23).

Figure A23. Actinomorphic

Actinomycetes: Filamentous prokaryotes rather than fungi as they once were assumed to be. ►*Streptomyces*, ►streptomycin, ►actinomycin

Actinomycin D: An antibiotic from *Streptomyces*; it is an inhibitor of transcription because it intercalates into the DNA between neighboring GC base pairs and hinders the movement of the transcriptase on the DNA template without interfering with replication; it is used in reverse transcriptase reactions to prevent self-primed second strand synthesis. Actinomycin D is a teratogen and carcinogen. (There are several other actinomycin antibiotics). ►*Actinomycetes*, ►*Streptomyces*, ►transcriptase, ►reverse transcription; Graves DE 2001 Methods Enzymol 340:377.

Action Potential: Rapid, transient, self-propagating electrical excitation in muscle or neuron membranes. It may mediate long-distance nerve signaling.

Action Spectrum: A representation of a degree of response to certain type of treatment(s), e.g., photosynthesis in relation to wavelength of irradiation. ►photomorphogenesis

Activating Enzyme: ►aminoacylation of tRNA

Activation Analysis: A nuclear technique used for the very sensitive detection of radionuclides for various purposes including forensic analysis. ►radionuclide

Activation Domain: Generally, a loop of the proteins where phosphorylation takes place at serine, threonine or tyrosine residues.

Activation Energy: The energy required for converting 1-gram molecular weight of a compound from the ground state to the transition state. It is required, from outside, by molecules and atoms to undergo chemical reaction(s). ►transition state

Activation of Genes: ►suppression, ►activator proteins

Activation of Mutagens: Many mutagens (and carcinogens) require chemical alterations to become biologically active. The mutagenic and carcinogenic properties of many agents overlap and thus active in mutagenesis and carcinogenesis. The activation generally requires enzymatic reactions. The most important enzymes are the mixed-function oxidases contained by the cytochrome P-450 cellular fraction. These reactions require NADPH and molecular oxygen and the general process is: RH (reduced reactant) + NADPH + H^+ + O_2 → ROH + $NADP^+$ + H_2O. These enzymes occur in multiple forms and can utilize a variety of substrates, hydrocarbons, amines and amides, hydrazines and triazines, nitroso compounds, etc. They occur in different tissues of animals, primarily in the endoplasmic reticulum of cells what is generally called microsomal fraction after isolation following grinding and centrifugal separation of the cellular fractions. These enzymes are subject to induction by phenobarbitals, methylcholanthrene and a variety of substrates. Other related activating enzymes are flavoprotein N-oxygenases, hydrolases, and reductases. Other enzymes of activating ability include various transferases that add glucuronyl, sulfuryl, glutathione, acetyl and other groups and either detoxify the compounds or further enhance their reactivity. The cellular and membrane transport, protein binding, excretion affect these reactions. Genetic differences exist among the species and individuals. Differences by age, circadian rhythm and nutritional status, etc., are known. If the clearance of these compounds from the body is slow, the risk for the individuals increases. ►promutagen, ►proximal mutagen, ►ultimate mutagen, ►environmental mutagens, ►mutagen assays, ►Ames test, ►bioassays of mutagenesis, ►cytochromes, ►P450; Baum M et al 2001 Chem Res Toxicol 14:686.

Activation Tagging: Random insertions of transcriptional enhancers of the 35S cauliflower mosaic virus promoter with the aid *Agrobacterium* vector into the plant genome resulting in misexpression and overexpression of many different genes concerned. ►cauliflower mosaic virus, ►T-DNA, ►Ti plasmid; Weigel D et al 2000 Plant Physiol 122:1003.

Activator: *Ac*, the autonomous element of the *Ac-Ds* controlling element system of maize (see *Ac*). Also, any DNA binding protein that enhances transcription, a positive modulator of an allosteric enzyme. More than one activator of transcription may operate at different activator binding sites of a single promoter. Their action may be synergistic, or each may have special affinity to a separate surface of the RNA polymerase II molecule or one stabilizes the other activator. ►allosteric control, ►modulation, ►transcriptional activator, ►*Ac-Ds*

Activator A: Synonymous with RF-C, a cellular replicator. ►RF-C

Activator I: Same as ►RF-C

Activator Proteins: Stimulate transcription of genes by binding to TATA box binding protein (TBP) and the recruitment of TFIID complex to the promoter. Sometimes they require coactivator metabolites for function. The primary role of these is probably the remodeling of the nucleosomal structure so DNA-binding proteins can access their target. The DNA has multiple binding sites for activators in the promoter region. The potency of the activation domains of the activators may vary. An activator may turn into a repressor by binding a corepressor. ►transcription factors, ►TBP, ►regulation of gene activity, ►promoter, ►co-activator, ►corepressor, ►transcriptional activator, ►enhancer, ►chromatin, ►nucleosome, ►VDR, ►recruitment, ►suppression, ►signal transduction, ►chromatin remodeling, ►GCN5; Evans R et al 2001 Genes Dev 15:2945.

Active Immunity: ►immunity

Active Site: A special part of an enzyme where its substrate can bind and where the catalytic function is performed, the catalytic site. ►substrate, ►enzymes, ►catalysis

Active Telomeric Expression Site: Variable surface glycoprotein (VSG) genes are responsible for the diversity of antigenic variants in *Trypanosomas*. These generate different antigenic properties of the parasite. There are about thousand genes in this gene family and their activation is interpreted by their transposition to the vicinity of the telomere, the expression site of the silent copies. ►*Trypanosomas*, ►mating type determination in yeast, ►silent site; Borst P, Ulbert S 2001 Mol Biochem Parasitol 114:17.

Active Transport: Passing solutes through membranes with the assistance of an energy donor required for the process. ►passive transport

Activin: Soluble protein that may contribute to the formation of dorsal and mesodermal tissues in the developing animal embryo; its activity may be blocked by *follistatin*. *Activins* belong to the family of *transforming growth factor-β* superfamily of proteins. They are serine/threonine protein kinases. Activins respond to Smad signal transducers. Activin receptor-like kinase 1 (ACVRLK1) modulates TGF signaling in angiogenesis. Its absence or deficiency results in lack of response to TGF-β family growth factors and mice afflicted by mid-gestation die due to fusion of major arteries and veins. Cultures rich in activin A facilitate endoderm production up to 80% of the experiments (D'Amour KA et al 2005 Nature Biotechn 23:1534). ►protein kinases, ►TGF, ►organizer, ►follistatin, ►SMAD, ►angiogenesis, ►fibrodysplasia ossificans progressiva; Luisi S et al 2001 Eur J Endocrinol 145:225.

Activity-Based Protein Profiling: Monitors the expression dynamics of a family of proteins on the basis of chemical tagging with common inhibitors. This type of test reveals more important information on the role of proteins in health and disease than measuring the quantity of proteins (See Liu Y et al 1999 Proc Natl Acad Sci USA 96:14694; Okerberg ES et al 2005 Proc Natl Acad Sci USA 102:4996).

Activity Coefficient: Obtained by multiplying with it the concentration of a solute to obtain its thermodynamic activity.

Actomyosin: A complex of actin and myosin. ►actin, ►myosin

ACTR (acetyl transferase): ►acetyl transferases

Actuarial Analysis: Analysis of life expectancy; it is generally compared in a cohort. ►cohort, ►life expectancy

Acuminate: Tapered (see Fig. A24).

Figure A24. Acuminate

Acupuncture: A traditional Chinese method of releasing pain by strategically employed punctures to the body by needles. The methods are not standardized and is used by different styles. Although the physiological bases are not understood, it may be an effective treatment. (See Ahn AC, Kaptchuk TJ 2005 Altern Ther Health Med 11:50).

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Acute Transforming Retrovirus: Contains a v-oncogene and it is an efficient oncogenic transformation agent. ►v oncogene, ►oncogenes, ►retrovirus

Acyclovir: see ►gancyclovir

Acyl Group: See Fig. A25 where R can be a number of different chemical groups. ►acetyl group

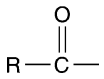

Figure A25. Acyl group

Acyl-CoA Dehydrogenase Deficiency (ACAD): Three different diseases have been described with short (SCAD, 12q22-qter), long (LCAD, 2q34-q35) and medium chain defects (MCAD, 1p31) involving β-oxidation of fatty acids. The clinical symptoms include hypoglycemia, dicarboxylaciduria, hyperammonemia, fatty liver, etc. Some of the symptoms overlap with those of the Reye syndrome and maple syrup urine disease. ►Reye syndrome, ►isovaleric acidemia, ►isoleucine-valine biosynthetic pathway

Acylation: Attaching one or more acyl groups to a molecule. ►acyl group

Acylcyclohexanedione: An inhibitor of gibberellin biosynthesis. ►plant hormones

Ad4BP: ►SF-1

Ad5 E1B: An adenovirus oncoprotein. ►adenovirus, ►oncogenes

ADA: Zn-containing proteins that transfer methyl groups to their own cysteine and thus repair aberrantly methylated DNA (e.g., 6-O-methylguanine), and by binding to specific DNA sequences it activates genes involved in conveying resistance to methylation. Some of the ADA proteins are involved in repression of transcription. ►adenosine deaminase, ►histone acetyltransferase

Adactyly: The absence of digits of the hand or foot. It may occur as part of several syndromes (see Fig. A26). ►Holt-Oram syndrome, ►polydactyly, ►ectrodactyly

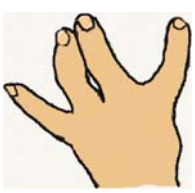

Figure A26. Adactyly

ADAM (a disintegrin and metalloprotease): A family of metalloprotease enzymes such as KUZ (kuzbanian), responsible for partitioning of neural and non-neural cells during the development of the central and peripheral nervous system. ADAMs may have proteolytic, cell adhesion, signaling and fusion functions of cell surface molecules. It is apparently involved with the Notch receptor function. ADAM motifs are found in the aggrecanase enzyme eroding cartilage in arthritis. ADAM 10 (α-secretase) cleaves also the amyloid precursor protein (APP). ►neurogenesis, ►bone morphogenetic protein, ►CAM, ►Notch, ►fertilin, ►cyritestin, ►arthritis, ►secretase, ►Alzheimer disease, ►metalloproteinase, ►cardiomyopathy hypertrophic; Stone AL et al 1999 J Protein Chem 18:447; in cancer: Fridman JS et al 2007 Clin Cancer Res 13:1892.

ADAM Complex (amniotic band sequence, congenital constricting band, amputations): Acronym for Amniotic deformity, Adhesions, Mutilations phenotype complexed with other anomalies caused by mechanical constriction of the amniotic sac, but there is evidence for the role of autosomal recessive inheritance. The phenotype may include bands on fingers, and loss of finger bones or even parts of legs (amputations), etc. ►limb defects; Keller H et al 1978 Am J Med Genet 2:81.

Adams-Oliver Syndrome: Autosomal dominant mutilations of the limbs, skin and skull lesions yet apparently normal intelligence. ►ectodermal dysplasia

Adaptation: Process by which organisms develop fitness to a special environment. Mutation provides the genetic variations from which the evolutionary process selects the genes that convey the best adapt.

Adaptation may be acquired by major mutations although most commonly it is based on mutations with small cumulative effects without serious deleterious pleiotropic or epistatic consequences. R.A. Fisher expressed adaptation in "geometric" terms (see algebraic figure)

$$\frac{1}{2}\left(1-\frac{r}{d}\right)$$

where r is the distance to what a mutation moves the population in a sphere (d) from the sphere of previous adaptation of A. If r is very small, the chances are equal to bring improvement or becoming deleterious. When however r moves beyond the sphere of A, he considered no chance for improvement. "The chance of improvement thus decreases steadily from its limiting value 1/2 when r is zero, to zero when r equals d." The probability for adaptive change—he concluded—is rapidly diminished when the change ($d/\sqrt{n}$) has manifold effects (n). Adaptation

actually limits diversification in bacterial populations (Buckling A et al 2003 Science 302:2107). In physiology, it defines adjustment to specific stimuli. Long-term evolutionary changes can be best studied under defined conditions by using bacterial cultures for thousands of life cycles (Elena SF, Lenski RE 2003 Nature Rev Genet 4:457). ►fitness, ►shifting balance theory of evolution, ►plasticity, ►noise, ►reaction norm; Travisano M 2001 Curr Biol 11: R440; Orr HA 2005 Nature Rev Genet 6:119.

Adapter Ligation PCR: ►capture PCR, ►polymerase chain reaction

Adaptins (AP-1, AP-2, AP-3): Major coat proteins in a multisubunit complex on vesicles. These proteins bind the clathrin coat to the membrane and assist in trapping transmembrane receptor proteins that mediate the capture of cargo molecules and deliver them inside the vesicles. ►clathrin, ►cargo receptors, endocytosis, ►epsin, ►AP1, ►AP180, ►arrestin; Robinson MS, Bonifacione JS 2001 Curr Opin Cell Biol 13:444.

Adaptive Amplification: A concept somewhat similar to adaptive mutation. It has been argued that the two are different because adaptive amplification—unlike mutation—is a flexible and more readily reversible alteration. The argument has been that if the days required to reform colonies equals the number of days after selection when, e.g., the original Lac^+ colony arose the original revertant was preexisting. If the days required to reform colonies is less than the number of days after selection when the revertant emerged, then the alteration permitting growth on lactose is attributed to an adaptive response to the selective condition. ►adaptive mutation; Hastings PJ et al 2000 Cell 103:723.

Adaptive Convergence: Similarity in morphology and function among unrelated species within a particular environment, e.g., fins on fishes and mammalian whales.

Adaptive Enzyme: Same as inducible enzyme. ►*Lac* ►operon

Adaptive Evolution: A theory that claims evolution is largely based on mutations that increase fitness of the individuals and species involved. In contrast, the neutral mutation theory postulates the significance of the role of random neutral mutations based on synonymous codon substitutions. The relative abundance of synonymous (D_s) and non-synonymous (D_n) mutations can be estimated as (a = adaptive substitution):

$a = D_n - D_s$ (P_n/P_s) where P_n and P_s stand for the numbers of non-synonymous and synonymous substitutions, respectively. Hence, α (the amino acid substitutions brought about by positive selection) is $\alpha = 1 - (D_sP_n)/(D_nP_s)$. By using this method, 45% of the amino acid substitutions in some *Drosophila* species appeared to be adaptive.

Parallel and convergent changes in different lineages indicate adaptive evolution. It can be studied experimentally by morphology or by comparative genomics. ►fitness, ►mutation beneficial, ►mutation neutral, ►genomics; Smith NGC, Eyre-Walker A 2002 Nature [Lond] 415:1022; Cooper TF et al 2003 Proc Natl Acad Sci USA 100:1072.

Adaptive Immunity: Develops in response to an antigen. ►acquired immunity, ►innate immunity

Adaptive Landscape: Represents the frequency distribution of alleles corresponding to fitness of the genotypes, e.g., *AAbb* and *aaBB* means the fixation (*peak*) of the allelic pairs (see Fig. A27).

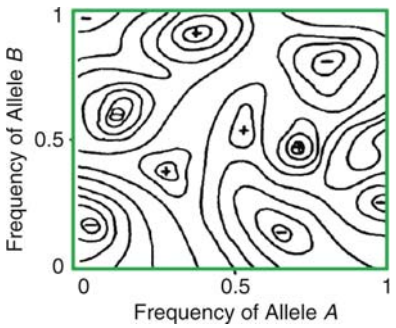

Figure A27. Adaptive landscape. (Modified after Mohay, J. 1996 Genetika)

The *pits* of fitness may mean the fixation of *AABB* or *aabb*, and the *saddle* usually corresponds to the polymorphic condition *AaBb*. A two-dimensional model of the allelic topography may represent the allelic constitutions with the corresponding fitness in a third dimension showing "mountain ranges" and "valleys."

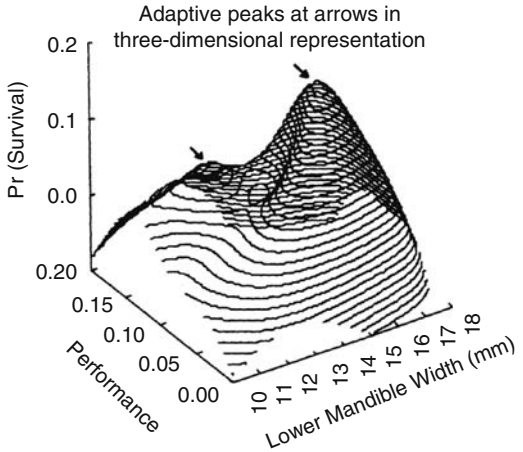

Figure A28. Adaptive topography (From Smith TB., Girman DJ 2000 In: Mousseau TA et al (eds) Adaptive Genetic Variation in the Wild. © Oxford Univ Press, New York p 139

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The landscape may be subject to evolutionary change due to change in allelic frequencies and the environment. The landscape may become complex if several allelic pairs are considered. The (+) and (−) signs indicate high and low fitness, respectively. The adaptive landscape may be represented also in three-dimensional plot (see Fig. A28). The term is the same as adaptive topography. The adaptive landscape of molecules can also be determined by engineered replacements at, e.g., coenzyme attachment sites of metabolic enzymes (Lunzer M et al 2005 Science 310:499). ►fitness, figs., ►mutational landscape models; Rokyta DR et al 2005 Nature Genet 37:441.

Adaptive Mutation: Occurs at higher frequency in response to conditions of selection although the mutation is not induced by the conditions of selection. A relevant assumption is that the gene number increase under the specific conditions facilitated "amplification mutagenesis." The phenomenon is not non-darwinian as it may appear. It takes place in three steps, e.g., (i) growth limitation favors the propagation of a subpopulation with an amplification of the *lac* gene, (ii) then lac^+ revertant cells are favored, (iii) eventually a stable lac^+ revertant allele arises and overgrows the colony (Hendrickson H et al 2002 Proc Natl Acad Sci USA 99:2164). The selective conditions do not increase the mutation rate but instead favor the growth of rare cells with a duplication of leaky *lac* alleles. A further increase in copy number (amplification) improves growth and increases the likelihood of a sequence change by adding more mutational targets to the clone (Kugelberg E et al 2006 Proc Natl Acad Sci USA 103:17319). Similar amplification of gene number can occur in various eukaryotes.

The increased frequency of mutation under some specific selection regimes may be attributed to the differences in genetic repair. Caution is warranted in calculating the mutation rate. If, e.g., 10 mutations are observed under both the selective and non-selective conditions but the number of survivors is 50 and 100, respectively, the apparent mutation rate is double in the first lot but it is caused only by the method of assessment, 10/50 and 10/100. It is customary to calculate the rate based on survivors but it remains unknown how many of the dead individuals were mutant. If it is assessed because of the input cells, the rate may be the same under the two conditions. ►directed mutation, ►adaptive amplification, ►neofunctionalization; Foster PL 1999 Annu Rev Genet 33:57; Hall BG 2001 Mol Biol Evol 18:1389.

Adaptive Peak: The highest value(s) of fitness in an adaptive landscape. ►adaptive landscape

Adaptive Radiation: Phyletic lines spread over a variety of different ecological niches resulting in a rapid adaptation to these locales and appearing in strikingly different forms. Competition for limited resources may form a basis for adaptive radiation (Chow SS et al 2004 Science 305:84). Adaptive mutation may account also for adaptive radiation as in sequential steps—as environmental changes take place—and the adaptive mutation is selectively reinforced. ►phylogeny, ►niche, ►diversity [Shannon—Weaver index], ►frequency-dependent selection; Francino MP 2005 Nature Genet 37:573.

Adaptive Response: Induction of (bacterial) repair enzymes, which activate glycosylases or O^6-methylguanine methyltransferase and thereby mutated DNA is repaired. The name comes from the property of adaptation to higher doses of mutagens after an initial shorter exposure; it is mediated by the *Ada* gene product (37-kDa) of *E. coli.* ►alkylating agent, ►chemical mutagens, ►DNA repair, ►glycosylases, ►methylation of DNA

Adaptive Value: ►fitness

Adaptor: tRNA is called an adaptor in older literature as it adapts the genetic information in DNA through mRNA to protein synthesis. ►tRNA, ►aminoacyl-tRNA synthetase, ►protein synthesis; Ibba M et al 2000 Trends Biochem Sci 25:311.

Adaptor Ligation PCR: Determines the flanking sequences of a DNA sequence by the use of nested promoters and DNA adaptor in order to amplify an entire stretch of the chromosome.

Adaptor Proteins (AP): Adaptor proteins play key roles in cellular signaling such as phosphorylation, dephosphorylation, signal transduction, organization of the cytoskeleton, cell adhesion, regulation of gene expression, all distinct yet interacting systems. Proteins equipped with the Rous sarcoma oncogen (Src) homology domains SH2 and SH3 mediate the interactions between the phosphotyrosine kinase receptors of mitogenic signals and the RAS-like G proteins. The SH2 domain selects the phospho-Tyr-Glu-Glu-Ile sequences. Phospholipase C (PLC-γ1) and the protein-tyrosine phosphatase (PTPase) recognize several hydrophobic residues following pTyr on the ligand-binding molecule. The SHC homology proteins and the insulin-receptor substrate (IRS-1) recognize somewhat different sequences: Asn-Pro-X-pTyr. The SH3 binding sites involve about 10 proline-rich amino residues. The SH3-binding peptides can bind either in $NH_2 \rightarrow COOH$ or in the reverse orientation. The SOS (son of sevenless) adaptor protein

binds to Grb2 (growth factor receptor-bound protein) is attached in C→N orientation. The pleckstrin domains are widespread in occurrence (serine/threonine and tyrosine kinases, and their substrates, phospholipases, small GTPases, dynamin, cytoskeletal proteins, etc.). Pleckstrin domains occur in cytoplasmic and membrane signaling molecules. The LIM domains facilitate binding of signaling molecules, transcription factors as well as the units of the cytoskeleton. These adaptor proteins may form partnerships with a variety of proteins and thus generate complex networks of signaling. (See separate entries mentioned; Hübener C et al 2001 Immunogenetics 53:337; Beer S et al 2001 Biochim Biophys Acta 1520:89).

Adaptors: ►linker

ADAR (adenosine deaminase of acting on RNA, ADAR1, ADAR2, ADAR3): ADAR2 edits the pre-mRNA of the glutamate-sensitive ion channel receptor B subunit and adenine is converted to inosine that behaves in coding as guanine. Thus, glutamine is replaced by arginine in the protein with over 99% efficiency. ADAR1 functions overlap with ADAR2 and ADAR3. ADAR3 is specific to the brain. The enzymes contain a double-strand-binding domain and a catalytic deaminase domain. Thus alternative forms of the protein appear. At the NH_2 terminus, it includes domain Zα, responsible for the high-affinity binding to Z DNA. Point mutations in AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionate) receptor may compensate for lethality in ADAR2-deficient mice. ADAR2 is concentrated in the nucleolus but can shuttle to the nucleoplasm and increasing editing of the endogenous substrate (Sansam CL et al 2003 Proc Natl Acad Sci USA 100:14018). Inositol hexakisphosphate (IP_6) bound to ADASR2 core is required for RNA editing (Macbeth MR et al 2005 Science 309:1534). ►mRNA, ►Z DNA, ►Z RNA, ►RNA editing, ►adenosine deaminase, ►DRADA, ►IP_5/IP_6; Wang Q et al 2000 Science 290:1765; Bass BL 2002 Annu Rev Biochem 71:817; Levanon EY et al 2005 Nucleic Acids Res 33:1162.

AddAB: An enzyme complex involved in double-strand DNA repair in Gram-positive bacteria in a manner similar to RecBCD in Gram-negative bacteria. In the Gram-negative α-proteobacteria, however the AddAB system can function. ►Gram-positive, ►RecBCD; Zuniga-Castillo J et al 2004 J Bacteriol 186:7905.

ADCC (antibody-dependent cell cytotoxicity): Mediates some of the immune responses. ►antibody, ►immune system; Hinterberger-Fischer M, Hinterberger W 2001 Expert Opin Biol Ther 1:1029.

Addiction: A complex phenotype relative to the abuse of drugs, alcohol, smoking or habituation to other non-natural behavior. It is generally controlled by multiple genes, deeply influenced by several social conditions, and commonly associated with antisocial behavior. It is assumed that the long-term abuse of these substances causes molecular changes in the neuronal signaling. The adaptation may modify the autonomic somatic functions causing dependence and when the agent is withdrawn, result in withdrawal anomalies. The agent may alter the motivational control system resulting in craving. Chronic use of morphine upregulates components of the cAMP signal transduction pathway. In mice, with a deletion of the CREBα element the withdrawal symptoms were reduced indicating that CREB-dependent gene transcription is a factor of opiate dependence. The major receptor for opiates (morphine, heroine) is the trimeric G protein-linked μ. Long-term opiate use decreases the μ-opiate receptor signaling without reducing the number of receptors and leading to tolerance and dependence. In non-addicted individuals, the opiate receptor opens an outward rectifying K^+ channel and reduces the phosphorylated state of a Na^+ channel. In an addicted individual the K^+ channel is shut off, however, and the G protein—adenylate cyclase activates a protein kinase (PKA) and the phosphorylated Na^+ channel moves sodium inward the locus ceruleus, a pigmented structure at the floor of the brain. As a consequence, the cyclic AMP response element (CRE) binding proteins (CREB) stimulate the transcription of RNA required for adaptation to the addictive drug. The psychoactive effects of cocaine can be superseded in rats by active immunization using a cocaine conjugate, GNC-KLH (a hapten and keyhole limpet hemocyanin). Addictive agents usually raise the dopamine level in the nucleus accumbens of the brain. Recently the glutamate receptors gained attention for their role in addiction and for their chemical blocking for a cure. The glutamate receptor seems to control the ΔFosB transcription factor and enhances the sensitivity to cocaine. The genetic component of various addictions (alcohol, opiates, cocaine, etc.) may exceed 50%. The genetic bases of addiction are generally polygenic and may be studied by the methods of quantitative genetics although the specific genetic factors responsible are hard to identify and few genetic tools exist for the identification of the determination. Heritability of response to addictive agents is generally determined based on comparison of monozygotic and dizygotic twins. Heritability of addiction to smoking and alcohol abuse may exceed 0.5; heritability to opiates and cocaine is even higher. Serotonin, nicotinic cholinergic, dopamine, cannabinoid-like receptors, neuropeptides may affect responses to various drugs. Addiction may

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occur also in rats (Deroche-Gamonet V et al 2004 Science 305:1014; Vanderschuren LJMJ, Everitt BJ *ibid* p. 1017). ►ion channels, ►G protein, ►cAMP, ►adenylate cyclase, ►CRE, ►CREB, ►behavioral genetics, ►keyhole-limpet hemocyanin, ►dopamine, ►glutamate receptors, ►neurotransmitters, ►alcoholism, ►smoking, ►bulimia, ►heritability, ►twinning; Nestler EF, Landsman D 2001 Nature [Lond] 409:834; Goldman D et al 2005 Nature Rev Genet 6:521.

Addiction Module: Represents a prokaryotic system with resemblance to apoptosis in eukaryotes. The module includes the products of two genes: one is long lasting and toxic, the other is short lived and protects against the toxic effect. The "addiction" is a dependence on the antagonist of the toxin. This system is usually controlled by plasmid elements. In the *hok-sok* module of the R1 plasmid the *sok* gene product is an antisense RNA, subject to degradation by a nuclease. Homologs of this plasmid system have been found also in the main bacterial chromosome. Encoded by the bacterial *rel* operon the MazE antitoxin protein is subject to degradation by the clpPA serine protease. It protects from the toxic effects of MazF toxin protein. MazE-MazF are regulated by the level of ppGpp which itself is toxic to the cells. MazE-MazF expression is regulated also by 3′,5′-bispyrophosphate, synthesized by the RelA protein under amino acid starvation. ►apoptosis, ►partitioning; Engelberg-Kulka H, Glaser G 1999 Annu Rev Microbiol 53:43.

Addison Disease (adrenocortical hypofunction, Xq28): An autosomal dominant defect of the kidneys cortical layer resulting in excess potassium and sodium in the urine, decreased levels of cortisol and hyperpigmentation of the skin. Some forms indicate autoimmune phenotype. ►adrenoleukodystrophy, ►pigmentation defects, ►kidney diseases, ►cortisol

Addison-Schilder Disease: An Xq28-chromosome-linked adrenocortical (kidney outer layer) atrophy and diffuse cerebral sclerosis (hardening). The cerebral lesions resemble the symptoms of multiple sclerosis. ►multiple sclerosis

Addition Lines: Carry an extra chromosome(s) coming from another genome. ►alien addition, ►*Haynaldia villosa* for photomicrograph

Additive Effects: Genes' additive effects means that each allele contributes quantitatively to the phenotype of an individual that carries it, i.e., there is no dominance. ►polygenic inheritance

Additive Genes: Each allele has a definite quantitative contribution to the phenotype without dominance within a locus and without epistasis between loci or overdominance between alleles. ►additive variance, ►quantitative genetics, ►heritability, ►epistasis, ►overdominance

Additive Variance: Each allele contributes a special value (quantity) to the phenotype and there is no interallelic (overdominance) or interlocus (epistasis) effects on the variance. ►genetic variance, ►heritability, ►QTL

Additivity of Genetic Maps: Ideally means that the distance between genes A–C is equal to the sum of the distance between A–B and B–C if the order of genes is A B C. To this generally valid rule exceptions exist because of genetic interference. ►mapping genetic, ►recombination frequency, ►interference, ►coincidence

Adducin: A membrane protein mediating the binding of spectrin to actin. ►spectrin, ►actin

Adduct: As a verb means to draw to the median plane or axial line. As a chemical it stands for the complex of two or more components such as the cyclobutane ring of pyrimidine dimers, benzo(a)pyrene-guanine, and other alkyl groups of mutagens added to nucleic acid bases. Lipid peroxidation generates various DNA adducts with mutagenic effects similar to that caused by exogenous carcinogens. This may be the cause by the "spontaneous" cases of carcinogenicity by high-fat diet. ►pyridine dimers, ►ethylmethane sulfonate, ►benzo(a)pyrene, ►excision repair, ►ABC excinuclease, ►malondialdehyde, ►pyrimidopurinones

Adelphogamy: Sib-pollination of vegetatively propagated individual plants. ►sibling

Adenine: A purine base in either DNA or RNA. purines.

Adenine Phosphoribosyltransferase (APRT, 16q24.3): Recessive deficiency of APRT may lead to dihydroxyadenine accumulation in the urine and kidney disease. APRT may repair cyclobutane pyrimidine dimers. ►cyclobutane dimer

Adeno-Associated Virus (AAV): A simple, icosahedral, non-enveloped, 22 nm, non-pathogenic, single-stranded DNA (4,681 nucleotides) virus that infects a wide range of cell types in various species and integrates preferentially into human chromosomal site AAVS1 at 19q13.2-qter most frequently as an inverted repeat (←--|--→). Some forms such as episomal and multimeric circular AAV are known. Several serotypes exist. Its loading capacity is ~4.7 kb. It has only two internally situated genes, *rep* (replication) and *cap* (capsid) encoding 4 replication (Rep78, Rep68, Rep52, Rep40) and 3 viral coat proteins (VP1, VP2, VP3) using different promoters and alternative splicing. AAV has two ~145-nucleotide inverted terminal repeats (ITR), which

form double-strand structure. During replication, the ss-DNA is the template for the new strand. In vector plasmids carrying AAV its DNA is double-stranded (see Fig. A29).

Figure A29. Adeno-associated virus

Cis-acting functions required for replication (*rrs*) and binding to the human chromosome site (Sp1, 19q13.3-qter), helicase, site-specific and strand-specific endonuclease activity, packaging, integration, excision, and initiator (*inr*) of transcription site for RNA are encoded within the ITR. AAV has been used as vector for gene therapy. The AAV vectors usually cannot carry more than 4.5 kb but because of the small size of the particles, they can penetrate easier small targets (e.g., skeletal muscles, neurons). The estimates of the frequency of integration of AAV vectors into chromosomal sites are not unanimous. Some vectors carry AAV concatamers, which have ~9 kb capacity. These vectors greatly benefit by the presence of adenovirus (AV) or herpes virus helper. In the presence of adenovirus helper, it may produce more than 100,000 particles per cell. AAV vectors transfect non-dividing cells or dividing cells and because of concatamer formation, they express transgenes for long periods and do not suffer immune rejection. The recombinant AAV molecule with deletions within the viral *rep* gene is called rAAV. The *rep* guides the integration into the host chromosome and facilitates non-homologous recombination. AAV vectors can target homologous mammalian chromosomal locations and alter ~1% of the cells without additional mutations. AAV may protect the cells against human melanoma or cervical carcinoma due to the product of the *rep* gene transcribed from the open reading frame beginning at map position of promoter p5. The *rep*-minus strains do not integrate to preferential sites. For infection, AAV requires a helper function provided by adenovirus or herpes virus. In the absence of a helper, AAV becomes latent but can be rescued. The AAV based vectors frequently used as a two-plasmid co-transfection system by relying on the complementary ITR–promoter-transgene and ITR-rep-cap packaging system. Unlike the adenoviral vector, AAV vectors remain in the cell. The host immune system usually does not react much to the AAV vectors beyond the initial stage of introduction. AAV vectors appear safe for the subjects and the environment (do not cause diseases) although in some instances unexpected tumors and chromosomal defects were observed. Tumor formation in mouse occurred at the chromosome 12 integration site that corresponds to human chromosome 14 (Donsante A et al 2007 Science 317:477). AAV can be targeted to specific cells either by the use of bispecific antibodies on the capsid that recognize AAV and the target. The tropism can be engineered also by specific amino acid insertions into the capsid for recognition of specific cell receptors. Although generally no serious immunological reaction against AAV occurs, the immune system may neutralize the passenger DNA. In the latter cases, immunosuppressive treatment may be beneficial. AAV has great potentials in gene therapy for different hereditary conditions. ►gene therapy, ►adenoma, ►herpes, ►viral vectors, ►parvoviruses, ►autonomous parvovirus, ►concatamer; Russel DW, Kay MA 1999 Blood 94:864; Miller DG et al 2002 Nature Genet 30:147; Nakai H et al 2003 Nature Genet 34:297; McCarty DM et al 2004 Annu Rev Genet 38:819.

Adenocarcinoma: Cancer of glandular tissues. ►pancreatic adenocarcinoma

Adenoma: Usually benign gland-shape epithelial tumor. The deficit of E-cadherin-mediated cell adhesion is one of the control steps in the change from adenoma to carcinoma. ►endocrine neoplasia, ►carcinoma, ►cadherins; Sieber OM et al 2002 Proc Natl Acad Sci USA 99:2954.

Adenomatosis, Endocrine, Multiple (MEN): The autosomal dominant MEN I (human chromosome 11q13) pancreatic adenonomas are prevalent, in MEN II pheochromocytoma and thyroid carcinoma (10q11) and in MEN III cancers of the nerve tissues are most common although the latter two conditions appear allelic in the pericentric region of human chromosome 10q. ►pheochromocytoma, ►SHC, ►adenoma, ►cancer

Adenomatous Polyposis Coli (APC): ►Gardner syndrome, ►FAP

Adenosine: Adenine with a ribose added (see Fig. A30). ►adenine, ►nucleoside

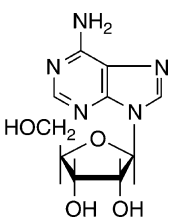

Figure A30. Adenosine

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Adenosine 3′, 5′ Cyclic Monophosphate (cAMP): Formed from ATP by adenylate cyclase enzyme. It has important regulatory functions as "second messenger" for microbial and animal cells. ►cAMP, ►adenylate cyclase, ►G-proteins, ►signal transduction

Adenosine Deaminase (ADA): An enzyme that hydrolyzes adenosine monophosphate to inosine. Its deficiency causes severe immunodeficiency and the patient's lymphocytes are disabled to fight infections successfully. ADA is synthesized in the cells for the purpose of detoxification of excessive amounts of adenosine or its analogs; it inactivates 9-β–D-xylofuranosyl adenine, a DNA damaging chemical, and thus it can be used as a dominant selection agent in tissue culture. Its synthesis in the cells can be overproduced over ten thousand times by a strong inhibitor of ADA, 2′-deoxycoformicin (dCF), and a transition-state analog for adenine nucleotide enzymes. It is encoded in human chromosome 20q13.11. RNA-specific adenosine deaminase (ADAR2, 21q22.3) is an editing enzyme. ►adenosine deaminase deficiency, ►SCID, ►severe combined immunodeficiency, ►mosaic, ►immunodeficiency, ►transition state, ►ADAR

Adenosine Deaminase Deficiency (ADA deficiency): Also known as severe combined immunodeficiency disease (SCID). ADA deficiency may be treated with gene therapy or bone marrow transplantation or by enzyme replacement with polyethylene glycol adenosine deaminase (Peg-ADA). In case of the defect, deoxyadenosine (dAdo) or deoxyadenosine triphosphate reaches toxic levels. Into T lymphocytes isolated from the patients, retroviral vectors introduce the normally functional human ADA gene and the lymphocytes are injected into the afflicted children. Upon periodically renewed treatment, symptoms of the disease (chronic infections, diarrhea and muscle weakness) usually recede. Post-exercise cramping of the muscles may be caused by inadequate level of this enzyme. The ADA gene was located to human chromosome 20q13 area. ►adenosine deaminase, ►SCID, ►Lesch-Nyhan syndrome, ►gout, ►gene therapy, ►immunodeficiency, ►viral vectors, ►lymphocytes, ►deamination, ►dyschromatosis symmetrica hereditaria

Adenosine Diphosphate: ►ADP

Adenosine Monophosphate Deaminase (AMPD1, 1p21-p13): Recessive deficiency of AMPD1 leads to cramps, myopathy and weakness after exercising. Most commonly, the enzyme in the skeletal muscles is affected and therefore it is called myoadenylate deaminase deficiency.

Adenosine Receptors: Mediate the activities of diverse cell types (neurons, platelets, lymphocytes, muscle cells) in response to adenosine released by the degradation of ATP. The four types of receptors are A_1, A_{2a}, A_{2b} and A_3. aggressiveness.

Adenovirus: A large mammalian (1.8×10^8 Da), icosahedral, (diameter about 80 nm) double-stranded DNA virus with ca. 36-kbp genetic material. The most commonly used serotypes for gene therapy are Ad2 and Ad5 although about 50 serotypes are known. The human adenovirus DNA has a 55-kDa protein covalently bond to both 5′-ends. The initiation of replication depends on a viral 80-kDA protein reacting with the first deoxycytidylic residue and its 3′-OH group serves as the starting point. The complementary DNA strand is a template. After replication, the 80-kDa protein is cleaved off but the 55-kDa protein stays on. The replication does not require the synthesis of Okazaki fragments because first, one of the strands is completed with the aid of the protein-dCTP primer, then the other strand is replicated. Replication can start at either end because of protein primer is used. Both strands of the DNA are transcribed into overlapping transcripts. The integrated viral DNA is generally smaller than the genome of adenoviruses. After lytic infection, a cell may release about 100,000 virus particles. Upon infection, it may produce a flu-type ailment, and can cause cancer upon integration into the genome. In humans, adenovirus is not carcinogenic and because it stays episomal it does not induce insertional mutation. The adenoviruses have broad host range and this makes them suitable for veterinary vaccine production. The adenovirus oncoprotein E1A induces progression of the cycle by binding to a protein complex p300/CBP. A histone acetylase (P/CAF) competes in this with E1A and inhibits its mitogenic activity. The main function of E1A is to disrupt the association between p300/CBP and the histone acetylase. The viral E1B gene encoded 55-kDa protein inactivates the p53 tumor suppressor gene and the cancerous proliferation begins. However, a mutant form of adenovirus (dl1520) that cannot express this 55 K protein can still replicate in cells that are defective in the p53 suppressor and consequently can lyse these defective cells. This finding offers a promise for the destruction of p53-deficient cancer cells by injection with dl1520 mutants. Normally wild type p53 (apoptosis) is a requisite for the productive infection (destruction of the cells) by wild type adenovirus. Adenoviruses have been used as vectors for genetic transformation after some regulatory sequences have been deleted and replaced. For the production of adenoviral vectors most commonly, cell line 293 is used.

This line carries the E1 viral gene in trans and thus enables replication of the vector that is deleted for it. Homologous recombination between the cell's chromosome and the vector should be avoided to prevent the formation of replication-competent adenovirus.

The maximal carrying capacity is about 6–8 kbp. Since adenovirus preferentially infects the respiratory tract, it may be used for somatic gene therapy of, for e.g., cystic fibrosis. It has also been used to transfer genes to skeletal muscles (see Fig. A31).

Figure A31. The general design of an adenoviral vector. ITR = inverted terminal repeat, Y= Ψ, packaging signal, E1 is replaced by the transgene and E3 is deleted in the majority of vectors. The removal of E1 is important to prevent the infectivity of the viral DNA. For the lost E1 function the host cells may provide complementation in trans. Recombination, however, may give a chance for regeneration of replication competent virus.

The cell can take up adenovirus vector and its load DNA by a specific virus receptor, e.g., CAR1, and the $\alpha_V\,\beta_3$ or $\alpha_V\beta_5$ surface integrins. In mice incubated in vitro with a Cre-expressing adenovirus vector, Cre-mediated recombination occurred at an efficiency of 49–76%, and the infected spermatogonial stem cells could reinitiate spermatogenesis after transplantation into seminiferous tubules of infertile recipient testes. No evidence of germ-line integration of adenovirus vector could be found in offspring but this possibility cannot be ruled out because there is no known mechanism that would prevent it (Takehashi M et al 2007 Proc Natl Acad Sci USA 104:2596). Usually the adenoviral vector, taken up by non-dividing or dividing cells, is not integrated into the human genome and thus does not lead to permanent genetic change and they have to be reapplied periodically (in days, weeks or months). The adenovirus proteins evoke rapid immune responses and that may be the cause of the short duration of the transformation effects. In addition, the current vectors may cause inflammation because of antivector cellular immunity. Immunosuppressive drugs (cyclosporin A, cyclophosphamide) may mitigate the immune response but may cause undesirable side effects.

The immunogenic property of the adenoviral vectors may eventually be exploited for immunological destruction of the targeted cancer cells. An advantage of this vector is that it can be used in very high titers (10^{11} to 10^{13} particles/mL). Adenovirus is not known to induce human cancer. Adenoviral vector-mediated interleukin-12 gene therapy seems to protect mice with metastatic colon carcinoma. Construction of improved vectors is of major interest. *Gutless* or *fully deleted* adenoviral vectors are *helper-dependent* because most of the viral genome is removed to reduce the risk of adverse immune reaction and increase the duration of expression. ►icosahedral, ►Okazaki fragment, ►replication, ►cancer, ►viral vectors, ►CAR1, ►titer, ►gene therapy, ►p53, ►cystic fibrosis, ►antivector cellular immunity, ►adeno-associated virus, ►tumor vaccination, ►seroswitch vector, ►targeting vector; Benihoud K et al 1999 Curr Opin Biotechnol 10:440; Frisch SM, Mymryk JS 2002 Nature Rev Mol Cell Biol 3:441.

Adenylate: Salt of adenylic acid.

Adenylate Cyclase (adenylyl cyclase): An integral membrane enzyme with an active site facing the cytosol, generating cAMP (cyclic AMP) from ATP and releases inorganic pyrophosphate (two phosphates). $G_{s\alpha}$ subunit-bound GTP activates this enzyme. The enzyme has a weak GTPase activity that eventually breaks the $G_{s\alpha}$—GTP links and thus turns off the cyclase function. The activation of the cyclase function is initiated by the hormone epinephrine, which binds to a membrane receptor and activates the G_s proteins. cAMP itself is degraded by cyclic nucleotide phosphodiesterase. The cellular level of Ca^{2+} regulates oscillation of its level. The type I enzyme is stimulated by neurotransmitters which elevate the level of Ca^{2+}. The Type II enzyme requires stimulation by $G_{\alpha S}$ in the presence of the $G_{\beta\gamma}$ subunits of the G protein. ►adenosine 3′►,5′►cyclic monophosphate, G_s, ►G-protein, ►GTP-ase, ►GTPase activating protein, ►cyclic AMP-dependent protein kinase, ►animal hormones, ►epinephrine, ►calcium ion channel, ►anthrax, ►junction of cellular network; Jaiswal BS, Conti M 2001 J Biol Chem 276:31698; Onda T et al 2001 J Biol Chem 276:47785.

Adenylate Kinase Deficiency (AK1): Dominant in human chromosome 9q34.1, it causes hemolytic problems. Several AKI alleles were named. Adenylate kinases catalyze the reversible transfer of the γ-phosphate from ATP to AMP and regulate adenine nucleotide metabolism and intracellular ATP levels. By 2005, six AK enzymes have been characterized (Ren H et al 2005 Proc Natl Acad Sci USA 102:303). ►hemolysis, ►hemolytic diseases

Adenylic Acid: It is a phosphorylated adenosine.

Adenylyl Cyclase: ►adenylate cyclase

Adenylosuccinase Deficiency (adenylosuccinate lyase, ADSL, 22q13.1): Normally the enzyme catalyzes the reaction: succinylaminoimidazole carboxamide ribotide→ aminoimidazole carboxamide ribotide and

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the removal of fumarate from adenylosuccinate to yield adenosine monophosphate. Homozygosity for the recessive mutations may cause autism, mental and psychomotor retardations. ►autism

Adenylylation: Addition of adenine to an amino acid near the active site in a protein (by the enzyme adenylyl transferase); it may regulate the activity of the target.

ADEPT (antibody-directed prodrug therapy): A prodrug is supplied to an organism afflicted by cancer. The prodrug itself is not toxic until it is enzymatically activated. Care should be taken that the enzymes of the body would not convert the prodrug automatically into a toxin. An antibody, specific for the cancer, is conjugated with an activating enzyme. The conjugate seeks up the cancer cells and by generating locally high concentration of the toxin it is expected to kill the cancer cells. It would be desirable that the toxin would not diffuse from the tumor into normal cells. Enzymes of potential use with prodrug→toxin:

Pseudomonas carboxypeptidase/glutamic acid derivatives→benzoic acid mustards, *E. coli* β-lactamase/cephalosporin derivatives→nitrogen mustards, yeast cytosine deaminase/5-fluoro-cytosine→5-fluorouracil, almond β-glucosidase/amygdalin→hydrogen cyanide, etc. ►magic bullet, ►vascular targeting; Xu G, McLeod HL 2001 Clin Cancer Res 7:3314.

ADH (antidiuretic hormone): A short peptide (vasopressin). antidiuretic hormone.

ADH (alcohol dehydrogenase): An enzyme catalyzing the reversible reaction: acetaldehyde + NADH + H^+ ⇆ ethanol + NAD^+

The ADH subunits (α, β, γ) are encoded in human chromosome 4q21. ►*adh*$^-$,►acetaldehyde dehydrogenase, ►mutant isolation, ►ethanol, ►allylalcohol

***adh*$^-$**: A mutant with a defective ADH enzyme. ►acrylaldehyde, ►mutation detection

Adhalin: ►muscular dystrophy

ADHD: ►attention-deficit hyperactivity

Adherence Reaction: The binding of molecules to the complement receptors of cell surface or agglutination of antibody and antigen complexes. ►antibody, ►complement, ►complement fixation

Adherens Junction: The cell surface where actin filaments attach. AJ is regulating cell adhesions, mediated by Rap1 GTPase. β-catenin, ►RAP1A, ►Knox, ►formin; AL, Brown NH 2002 Science 295:1285; Tepass U 2002 BioEssays 24:690.

Adherin: Chromosomal proteins that are similar in function to cohesin. ►sister chromatid cohesion

Adhesion: Sticking together, e.g., water molecules clinging to various surfaces. ►integrins, ►selectins, ►cadherins, ►plakoglobin, ►vinculin, ►talin, ►adherens junction

Adhesion Belt: Adherens belt connects neighboring cells. ►adherens junction

Adhesion Plaque (focal contact): The spot where a cell is anchored to the extracellular matrix by transmembrane proteins.

Adipocere (grave wax): Hydrolyzation product of body fats after death; its formation may help the preservation of DNA of the brain in some ancient animal/human remains. ►ancient DNA

Adipocyte: Fat storage cell; it is used as a depository of excess caloric intake or reserve when expenditure exceeds intake of calories. The white adipose stores energy as triglycerides, the brown adipose tissue is involved in thermogenesis (see Fig. A32). Membrane-associated metalloproteinase, MT1-MMP modulates pericellular collagenase and subsequently the growth of white adipose tissue cells (Chun T-H et al 2006 Cell 125:577). Adipocyte differentiation is regulated by the CCAAT/enhancer-binding proteins, adipocyte differentiation determinant (ADD1)/sterol response element-binding protein (SREBP1), and the peroxisome proliferator-activated receptors (PPAR). Sequential phosphorylation of CCAAT enhancer-binding protein by MAPK and GSK3β in vitro leads to DNA-binding function and clonal expansion of adipocytes (Tang Q-Q et al 2005 Proc Natl Acad Sci USA 102:9766). In addition retinoic acid, vitamin D_3, thyroid hormone receptors are involved. The retinoic receptors (RXR) are indispensable for the viability of mice. Adipocytes secrete leptin, adiponectin, resistin, TNF-α IL-6 and visfatin (Fukuhara A et al 2005 Science 307:426). ►retinoic acid, ►PPAR, ►vitamin D, ►animal hormones, obesity, ►resistin, ►brown fat, ►mesenchyma, ►MAPK, ►GSK3β; Gregoire FM et al 1998 Physiological Revs 78:783; Rosen ED, Spiegelman BM 2000 Annu Rev Cell Dev Biol 16:145; Zhang J-W et al 2004 Proc Natl Acad Sci USA 101:43; regulation of energy balance by adipocytes; Rosen ED, Spiegelman BM 2006 Nature [Lond] 444:847.

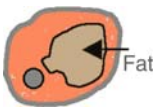

Figure A32. Adipocyte

Adiponectin: A cytokine produced by adipocytes in response to metabolic or extracellular signals. It

lowers blood glucose level and reduces the level of triglycerides in the muscles and the production of fat. It may be exploited for treatment of insulin-resistant diabetes. ►cytokines, ►triglyceride, diabetes, ►osmotin, ►resistin, ►obesity; Yamauchi T et al 2001 Nature Med 7:887; Berg AH et al ibid. p. 947.

Adipose: Related to fat, e.g., adipose tissue = fat tissue.

Adjacent Disjunction: Neighboring members of translocation rings or chains move to the same pole; adjacent-1 when centromeres are non-homologous, adjacent-2 when centromeres are homologous (non-disjunctional) at the poles. ►translocation chromosomal

Adjacent Distribution: ►adjacent disjunction

Adjuvant, Immunological: If the immune response to an antigen is unsatisfactory because of the small amount present, the immune reaction may be enhanced by protecting the antigen from degradation and promoting slow release and increase its uptake by macrophages. For this purpose mineral oils, alum (a hydrated aluminium oxide), charcoal, Freund adjuvant, specific nucleotide sequences, CD154, etc. can be used. ►immune response, ►immunization genetic, ►antigen, ►Freund adjuvant, ►vaccine, ►CD154

Ad Libitum (ad lib.): As much as wanted; for e.g., feeding animals at level they wish to eat.

ADM (automated digital microscopy): ►ACIS, ►FAST, ►microscopy

Admissibility Criteria: Legal concepts concerning the appropriateness whether a certain type of evidence, scientific method or logical arguments would be helpful for the jury to determine the facts in the court. Regarding scientific evidence, the judge decides, whether the methodology and techniques have been validated by peer reviews and publication in respected publications, whether the techniques have an acceptable error rate, and the methodology is generally acceptable by the scientific community (*Daubert factors*). The scientific methods generally improve with time and so the admissibility criteria is also subject to change within the above guiding principles. ►forensic genetics

Admixture in Populations: May take place when two potentially interbreeding populations share a habitat for a period. When the frequency of about 50 or more markers is analyzed, statistical information may be derived on the extent and time of the admixture (admixture mapping: Patterson N et al 2004 Am J Hum Genet 74:979). Availability of SNP markers may permit association studies between disease genes and SNPs even when this approach may not yield much information on the molecular associations. Using nine autosomal markers (and mtDNA), ten populations of African descent were analyzed by sampling different regions of the U.S. for European admixture. In Jamaica 6.8% and in New Orleans 22.5% appeared introgressive. The gene flow from Europeans was sex-biased, the male contribution was substantially higher than that by females (Parra EJ et al 1998 Am J Hum Genet 63:1839). ►introgression, ►linkage disequilibrium; Chikhi L et al 2001 Genetics 158:1347; Zhu X et al 2005 Nature Genet 37:177.

Admixture Mapping: Chromosomal blocks can remain intact in linkage disequilibrium after admixture of different populations. These blocks eventually decay because of recombination yet, based on the linkage disequilibrium, gene loci can be mapped. (Chakraborty R, Weiss KM 1988 Proc Natl Acad Sci USA 85:9119)

aDNA: ancient DNA. ►ancient DNA

Adnfle: ►epilepsy

AdoMet: S-adenosyl-L-methionine (current abbreviation is SAM) is a methyl donor for the enzymes guanosine 7-methyl transferase and the 2′-O-methyl transferase enzymes in the cap of pre-mRNAs and for other methylation reactions. ►SAM, ►cap, ►methylase, ►methylation of DNA, ►methylation of RNA, homocystinuria, ►methionine adenosyl transferase; LeGros L et al 2001 J Biol Chem 276:24918.

Adopted Children: Frequently used in human genetics to determine the relative effects of genes and environment. These studies are sometimes hampered, however, because either the families do not have biological children or the biological parents of the adopted children are not available for examination. According to civil law, adopted children may lose any legal ties to and identity with the natural parents. This loss of identity may carry some genetic caveats because of chances of inbreeding due to lack of information about descent. These problems are similar to the ones encountered by artificial insemination using anonymous sperm donors. ►twinning, ►artificial insemination

Adoptive Cellular Therapy (adoptive transfer): Infusion of immune effector cells (NK cells, macrophages, γδ T cells, αβ T cells, B cells, etc.) for the treatment or prevention of disease (lymphoma, leukemia, myeloma). Although this may appear an attractive alternative to chemotherapy or radiation, the allogeneic cells may induce graft-versus-host disease (immune rejection). To avoid these complications herpes simplex virus thymidine kinase gene (HStk) may be targeted to the malignant cells by a Moloney murine leukemia retroviral vector. This vector selectively seeks

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up dividing cells. Since cancer cells divide more frequently than normal cells, the vector does not usually hit normal cells. The cells are then infused by ganciclovir, which when metabolized to ganciclovir triphosphate it is incorporated into DNA and RNA resulting in selective termination of replication in the $HStk^+$ cells by this suicide technique. More differentiated tumor-specific $CD8^+$ T cells were less effective than naïve ones for in vivo tumor treatment. The possible causes may be down-regulation of lymphoid homing and co-stimulatory molecules, inability to produce IL-2 and access homeostatic cytokines and entry into a pro-apoptotic and senescent state (Gattinoni L et al. 2005 J Clin Invest 115:1616). ►cell therapy, ►gene therapy, ►ganciclovir, ►TK, ►Moloney mouse leukemia oncogene, ►viral vectors, ►suicide vector, ►stem cells, ►diabetes; Link CJ et al 2000 Stem Cells 18:220.

ADP: Adenosine 5′-diphosphate, a phosphate group acceptor in various cellular processes. It is produced by hydrolysis of ATP; it can also regenerate ATP by oxidative phosphorylation.

ADP-Ribosylation Factor: ►ARF

Adr: A positive regulator protein of transcription.

Adrenal: Adjacent or pertinent to the kidney.

Adrenal Hyperplasia, Congenital (CAH): Occurs in both X-linked and autosomal forms and apparently controlled by several loci. Cortisol deficiency is involved. The X-linked form is attributed to gonadotropin deficiency. The steroid hormone overproduction indicates a defect in steroid 21-hydroxylase, encoded within the boundary of the HLA complex in human chromosome 6p21.3. The affected female babies are masculinized. Masculinization is preventable by the administration of dexamethasone but side effects may occur. It may be associated with Addison disease (hypotension, anorexia, weakness and pigmentation). One form of the disease is accompanied by difficulties in salt retention in the newborns. The prevalence is about 7×10^{-5}. The 17-α-hydroxylase deficiency is encoded at 10q24.3 and it involves an excessive amount of corticosterones and hypertension and hypokalemic alkalosis (increase of bases [e.g., K^+] yet lower pH). An autosomal form in chromosome 8q21 is deficient in 11-β-hydroxylase and/or corticosteroid methyl oxidase II (HSDB, 1p13.1) occurs at a frequency of 1×10^{-5}. Masculinization may be caused by several other genetic anomalies and by various medications administered to the mother or maternal androgen-producing tumors. Prenatal diagnosis may use allele-specific PCR on DNA from chorionic villi. ►HLA, ►hermaphroditism, ►genital anomaly syndromes, ►adrenal hypoplasia, ►Addison disease, ►STAR, ►dexamethasone, ►PCR, ►chorionic villi, ►congenital adrenal hyperplasia

Adrenal Hypoplasia, Congenital (AHC): Characterized by abnormal underdevelopment (hypoplasia) of the genitalia and the gonads, insufficient function of the kidneys, hypoglycemia (reduced blood sugar), seizures, etc. Several forms of the disease (hypoadrenocorticism, polyglandular autoimmune syndrome, Addison disease) were reported with autosomal recessive inheritance. The X-chromosome-linked DAX1/AHC (Xp21.3-p21.2) locus encodes a dominant negative regulator of transcription, a nuclear hormone receptor protein with a DNA-binding domain. The DAX-1 transcription is mediated by the retinoic acid receptor. AHC may modify male determination by SRY and it seems to regulate also the steroidogenic factor Sf-1 but it does not affect ovarian development. ►hypogonadism, ►Kallmann syndrome, ►adrenal hyperplasia, ►epilepsy, ►retinoic acid, ►RAR, ►dominant negative, ►transcriptional activator, ►SRY, ►Sf-1, ►Addison disease

Adrenaline: ►epinephrine, ►animal hormones

Adrenergic Receptors: Occur in the forms of α_1, α_2, β_1, β_2 distinguished on the basis of their responses to agonists and antagonists and tissue-specificity. They all respond to the adrenal hormones, epinephrine and norepinephrine. ►epinephrine, ►membrane proteins, ►receptors, ►agonist, ►antagonist, ►arrestin, ►hypotension, ►GRK2

Adrenocortical: Pertains to the cortex (the outer layer) of the kidney.

Adrenocorticotropin (ACTH): A pituitary peptide hormone that controls the secretion of steroid hormones of the kidney in response to cAMP. ACTH unresponsiveness (familial glucocorticoid deficiency) is recessive autosomal defect of resistance to ACTH, causing hypoglycemia and childhood infections. Mutations in ACTH receptor (melanocortin 2 receptor) cause familial glucocorticoid deficiency (FGD 2) in chromosome 21q22.1. The mutation in FGD 2 involves the melanocortin 2 receptor accessory protein (Metherell LA et al 2005 Nature Genet 37:166). ►cAMP, ►glucocorticoids, ►cortisol, ►ACTH, ►POMC, ►melanocortin

Adrenodoxin: An electron carrier iron-sulphur protein in the mitochondria of the kidney cortex and assist cholesterol biosynthesis. ►cerebral cholesterinosis

Adrenoleukodystrophy (ALD, Addison disease, Xq28): The X-linked neonatal form is a defect in peroxisome assembly. The disease is associated with very long chain fatty acid (VLCFA) acyl coenzyme A synthase

defects. Neural degeneration and blindness are the consequences of the disease. Autosomal forms encoding different peroxins and peroxin receptors are at 2p15, 12p13.3, 7q21-q22. ►microbodies, ►Zellweger syndrome, ►Refsum disease, ►peroxins

Adrenomedullin: A 22-amino acid vasodilator, a calcitonin-related peptide. In its absence hydrops fetalis may develop. ►hydrops fetalis

Adriamycin: ►doxorubicin

Adrogenital Syndrome: A complex genetic disorder based on anomalies of steroid biosynthesis and adrenal hyperplasia. Gene frequencies vary a great deal in different populations from 0.026 of Alaskan Eskimos to 0.004 in Maryland, USA. ►adrenal hyperplasia, ►allelic frequency, ►steroid hormones

Adsorption: The tendency of molecules to adhere to a surface (different from absorption that is uptake through a membrane).

Adsorption Chromatography: ►column chromatography, ►thin layer chromatography

Adsorptive Endocytosis: ►receptor-mediated endocytosis

Advantage of Heterozygotes: Indicates that fitness (the reproductive value) of the heterozygotes exceeds that of both types of homozygotes in a population and this may lead to balanced polymorphism. ►balanced polymorphism, ►polymorphism, ►fitness

Advantageous Mutations: Favored by a particular environment and they are expected to propagate under steady-state conditions by a rate per generation: $v = \sigma\sqrt{2s}$ where σ is the standard deviation caused by diffusion (migration) and s = selective advantage in the absence of dominance. E.g., if σ = 10 km, and $s = 0.02$ then the advance per generation in kilometers will be $10\sqrt{2x0.02} = 2$ then it would take 250 generations to advance 500 km. (►mutation, ►mutation beneficial, ►migration, ►selection coefficient; Cavalli-Sforza LL, Bodmer WF 1971 The Genetics Of Human Populations, Freeman, San Francisco, California.

Adventitia: The outer coating of organs by lose connective tissues composed mainly of fibrillin and elastin.

Adventive Embryos: Adventive Embryos develop from the diploid tissues of the plant nucellus (without fertilization); they occur commonly in citruses. ►apomixia, ►nucellus

AE Genes: Annotated expressed genes. ►annotation, ►ANE genes, ►NAE genes

Aecidiospore: A dikaryon of plant rust fungi formed through a sexual process that did not involve nuclear fusion; the aecidiospores are products of the aecidium, a group of sporangia. ►aecidium, ►dikaryon, ►sporangium, ►fungal life cycle

Aecidium or aecium: A fruiting structure of fungi (Basidiomycetes-Uredinales) such as *Puccinia graminis tritici*. Aecidia are formed only on the intermediate host, barberry, but the spores infect only wheat.

Aedes egypti: The mosquito, which transmits yellow fever and dengue fever viruses. (See Rai KS, Black WC 1999 Adv Genet 41:1). The draft sequence of its genome has been determined as ~1376 million base pairs an it is about 5 times the size of the genome of the malaria vector *Anopheles gambiae*. Nearly 50% of the *Ae. aegypti* genome consists of transposable elements (Nene V et al 2007 Science 316:1718). ►Anopheles mosquito, ►malaria

Aegilops caudata: A diploid representative of the *Triticum* genus (2n = 14) carrying the 7-chromosome C genome (current name *Triticum dichasians*). *Aegilops cylindrica*: an allotetraploid of the wheat genus containing the CD genomes (C from *T. dichasians* and D from *T. tauschii*). Current name *Triticum cylindricum*. *Aegilops squarrosa: Triticum tauschii* by current name, is a diploid species in the wheat genus with the D genome (see Fig. A33).

Figure A33. Glume of *T. peregrinum*. (Courtesy of Drs. Gordon Kimber and Moshe Feldman)

Aegilops umbellulata, by current name *Triticum umbellulatum*, a diploid species of the wheat genus with the C^u genome. *Aegilops variabilis*, currently *Triticum peregrinum,* a species of the wheat genus; occurs in nature both as tetraploid (DM) and hexaploid (DDM) genomic constitution. ►*Triticum*

Aegricorpus: A genetic-physiological complex determined by the host-pathogen interaction; the phenotype of the disease in plants. ►host-pathogen relations, ►Flor's model

Aequorin (GFP): Luminescent protein (green fluorescent protein of 238 amino acids) from jellyfish (*Aequorea victoria*); its activation is dependent on the level of the available Ca^{2+} and on this basis minute quantities and differences in this ion can be measured

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by optical means within the range of 0.5–10 mM. This may be of major importance because calcium may play regulatory functions in all eukaryotic cells. The chromophore results from the cyclization and oxidation of the Ser^{65} (Thr^{65})Tyr^{66} Gly^{67} amino acid sequence in the central helix of the 11-stranded β barrel. Aequorin has also the advantage that is non-invasive and non-destructive label in various organisms. Its excitation peaks are at 395 and 475 nm, and the emission peak of the pure GFP is at 470 nm. Mutant proteins with higher absorption peaks and different colors (red, yellow) exist. By the use of fluorescence resonance energy transfer (FRET), linking GFP reversibly to peptide spacers result in conformational changes and altered light emission (color). GFP is sensitive to pH, temperature, and prior illumination. Excitation by 488 nm light increases fluorescence 100 folds and remains stable for days (Patterson GH, Lippincott-Schwartz J 2002, Science 297:1873). The gene has been cloned and sequenced and has been widely used in animals and plants, in various modified forms, as a reporter gene. GFP is a strong immunogen. ►calmodulin, ►Renilla GFP, ►BFP, ►EGFP, ►FRET, ►drFP583, ►barrel; Methods in Enzymology, vol 302, 1999; Tsien RY 1998 Annu Rev Biochem 67:509; Labas YA et al 2002 Proc Natl Acad Sci USA 99:4256; van Roessel P, Brand AH 2002 Nature Cell Biol 4:E15; http://www.conncoll.edu/ccacad/zimmer/GFP-ww/GFP-1.htm.

AER: Apical ectodermal ridge.

Aerobe: An organism that uses oxygen as the terminal electron acceptor in respiration. ►electron acceptor, ►respiration

Aerobic: A reaction (or organism) requires or takes place in the presence of oxygen.

AF (activation function protein): Activates and recruits co-activators of gene expression.

a/α-Factors: ►mating type determination in yeast

Affected Individual: Expresses a particular (disease) trait.

Affected-Relative-Pair Method: Similar to ASP, but other relative pairs are used.

Affected-Sib-Pair Method: (ASP): A non-parametric method for linkage analysis of susceptibility genes. For this purpose the risk ratio (λ_s) is determined, that is the risk of a sib of an affected proband compared to the average prevalence in the population. For e.g., diabetes has a prevalence of 0.004 in the general population but its incidence among sibs of affected individuals is 0.06, hence $\lambda_s = 0.06/0.004 = 15$. This λ_s is for all loci responsible for the phenotype. The larger λ_s the higher is the genetic contribution. It is also affected by the interaction (can be multiplicative or additive) of the various factors contributing to the phenotype. The strength of the proof for linkage depends on the so-called *maximal lod score* (MLS) symbolized by T and means the log odds in favor of linkage. Usually, the estimation is carried out in steps by selecting at each step linkage with markers increasing from T>1.0. Statistically valid linkage is expected when the T score reaches or exceeds 3. The T value may also increase by the use of larger populations. Recombination decreases MLS and the use of multiple loci increases the estimate. Another advantage of this approach is that both recessive and dominant alleles can be studied. It is applicable also for quantitative traits. This procedure may not necessarily applicable only to sibs but cousins or other close relatives (uncles, aunts) may also be included. ►recombination, ►frequency, ►maximum likelihood method applied to recombination, ►lod score, ►non-parametric tests, ►allele sharing, ►GSMA; Dupuis J, Van Eerdewegh P 2000 Am J Hum Genet 67:462.

Affective Disorders: Psychological illnesses, psychoses. manic depression, ►autism, ►hyperactivity [ADHD], ►Tourette's syndrome, ►neurodegenerative diseases, ►bipolar mood, ►unipolar depression, ►schizophrenia, ►paranoia, ►obsessive-compulsive behavior, ►addiction; Evans KL et al 2001 Trends Genet 17:35.

Afferent: Conducting or transferring toward the middle.

Affibody: Engineered binding protein using the 58 amino acid Z domain of *Staphylococcus aureus Protein* A (SPA). SPA strongly binds the Fc domain of immunoglobulins. ►antibody, ►receptin; Wahlberg E et al 2003 Proc Natl Acad Sci USA 100:3185.

Affine Gap Cost: Expresses the "penalty" for gaps in a sequence alignment also according to the length of a gap. ►genome projects, ►contig

Affinity (Michie D, Wallace ME 1953 Nature [Lond] 171: 26): Unlinked genes segregate to the same gamete more frequently (quasi-linkage, Robinson, R. 1971) or less frequently (reverse linkage) than expected on the basis of randomness (Bailey NTJ 1961 Introduction to the mathematical theory of genetic linkage, Oxford, Clarendon Press, England). (►translocation chromosomal) In immunogenetics: the intensity of interaction between a particular antigen receptor and its epitope. ►epitope

Affinity Capture: ►acesims

Affinity Chromatography: Polyadenylated mRNA can be separated from other RNAs by adsorption on oligo T (thymine) cellulose or sepharose columns by virtue of the complementarity of the A and T bases. Similar

procedures are used for the purification of antibodies on immobilized antigen media (antibody purification) and DNA-binding proteins can be isolated and enriched by a factor of 10^4 with the aid of affinity chromatography. ►gel retardation assay, ►cDNA library screening, ►immunoprecipitation

Affinity Labeling: Most commonly a photo-affinity hapten is used (i.e., one that is activated only upon illumination). The affinity label is bound to the antigen-binding site amino acids of the antibody and thus reveals the site on the antibody where the attachment is taking place. ►hapten, ►antigen, ►antibody

Affinity Maturation: Selection of cells with high affinity for the antigen as clonal selection progresses. It takes place by accumulation of mutations in the *germinal center* of a lymphoid follicle in the paracortex of a lymphoid node and combinatorial assembly of the variable, joining and diversity sequences of the immunoglobulin genes. These alterations take place in response to the antigens arriving there through small capillary veins on the surface of the antigen-presenting cells and helper T cells. Immunoglobulin G (IgG) usually responds well after the second immunization. Affinity maturation is also a process for the selection of memory cells. TRAF and CD40 regulate the affinity maturation. ►clonal selection, ►antibody, ►antigen-presenting cell, ►immune response, ►repertoire shift, ►immunoglobulins, ►hapten, ►memory immunological, ►lymphoid organ, ►TRAF, ►CD40, ►vaccine; Ahonen CL et al 2002 Nature Immunol 3:451; Meffre E et al 2001 J Exp Med 194:375.

Affinity Purification: Required unless the antibody reacts with more than one antigen. If this is not the case, an affinity chromatography column is prepared by using pure antigen. Alternatively, monoclonal antibody must be used or the immunoglobulin library must be carefully analyzed for true or false positive immune reactions. ►antibody, ►antigen, ►monoclonal antibody, ►TAP

Affinity Tag: A short peptide or protein domain is fused to all members of a set of proteins. The tag facilitates the selective binding of these proteins to specific resins and thereby isolation, purification and elution under conditions that retain their activity (Nilsson J et al 1997 Protein Exp Purif 11:1).

Affinity-Directed Mass Spectrometry: Detects interaction between proteins, receptors-ligands, proteins-nucleotides, etc. ►mass spectrum, ►TAP

AFI: amaurotic familial idiocy, now called Tay-Sachs disease (TSD). ►Tay-Sachs disease

Afibrinogenemia: 4q28 recessive deficiency of fibrinogen (blood coagulation factor I). The afflicted individuals bleed very heavily after injury. Periodic blood accumulation under the skin (ecchymosis), nose bleeding (epistaxes), bloody tumors (hematomas), bloody cough (hemoptysis) or stomach-intestinal or genitourinary bleeding occur. Characteristically, for longer periods no symptoms appear. Therapy is intravenous injection of concentrated human fibrinogen. ►antihemophilic factors, ►hemophilia, ►dysfibrinogenemia, ►fibrin-stabilizing factor

Aflatoxins: Group of heterocyclic mycotoxins produced under appropriate conditions by the *Aspergillus flavus* and *Aspergillus parasiticus* fungi (see Fig. A34). The aflatoxins are extremely carcinogenic because they affect DNA synthesis. The LD_{50} of aflatoxins orally administered to monkeys may be as low as (1750) µg per kg. Aflatoxin may be a contaminant on grains, peanuts, dry chili pepper, and on many other material humans and animals eat or are exposed to. Aflatoxins frequently cause mutations in *p53* tumor suppressant at codon 249 (AGG→AGT) resulting in hepatocarcinomas. The 8,9-oxide of aflatoxin B forms a mutagenic adduct in the DNA at N^7-guanine. ►environmental mutagens, ►p53, ►toxins, ►mycotoxins, ►adduct; Smela ME et al 2001 Carcinogenesis 22:535; Cary JW et al 2002 Biochim Biophys Acta 1576:316.

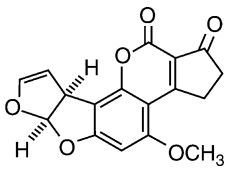

Figure A34. Aflatoxin

AFLP (anonymous fragment length polymorphism, amplified fragment length polymorphism): DNA fingerprinting technique involving restriction enzyme digestion and amplification of special fragments by PCR. It can be used for mapping genes or for the estimation of nucleotide diversity in populations. ►DNA fingerprinting, ►PCR, ►restriction enzymes, ►anonymous DNA segment, ►VNTR; Vos PR et al 1995 Nucleic Acids Res 23:4407; Saunders JA et al Crop Sci 2001 41:1596; Breyne P et al 2002 Proc Natl Acad Sci USA 99:14825.

African Green Monkey (*Cercopithecus aethiops*): Kidney cells are the best laboratory host for the propagation of SV40 (Simian virus 40). ►SV40, ►cos, ►Cercopithecidae

AFS: ►affected-sib-pair method

After Morning Pill: ►hormone receptors [RU-486]

A

Agameon: A species without sexual reproduction.

Agamic: A species reproducing asexually (without gametes).

Agammaglobulinemia: Occurs as an X-chromosomal (congenital) and autosomal defect in the synthesis of γ-globulin, a component of the heavy chain of antibodies. The X-chromosome-linked (Xq21.33) is frequently called Bruton's agammaglobulinemia (XLA). The protein responsible is tyrosine kinase of 659 amino acids, encoded by 19 exons. The manifestation of XLA may differ in different families, indicating the involvement of several genes. It is conceivable that the defect is caused by rearrangement of the genes involved. Some of the individuals have truncated V regions of the antibody. In the afflicted persons the IgG and IgM content is generally no more than 1% of the normal. The absence of plasma cells from the lymph nodes, spleen, intestine and bone marrow is also a basic defect. The patients are very susceptible to pyogenic infectious bacteria (staphylococci, pneumococci, streptococci, and *Hemophilus influenzae*). Pus-forming inflammation of the sinuses, pneumonia, meningitis (inflammation of the brain), furunculosis (boils) are common but can be prevented by the use of antibiotics or raising the γ-globulin levels by regular injections. Without treatment, these infections may become fatal. The afflicted children are not more susceptible to viral, enterococcal, gram-negative bacteria, protozoan or the majority of fungal infections. Another X-chromosome linked or autosomal agammaglobulinemia causes susceptibility to bacterial, fungal and viral infections and leukemia. This is generally accompanied by lymphopenia (decrease of lymphocytes in the blood). This disease is generally detected after the discontinuation of breast-feeding of the babies or near the end of the first year of life. Agammaglobulinemia may occur also as an acquired disorder with onset at different ages, generally as a follow-up to other diseases. The prevalence is about 0.5 to 1×10^{-5}. ►gammaglobulin, ►immunoglobulins, ►immune system, ►antibody, ►hypogammaglobulinemia/common variable immunodeficiency, ►immunodeficiencies, ►achondroplasia, ►cancer, ►BTK

Agamospecies: Reproduces by non-sexual means, e.g., parthenogenesis, apomixia. ►species, ►parthenogenesis, ►apomixia, ►asexual reproduction

Agamospermy: Seed production without fertilization, ►apomixis. ►parthenogenesis, ►diplospory, ►apospory, ►adventitious embryos, ►apomixis

Aganglionosis: Congenital lack of intestinal ganglions. ►Hirschsprung disease

Agar: Gelling agent produced from marine algae with various degrees of purification (bacteriological agar, noble agar) and used for microbial and plant cell culture media. ►gellan gum, ►agarose

Agarose: A purified linear galactan hydrocolloid isolated from marine algae. In the crude form, it is generally contaminated with salts and other substances, polysaccharides, proteins. Some commercial products are highly purified. It is used for electrophoretic separation of oligo and polynucleotides from 0.1- to 60-kb range, depending on the concentration of this matrix. The higher concentration (2%) separates the smallest molecules whereas the lowest concentration (0.3%) permits the separation of the largest fragments. 0.9–1.2% are the most commonly used concentration ranges separating 0.4- to 7-kb fragments. Contaminations of the agarose may interfere with further enzymatic handling of the eluted DNA. ►electrophoresis, ►gel electrophoresis

Agave (sisal): Basic chromosome number x = 30 and the various plant species may be diploid, triploid or pentaploid. The plant has been used for medicinal purposes as laxative; and its juice may cause abortion.

Advanced-glycation end product (AGE): A sugar-derived carbonyl group added to a free amine that forms an adduct after rearrangement producing AGEs. Age may cross-link amino groups in macromolecules and thus may promote aging, accelerate diabetes and may participate in other reactions. The cross-links may be broken by *N*-phenacetylthiazolium bromide and may have therapeutic application. ►Alzheimer disease, ►aging, ►diabetes, ►adduct; Pushkarsky T et al 1997 Mol Med 3:740.

Age: The time since the birth of an individual. Prenatal age is more difficult to determine. Ultrasonic measurements are frequently compared with tables obtained by empirical data.

Age and Mutation in Human Populations: Expressed by the formula $\mu_t = \alpha t + \mu_0$ where mutation rate at a given time is μ_t, α is the mutation rate per cell divisions and μ_0 the initial frequency of mutation. It is expected that mutation rate increases as the number of cell divisions increases in the spermatogonia and oogonia. The available data indicate that chondrodystrophy (achondroplasia, a dominant dwarfness) and acrocephalosyndactyly (Apert's syndrome, pointed top of the head and syndactyly [webbing in between or attachment of the fingers and toes]) increases at birth by about 2–4 fold with paternal age from 25 to 45 years. Other dominant mutations show similar tendencies but with much less clear differences. The human eggs may be different because new egg cells are not formed in the female babies after birth; the oogenesis is almost complete in the newborn. Nevertheless, some age differences are still expected.

Chromosomal aberrations (trisomy) in the eggs may increase, however, from 1/2300 at age 20 to 1/46 after 45, probably because of the prolonged meiotic dictyotene stage (diakinesis). Some of the eggs complete meiosis before each ovulation, a period extending over 30–40 years. Trisomy in sperm is much less common, partly because it is the product of new divisions, partly because the disomic sperm may be at a disadvantage in competition for fertilization. A normal human ejaculate may contain 25–40 million sperm cells. The increase of mitochondrial mutation rate by aging is equivocal. Accumulation of mutations by aging is organ-specific in mice. ►mutation rate, ►gonads, ►Apert syndrome, ►syndactyly, ►gametogenesis, ►trisomy, ►longevity; Dollé MET et al 2002 Nucleic Acids Res 30:545.

Age Correlation between Mates: Much higher in consanguineous marriages than in unrelated mates. On an average, age correlation makes first-cousin marriages about twice, second cousin marriages about 1.7 times and third cousin marriages about 1.4 times as frequent as if there would be no correlation between the ages at marriage. Since some of the human hereditary diseases have late onset, the greater the age at marriage may reduce the reproduction of genes with late manifestation also the afflicted persons may not marry or chose not to have children if they marry. ►consanguinity

Age of Onset of Disease: The probability can be calculated: $(1 - \varphi_1)(1 - \varphi_2)\ldots(1 - \varphi_{x-1})$ where φ_x = the probability of onset between ages x and x + 1 the probability of surviving to age x before onset is $l_x = (1 - q_1)(1 - q_2)\ldots(1 - q_{x-1})$ where q_x = the probability of dying at age x before the onset of the condition. ►aging

Age of Parents and Secondary Sex Ratio: Slightly decreasing from 0.517 to 0.516 at parental age group 15–19 to 0.512–0.511 at parental age 45–49. Based on very large samples examined, the age gap between parents does not affect significantly the sex ratio. ►sex ratio

Age-Specific Birth and Death Rates: The probability that an individual of a certain age dies (or gives birth) within the following year is determined by population projection matrices. The numbers of giving birth and death rates in a time interval can be determined by 1-B/N for birth per women extracted from available census figures. One such study in (1966) found that among women in the age group of 15–30 and 30–45 the mean number of children born per women was 1.37 and 0.465, respectively. The studies found that the average survival of age groups 0–15, 15–30 and 30–45 were 0.992, 0.988, and 0.964, respectively. Thus, if one takes a sample of 30 woman of age group 0–15 they will give birth to 30 × 1.37 = 41.1 children. In the age group 30–45, dealing with 20 human females, the prediction will be 20 × 0.465 = 9.3, etc. Similarly, the survivors expected in the age group 0–15 will be 40 × 0.992 = 39.68, in the age group 15–30 the expectation is 30 × 0.988 = 29.64, by the end of the respective periods, etc. The natural logarithm of the annual growth rate is called the *intrinsic rate of natural increase of the population*, and it means that once a stable equilibrium is reached for the various age groups it will increase by this intrinsic rate per year. Example: if the population growth at equilibrium at 15 years cycles is 1.307 then the annual $r = ln(1.307)^{1/15} \cong 0.0178$. The age-specific birth and death rates and *r* must be determined for each population because considerable variations may exist from time to time even in the same group, depending on cultural and economic conditions. A statistical survey indicates that women with later onset of menopause live longer. At the present period the estimated maximal human life span is about 120 years. ►human population growth, ►menopause, ►longevity, ►mortality; Bongaarts J, Feeney G 2003 Proc Natl Acad Sci USA 100:13127.

Agent Orange ($Cl_3C_6H_2OCH_2COOH$): Herbicide containing mainly the synthetic auxin 2,4,5-trichlorophenoxy acetic acid (2,4,5-T). It had been used as a defoliating agent and brush killer. The LD_{50} of 2,4,5-T for mammals is 500 mg/kg, however, there are reports of much lower doses of high toxicity particularly at subcutaneous injection. It is frequently contaminated by dioxin, a carcinogen. The symptoms of Agent Orange exposure can be anorexia, hepatotoxicity, chloracne, gastric ulcers, porphyrinuria, porphyria, teratogenesis, leukemia, etc. Genes in the plasmids derived from *Pseudomonas ceparia* may degrade 2,4,5-T. ►LD_{50}, ►anorexia, ►hepatotoxicity, ►acne, ►chloracne, ►ulcer, ►porphyria, ►teratogenesis; Ngo AD et al 2006 Int J Epidemiol 35:1220.

AGGA Box: An upstream transcriptional regulatory site. ►transcription factors, ►promoter

Agglutination: Also known as clumping occurs when two different blood types are mixed or when bacteria are exposed to specific antisera. The basis of this phenomenon is a component of the complement on the antibody ($C1_q$) protein that binds to the Fc region of the IgG heavy chain and that is followed by a change in conformation of the antibody. The binding of the epitope to the antibody triggers this process. ►immunoglobulins, ►antibody, ►epitope, ►complement

Agglutinin: An antibody that causes agglutination of cognate antigen. ►abrin

A

Aggrecan: A chondroitin sulfate proteoglycan of the cartilage (Schwartz NB et al 1999 Progr Nucleic Acid Res Mol Biol 62:177).

Aggrecanase: ►arthritis

Aggregation: Aggregation of proteins/fragments of proteins may impair the ubiquitin-proteasome degradatory system. ►ubiquitin

Aggregation Chimera: Produced in vitro by the assembly of genotypically different early (8-cell) embryonic cells. ►chimera, ►allophenic, ►multiparental

Aggregation, Familial: The increased incidence of genetically determined traits among relatives, e.g., among natural children and parents compared with unrelated adoptive children. ►heritability, ►recurrence risk

Aggregulon: A protein complex involved in activation and repression of genes; the term re-glomerate was used in the same sense.

Aggresome: An aggregate sink of insoluble misfolded proteins in the endoplasmic reticulum or close to the microtubule organizing center (MTOC) containing chaperones, proteasome and proteasome activator complexes. Some viruses generate aggresomes-like structures for replication. These virus factories are assembled in the vicinity of MTOCs and recruit vimentin, chaperones, ubiquitin and mitochondria similarly to regular aggresomes. Some viruses form nuclear aggresomes others replicate in cytoplasmic aggresomes. Cells with aggresomes can undergo normal mitosis. The aggregated proteins are asymmetrically distributed to one of the eukaryotic daughter cells, leaving the other daughter (the one that divides further) free of accumulated protein damage (Rujano MA et al 2006 PloS Biol 4:e417). ►endoplasmic reticulum, ►proteasome, ►chaperone, ►ataxin, ►virioplasm, ►autophagy; Kopito RR 2000 Trends Cell Biol 10:524; Kolodziejeska KE et al 2005 Proc Natl Acad Sci USA 102:4854; Wileman T 2006 Science 312:875.

Aggression: A behavioral trait with great variance in animal and human populations; it may be an expression of innate self-assertion, frustration or a response to antisocial behavior encountered. It may be the consequence of affective disorders and mental illness (paranoia). Evolutionists attribute aggression to the means of survival in the struggle for life, and it is observable among the majority of animals. Accordingly, in subhuman beings it is instinctive and largely depends on the species concerned. Among humans, it has an animal component but it is determined also by the ethical and cultural factors of the individual and the standards of the population. While animals are not credited with conscientious value judgments, in human societies, the moral, ethical, religious and cultural principles may predominate. All normal human ethnic groups appear to have a condemning attitude toward violence. Yet mainly humans display violent aggression within species. It has been suggested that the human species lack the ability of submission, a widely common ability among other mammals. In the male, vole antidiuretic hormone (vasopressin) may be responsible for aggression. The genetic basis of aggressive behavior is generally not understood although it is known that a deficiency, e.g., in hypoxanthine-guanine phosphoribosyl transferase may result in hostile and self-mutilating behavior. The major problem is concerned with the large non-biological but cultural component of aggression. Unfortunately, human societies treat the cultural problem with double standards: killing and violent behavior is condemned yet major religions approve patriotic or holy wars with the weapons of mass destruction. The questions remain unsettled whether capital punishment is appropriate for killers, is induced abortion an act of aggression, is euthanasia a merciful act or just another form of taking life? To what extent are criminals predestined by their genetic endowment to aggression and how much is the role of the social environment, and the free will? Obviously, some of the answers are beyond the scope of genetics. Mice deficient in α-calcium-calmodulin kinase II displayed reduced levels of serotonin and aggressive behavior. Mice with knocked-out adenosine receptor ($A_{2a}R$) display high blood pressure and aggressiveness. ►behavior genetics, ►submission signal, ►ethics, ►morality, ►instinct, ►Lesch-Nyhan syndrome, ►nitric oxide, ►calmodulin, ►serotonin, ►behavior in humans, ►personality, ►mental illness, ►paranoia, ►adenosine receptors, ►antidiuretic hormone.

Aggressiveness: Aggressiveness of a plant pathogen is measured by the evocation of a disease phenotype, depending on the genotype of the pathogen, that of the host and environmental factors.

Aging: An exponential increase in mortality as a function of time or cell divisions. Some type of irreversible alterations in the DNA may determine aging. In older cells, the chromosomal telomeres are shortened. Cloning by nuclear transfer can reverse this cellular aging (Hayflick limit), yet the aging pattern of the nuclear donor cell lines is genetically determined and it is conserved by nuclear transfer (Clark AJ et al 2003 Nature Cell Biol 5:535). In skeletal muscle stem cells, regeneration is impaired due to loss of Notch signaling. In liver cells, the decline is due to a complex of C/EBP and Brahma (chromatin remodeling factor). In aged mouse progenitor cells young serum restored the aforementioned functions (Conboy IM et al 2005 Nature [Lond] 433:760). In the aging heart tissue of the mouse there is a stochastic down-regulation of

gene expression compared to young hearts (Bahar R et al 2006 Nature [Lond] 441:1011).

The frequency of nondisjunction dramatically increases by age, e.g., the incidence of Down syndrome may increase 200 fold in the offspring of just pre-menopausal mothers. The autosomal recessive Werner syndrome (gene frequency 1 to 5×10^{-3}) involves premature aging (graying of hair, atrophy of skin, osteoporosis, decreased libido, and increased risk of cancer) is characterized also by non-ketotic hyperglycinemia. Progeria (Hutchinson-Gilford syndrome), another autosomal recessive trait, also causes very early senescence. The Rothmund-Thomson, Cockayne, and Down syndromes, trichothiodystrophy and ataxia telangiectasia, all involved with defects in maintaining DNA integrity, display progeroid symptoms (Hasty P et al 2003 Science 299:1355). Severe mutation in the xeroderma pigmentosum F gene (*XPF)* can lead to profound crosslinking sensitivity and progeroid symptoms. This gene encodes an endonuclease, similar to that encoded by RAD1 in yeast. Expression data from XPF–ERCC1-deficient mice indicate increased cell death and anti-oxidant defenses, a shift towards anabolism and reduced growth hormone/insulin-like growth factor 1 (IGF1) signaling (Niedernhofer LJ et al 2006 Nature [Lond] 444:1038).

Aging has been attributed to defects of the immune system and to diminished activity of superoxide dismutase, an enzyme normally destroying the highly reactive radicals that arise due to irradiation and aerobic metabolism. During aging of healthy individuals, the rate of loss or organ function is variable but with some exceptions (endocrine, thermoregulatory and gastrointestinal systems, which lose faster) it is generally between 0 to 2% annually (Sehl ME, Yates FE 2001 J Geront A Biol Sci Med Sci 56:B198). Aging increases the potentials for cancer by some partly understood processes (Finkel T et al 2007 Nature [Lond] 448:767)

It has been suggested that aging is the result of degenerative changes in the mitochondria, the formation of aberrant DNA circles. Recent information fails to support increased point mutation rate in the control region of cultured fibroblast mitochondrial DNA among normal individuals or persons with neurodegenerative diseases (Chinnery PF et al 2001 Am J Hum Genet 68:529). Defective mitochondrial DNA polymerase γ results in premature aging in mice (Trifunovic A et al 2004 Nature [Lond] 429:417). It seems that premature aging in mutable mtDNA is caused by the mutator activity without affecting the production of ROS, reactive oxygen species (Trifunovic A et al 2005 Proc Natl Acad Sci USA 102:17993). Aging mitochondria frequently show deletions (Bodyak N et al 2001 Hum Mol Biol 10:17). Some genes are silenced by methylation and others are activated by demethylation during aging. By-products of oxidative phosphorylation, hydrogen peroxide and superoxide may accumulate during senescence. Over-expression of catalase in the mitochondria of transgenic mice extended life span (Schriner SE et al 2005 Science 308:1909). Aging causes primarily functional losses in the neurons rather than large-scale losses of the neurons. Atrophy, decrease of receptors, accumulation of fluorescent pigments and cytoskeletal abnormalities in the brain occur in aging mammals (see Fig. A35).

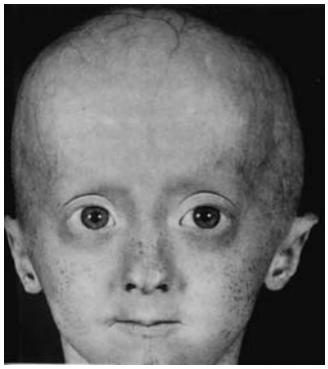

Figure A35. Progeria. (From Bergsma, D. ed. 1973 Birth Defects. Atlas and Compendium. By permission of the March of Dimes Foundation)

Microarray hybridization of aging neocortex and cerebellar tissues of mouse, involving (6347) genes, indicated inflammatory responses, oxidative stress and reduced neurotrophic support. Caloric limitations retarded some of the symptoms by decreasing glucose and insulin-like growth factor level in the plasma (Longo VD, Finch CE 2003 Science 299:1342). Caloric restriction limits aging, probably by reducing oxidative stress and promotes proliferation of mitochondria through a peroxisome proliferation-activated receptor coactivator 1α signaling (López-Lluch G et al 2006 Proc Natl Acad Sci USA 103:1768). Reduced body temperature in mice also increased life span (Conti B et al 2006 Science 314:825). Insulin/insulin-like growth factor signaling promotes growth, energy storage and shorten life cycle. Transcription factor FOXO (regulator of pro-apoptotic and cell cycle genes) and June-N-terminal kinase (JNK, a stress factor) may prolong life span (Wang MC et al 2005 Cell 201:115). Mouse with 5-adenylylcyclase knocked out (*AC5* KO) is resistant to cardiac stress and have increased median lifespan of 30%. *AC5* KO mice are protected from reduced bone density and susceptibility to fractures of aging. Old *AC5* KO mice are also protected from aging-induced cardiomyopathy, e.g., hypertrophy, apoptosis, fibrosis, and reduced cardiac function. Significant activation of the Raf/MEK/ERK

A

signaling pathway and upregulation of cell protective molecules, including superoxide dismutase were detected. Fibroblasts isolated from *AC5* KO mice exhibited ERK-dependent resistance to oxidative stress (Yan L et al 2007 Cell 130:247).

An analysis of gene expression of humans indicates that a set of genes display reduced expression after age 40. These genes involve synaptic plasticity, vesicular transport and mitochondrial function. In contrast, genes concerned with stress response, anti-oxidation and DNA repair are induced. The promoters are damaged in the aged cortex of the brain due to reduced DNA base excision (Lu T et al 2004 Nature [Lond] 429:883). Aging is not caused by the activation of specific genes rather it is the consequence of decline in maintenance factors and the accumulation of damage (Kirkwood BL 2005 Cell 120:437). Mutations in genes affecting endocrine signaling, stress responses, metabolism and telomeres can increase the life span as well as changes delaying age-related disease pathways (Kenyon C 2005 Cell 120:449). In *Caenorhabditis* superoxide dismutase and catalase reduced aging significantly. This causes delays in mitochondrial replication. The slow replication leaves unprotected the D loop of mtDNA, possibly increasing the chances for deletions and mutations (see Fig. A36).

During normal aging the same lamin A cryptic splice site and histone modifications take place as in Hutchinson-Gilford progeria (Scaffidi P, Misteli T 2006 Science 312:1059). Anticonvulsant drugs (ethosuximide) prolonged life of *Caenorhabditis* (Evason K et al 2005 Science 307:258). Misregulation of mitosis caused by gradual defects in cell cycle control proteins, chromosomal movement, etc. may also be players in aging. Voltage-activated Ca^{2+} influx into the brain neurons is accelerated during aging.

Hereditary premature aging is also known in animals. The mouse autosomal recessive gene *klotho*—encoding β-glucuronidase (Chang Q et al 2005 Science 310:490)—seems to be a regulator of several symptoms of aging and represses insulin-like growth factor (IGF) signaling (Kurosu H et al 2005 Science 307:1829). A klotho allele in humans, KL-VS (13q12) potentially increases the susceptibility to coronary artery disease (Arking DE et al 2003 Am J Hum Genet 72:1154). Klotho regulates the transient receptor potential ion channel (TRPV5) by hydrolyzing extracellular sugar residues on TRPV5 and regulates calcium concentration in the blood. Calcium deposits can cause arterial disease. Klotho converts the fibroblast growth factor to a kidney special FGF23 receptor (Urakawa I et al 2006 Nature [Lond] 444:770).

The product of this gene shares sequence similarities with β-glucosidase proteins. In *klotho*$^{-/-}$ mouse the level of μ-calpain is specifically activated and it leads to degradation of the cytoskeletal protein α_{II}-spectrin (Manya H et al 2002 J Biol Chem 277:35503). In *Caenorhabditis*, mutations are known that in combination may extend the life of the nematodes through two different pathways up to five fold. Mutation in succinate dehydrogenase cytochrome b causes oxidative stress and premature aging in the nematodes. In *Drosophila* the *mth* (*methuselah*) mutant line, encoding apparently a protein with homology to GTP-binding proteins with seven-transmembrane domain receptors, extends the life by about 1/3.

In yeast, activated GTPase (RAS), inactivation of the *LAG1* gene (encoding a membrane-spanning protein) and the *SIR* silencing complex extend life span (Hekimi S, Guarente L 2003 Science 299:1351). Aging in mammals seems to be associated with aging of the lymphocytes and their function. DNA microarrays can detect gene expression changes during development/aging and it seems that the processes show great similarities between *Caenorhabditis* and *Drosophila* (McCarroll SA et al 2004 Nature Genet 36:197). The telomerase enzyme has also been implicated in aging. Since aging usually occurs after the reproductive period, it is no longer the object of natural selection (antagonistic pleiotropy). Population geneticists entertain two genetic mechanisms for aging: the accumulation of deleterious mutations and increase in antagonistic pleiotropy among gene loci. Some population display *altruistic aging*, i.e., aging becomes beneficial for the younger groups of individuals. In rodents, calorie restricted (CR) diet has substantial anti-aging effect. In yeast, the replicative lifespan is increased by deleting *TOR*, *SCH9* (limiting caloric uptake) and deletion of *FOB1* genes (limiting ribosomal DNA replication). Several other deletions are also increasing lifespan of yeast (Kaeberlein M et al 2005 Science 310:1193). Mammalian cell survival is promoted by caloric restriction through the induction of the SIRT1 deacetylase. SIRT1 (Sir2) deacetylates the repair factor Ku70, which moves away the pro-apoptotic Bax protein from the mitochondria and thus inhibits apoptosis, which is associated with aging. Mitochondrial mutations due to proof-reading deficiency of DNA polymerase γ caused various mutations in mouse mitochondria but only an increase in apoptotic markers furthered aging (Kujoth GC et al 2005 Science 309:481).

Insulin and insulin-like growth factor attenuate the SIRT effect (Cohen HY et al 2004 Science 305:390). Aging has been attributed also to the gradual loss of the telomeric DNA repeats. It has been suggested that the secretion of inflammatory cytokines may be a contributing factor. The life expectancy in years in the USA changed from 47 to 76 from (1900) to 2000.

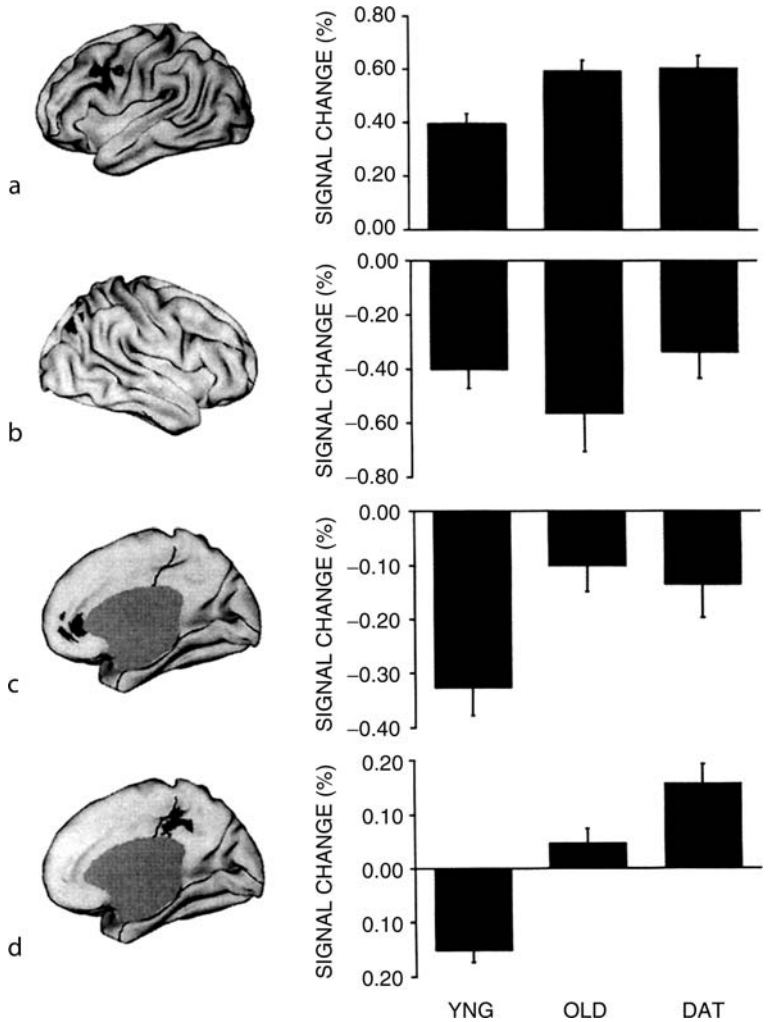

Figure A36. Brain activity in aging and Alzheimer disease. The brain was scanned by magnetic resonance imaging in four angles of the cortex. (a) left frontal, (b) right lateral parietal, (c) medial frontal and (d) medial parietal/posterior cingulate. The relative activity in each region is shown by bars and standard error for young adults (yng), healthy old (old) and older adults with early-stage alzheimer type dementia (dat). Noteworthy is that young adults deactivate specific brain regions during active task performance. The deactivated regions overlap with those that show reduced resting metabolic activity in aging and dementia. The most critical difference between healthy and alzheimer dementia is shown at (d). (Courtesy of Lustig C et al 2003 Proc Natl Acad Sci USA 100:14504 by permission. Copyright National Academy of Sciences USA, 2003). In mice the metaproteinase Zmpste24 is essential for lamin A of the nuclear envelope and its deficiency results in senescence by activation of p53 (Varela I et al 2005 Nature [Lond] 437:564)

In Sweden, the maximum life expectancy increase between (1861) and (1999) was 0.44 year per decade. The heritability of aging based on twins of humans is about or less than 0.35. The evidence for the role of mitochondria in aging has been questioned. Age-associated decline of cognitive abilities seem to be correlated to neuronal atrophy in the subcortical regions of the brain and the process may be prevented by neurotrophin or neurotrophin gene therapy. Somatic transfer of CREB gene into the hippocampal region of the brain of 15 months old rats reduced memory loss (Mouravlev A et al 2006 Proc Natl Acad Sci USA 103:4750). ►senescence, ►Hayflick's limit, ►longevity, ►killer plasmids, ►chromosome breakage, ►DNA repair, ►Werner syndrome, ►progeria, ►Hutchinson-Gilford syndrome, ►Cockayne syndrome, ►Bloom syndrome, ►Alzheimer disease, ►xeroderma pigmentosum, ►ERCC, ►longevity, ►superoxide dismutase, ►ion channels, ►RAS, ►lymphocytes, ►telomere, ►telomerase, ►cytokines, ►selection, ►silencer, ►RAS, ►mating type determination in yeast, ►mortality, ►apoptosis,

A

►heritability, ►pleiotropy, ►ROS, ►disposable soma, ►MARS model, ►mitochondrial mutations, ►substantia nigra, ►insulin, ►Ku70, ►sirtuin, ►Bax, ►control region of mitochondrial DNA, ►estradiol, ►neurotrophins, ►gene therapy, ►lamins, ►p53, ►CDC42, ►apoptosis, ►phenoptosis, ►CREB, ►brain human; Cortopassi GA, Wong A 1999 Biochim Biophys Acta 1410:183; Jazwinski SM 2000 Trends Genet 16:506; Kenyon C 2001 Cell 105:165; Finch CE, Rivkun G 2001 Annu Rev Genomics Hum Genet 2:435; Pletcher SD et al 2002 Current Biol 12:712; Holzenberger M et al 2003 Nature [Lond] 421:182; Longo VD et al 2005 Nature Rev Genet 6:866; Wallace DC 2005 Annu Rev Genet 39:359; factors and theories of aging review: Hekimi S 2006 Nature Genet 38:985; genomic resources of human aging: http://www.senescence.info/, microarray resources on aging: http://gan.usc.edu.

Aglycon: Protein or lipid linked to a polysaccharide.

α-1,4-Glucosidase Deficiency: ►acid maltase

Agonadism, Familial: Absence of gonadal tissue; usually part of a syndrome. ►azoospermia

Agonescence: Telomere-shortening dependent cell senescence and may be abrogated by telomerase. ►senescence

Agonist: Activates a receptor. *Inverse agonists* are antagonists of overexpressed receptors.

Agonistic Behavior: Combative behavior. ►aggression

Agoraphobia: A psychological disorder of fear from certain conditions or venues.

Agouti: Alternating light and dark bands on individual hairs of the fur in mammals such as mouse, rat, rabbit (see Fig. A37). The genes *agouti* and *extension* determine the relative amounts of eumelanin (brown-black) and phaeomelanin (yellow-red) pigments. *Extension* encodes the receptor of the melanocyte-stimulating hormone (MSH) and *agouti* is a signal sequence in the hair follicle, inhibiting eumelanin production and the melanocortin receptor, an MSH receptor. Agouti has been cloned and sequenced; it contains 5 exons but two of them are not translated. The secreted protein products have 131 amino acid residues. The alleles that produce increased amounts of pheomelanin makes the mice more prone to late-onset obesity and diabetes. An agouti-related protein (AGRP), a neuropeptide, may increase several fold in obese mice. A^y and A^{vy} increase the liability to neoplasias and others cause embryonic lethality. ►pigmentation of animals, melanin, ►melanocyte-stimulating hormone, ►melanocortin, ►ghrelin; Dinulescu D, Cone RD 2000 J Biol Chem 275:6695.

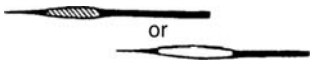

Figure A37. Agouti hair pattern

Agretope: The part of an antigen that interacts with a desetope (antigen-binding site) of a MHC (major histocompatibility) molecule. ►desetope, ►epitope, ►histotop, ►antigen

Agricultural Measures: ►measurement units

1 hectare (ha) = 10 m^4 = 2.47109 acres; 1 acre = 0.40469 hectare; 1 square kilometer = 100 hectares; 1 square mile = 640 acres = 259 ha.

1 bushel (bu) = 35.2393 liters = [approximate values]; *wheat* = 60 lb = 27.215 kg, *paddy rice* = 45 lb = 20.412 kg, *corn* (maize) = 56 lb = 25.401 kg, *soybeans* = 60 lb = 27.215 kg, *rye* = 56 lb = 25.401 kg, *sorghum* 56 lb = 25.401 kg, *barley* = 48 lb = 21.772 kg, *potatoes* = 60 lb = 27.215 kg, *oats* = 32 lb = 14.515 kg, *apples* = 48 lb = 21.772 kg.

1 box of *oranges* (California, Arizona) = 77 lb = 34.926 kg, (Florida, Texas, Louisiana) = 90 lb = 40.823 kg, 1 box of *lemons* = 79 lb = 35.843 kg.

1 bale *of cotton* (U.S.) = 480 lb = 217.723 kg.

100 kg per hectare = 1.49 bushel (60 lb) per acre; 1 bushel (60 lb) per acre = 67.3 kg per hectare.

1 metric ton = 0.98421 long tons = 1.10231 short tons = 10 metric quintals.

Agricultural Productivity: Affected by genetic improvement of plants and animals and improved husbanding and cultural practices. Between the years (1951) and (1980) the overall plant productivity in the USA increased 166% and that of animals to 144%. The yield of maize after the introduction of hybrids increased to about 500%. ►heterosis, ►QTL

Agrin: A natural glycoprotein (200 kDa) causing the aggregation of acetylcholine receptors on muscle cells in vitro and in vivo is used for the formation of neuromuscular junctions and the T lymphocytes. The process also requires a muscle-specific protein kinase (MuSK). α3Na^+/K^+-ATPase is the neural receptor for agrin (Hilgenberg, LGW et al. 2006 Cell 125:359). Agrin deficient mutant mouse is inviable. Agrin may restore function in muscular dystrophies caused by mutation in laminin. ►acetylcholine receptors, ►laminin, ►neuregulins; Trautmann A, Vivier E 2001 Science 292:1667; Moll J et al 2001 Nature [Lond] 413:302; Misgeld T et al 2005 Proc Natl Acad Sci USA 102:11088.

Agrobacterial Vectors: ►cointegrate vectors, ►binary vectors, ►transcriptional gene fusion vector, ►translational gene fusion vectors

Agrobacterium Mini-Plasmid: Carries the T-DNA, including its borders, but it is free of other segments, including the *vir* genes. *Agrobacterium tumefaciens*, ►T-DNA

Agrobacterium rhizogenes: A bacterium closely related to *A. tumefaciens*. It induces hairy roots rather than crown gall on the host plants. The genes responsible for the formation of hairy roots reside in the *Ri* plasmid. The hairy root tissues, unlike crown gall, readily regenerate into plants. The *Ri* plasmid has been used similarly to the *Ti* plasmid to construct plant transformation vectors. In *Nicotiana glauca* DNA sequences (*Ngrol*) homologous to the left segment of the T-DNA of the *Ri* plasmid have been detected. This observation indicates horizontal interspecific gene transfer. (►*Agrobacterium tumefaciens*, ►*Ri* ►plasmid, ►crown gall MoriguchiK et al 2001 J Mol Biol 307:771).

Agrobacterium tumefaciens: A soil born plant pathogenic microorganism of the family of *Rhizbiaceae*. It is responsible for the crown gall disease (tumor) of the majority of wounded dicotyledonous plants and it also infects a few monocots (*Liliaceae, Amaryllidaceae*). Several of its characteristics are similar to *Rhizobium, Bradyrhizobium* and *Phyllobacterium* species (see Fig. A38). The pathogenicity is coded in genes within the T-DNA of its Ti (tumor-inducing plasmid). T-DNA containing plasmids are the most important transformation vectors of plants. The T-DNA (transferred DNA) is an about 21 kb segment of the Ti plasmid with two direct repeat flanks bordering the oncogenes (responsible for tumorigenesis in the wild type plasmids), and some of the opine genes. Molecular biologists most widely use the Agrobacterial strains A6 and C58, containing octopine and nopaline encoding Ti plasmids, respectively. Certain *Agrobacteria* strains have *limited host range* (LHR) caused by an altered *virA* gene in the Ti plasmid. The *supervirulent* strains on the other hand overproduce the VirG protein. The infection of some species of plants is limited. Inhibition of purine synthesis leads to supersensitivity to infection in yeast, *Arabidopsis,* tobacco and *Ageratum* plants (Roberts RL et al 2003 Proc Natl Acad Sci USA 100:6634).

Figure A38. Crown gall

For the transfer of the T-DNA to other cells, including plant cells, requires the formation of a conjugation tube (pilus) controlled by virulence genes *virA, virG, virB1* to *virB1*1. Altogether about 12 genes are involved in the transfer. *Agrobacterium tumefaciens* C58 has one ~2.1-Mb linear chromosome and three circular DNA plasmids (~2.8 Mb, ~0.54 Mb, ~0.21 Mb). Its total genome is ~5.67 Mb. The total number of assigned protein-coding genes is 1286, 1715, 333 and 141, respectively. The T-DNA is located in the 0.21 Mb plasmid. *Agrobacteria* can transfer DNA also to yeast and some other fungi. The T-DNA can integrate from binary vectors also into human HeLa cells (Kunik T et al 2001 Proc Natl Acad Sci USA 98:1871). Transferring the T-DNA into plant symbiotic bacteria such as *Rhizobia* enables these bacteria to transfer genes into plants (Broothaerts W et al 2005 Nature [Lond] 433:629). (►Ti plasmid, ►T-DNA, ►virulence genes of *Agrobacterium*, ►transformation [plants], ►host–pathogen relation, ►BIBAC, ►transformation genetic; Koncz C et al 1992 Methods in Arabidopsis Research, In: Koncz C et al (eds) World Scientific Publ. Co., Singapore, p. 284; Tzfira T et al 2000 Annu Rev Microbiol 54:187; Kunik T et al 2001 Proc Natl Acad USA 98:1871; Wood DW et al 2001 Science 294:2317).

Agrocin 84: The non-plant-pathogenic *Agrobacterium radiobacter* synthesizes this compound and it is taken up by *A. tumefaciens* carrying agrocinopin. Agrocin associated with a toxin moiety is toxic to *A. tumefaciens* because it inhibits leucyl-tRNA synthethase. ►*Agrobacterium tumefaciens*, ►crown gall; Reader JS et al 2005 Science 309:1533; Kim J-G et al 2006 Proc Natl Acad Sci USA 103:8846.

Agrocinopine: A phosphorylated sugar, an opine, produced in octopine plasmids from mannopine by the enzyme agrocinopine synthase. ►*Agrobacterium*, ►opines, ►octopine

Agroinfection: A method of plant transformation. More than one genome of the double-stranded DNA of Cauliflower Mosaic Virus is inserted in tandem within the T-DNA of *Agrobacterium tumefaciens*. Such a construction permits the escape of the viral DNA from the bacterial plasmid once it was introduced into plants. Gemini viruses can be introduced into plants in a similar way. ►cauliflower mosaic virus, ►geminiviruses, ►transformation genetic; Grimsley N et al 1989 Mol Gen Genet 217:309.

Agropine: Bicyclic phosphorylated sugar derivative of glutamic acid; it is synthesized by *Agrobacterium* strain Ach5. opines.

A

Agropyron (x = 7): A genus of grasses; their chromosomes are homoeologous to that of several species within the genus of wheat and can be substituted to introduce agronomically useful genes (e.g., disease resistance). Some hybrids are known as perennial wheat, a forage crop. ►chromosome substitution, ►alien transfer, ►homoeologous chromosomes

αGT (glucosyltransferase uridine 5′-diphosphate galactose β-D galactosyl-1,4-*N*-acetyl-D-glucosaminide α(1-3)galactosyltransferase, E.C.2.4.1.151): Synthesizes the carbohydrate epitope Galα 1-3Galβ1-4GlcNAc-R, which reacts with natural antibodies forming a barrier to xenotransplantation. Murine bone marrow cells transgenic for αGT may overcome the production of xenoreactive antibodies. This principle may facilitate the development of techniques to facilitate organ transfer between animals and humans. ►epitope, ►xenograft, ►transgenic, ►antibodies, ►epitope

AGRP (agouti-related protein): ►agouti, ►obesity

α-Helix: A secondary structure of polypeptides with maximal intrachain hydrogen bonding. A most common conformation, when after 5.4 Å high, five right turns of an amino acid chain, every 18th amino acids occupy the same line as the first. ►pitch, ►protein structure

Ahonen Blood Group: A rare type, distinct from ABO, MNS, P, Rh, Duffy, Kidd and Dembrock. ►blood groups

AHR: ►arylhydrocarbon receptor

AIB: A steroid receptor implicated in breast cancer. ►breast cancer, ►steroid hormones; Anzick SL et al 1997 Science 277:965.

Aicardi-Goutières Syndrome (AGS1 3p21; AGS2 13q14.3, AGS3 11q13.2, AGS4 19p13.13): A heterogeneous disease, a progressive encephalopathy with calcification of the basal ganglia, excessive number of lymphocytes in the cerebrospinal fluid (lymphocytosis), brain atrophy and early death after birth. Elevated level of interferon α in the brain fluids—in the absence of infection—is a marker for the disorder. AGS1 is caused by mutation of TREX1, a DNA repair exonuclease. AGS2 is due to mutation of endoribonuclease H β-subunit. AGS3 involves mutation in the C subunit of ribonuclease H and AGS4 is mutant in ribonuclease H A subunit. ►ribonuclease H; Crow YJ et al 2000 Am J Hum Genet 67:213; Crow YH et al 2006 Nature Genet 38:910.

AICD: ►memory immunological

AID: Artificial insemination by donor. artificial insemination, ►AIH, ►ART, ►acquired immunodeficiency

AID (activation-induced deaminase): The main cause of somatic hypermutation (10^{-3} to 10^{-4} per base) and its deficiency obliterates somatic hypermutation and class switching in the development of the secondary repertory of antibody molecules, the last step in the generation of functional antibodies. The main targets of AID are cytidines in single-stranded DNA or in double-stranded DNA during transcription. It erases methyl marks during development. Although immunoglobulins are the main targets of AID, other genes and bases besides C are also affected primarily in a binding motif of the enhancer/promoter region (Kotani A et al 2005 Proc Natl Acad Sci USA 102:4506). Protein kinase A (PKA) mediated phosphorylation is a critical factor in B cell antibody diversification (Basu U et al 2005 Nature [Lond] 438:508). ►immunoglobulins, ►antibody, ►antibody gene switching, ►class switching, ►immune system, ►epigenetics, ►APOBEC, ►UNG; Martin A et al 2002 Nature [Lond] 415:802; Conticello SG et al 2005 Mol Biol Evol 22:367)

AIDS: ►acquired immunodeficiency syndrome

AIF (apoptosis-inducing factor): A mammalian mitochondrial flavoprotein (M_r 57K) with homology to prokaryotic oxidoreductases. The encoding gene was located to human chromosome Xq25-q26. From purified mitochondria AIF liberates—by increasing membrane permeability—cytochrome-c and caspase-9 and when injected into the nuclei it causes DNA breakage and thus promotes apoptosis. ►apoptosis, ►APAF, ►mitochondrial diseases in humans, ►mtPTP, ►CAD, ►ACINUS, ►L-DNase II; Wang X et al 2002 Science 298:1587.

AIG (anchorage independent growth): Normal mammalian cells grow in monolayer anchored to a solid surface. Tumor cells grow independently of anchorage. ►anchorage, ►tumor, ►cancer, ►CATR1, ►oncogenes

AIH: Artificial insemination by husband. AID, ►artificial insemination, ►ART

AIMS: *Arabidopsis* information database at Michigan State University. ►*Arabidopsis thaliana*

AIR: Mitotic kinase acting on histone.

AIRE: An autoimmune regulatory protein of ~545 amino acids; when defective it is responsible for the autoimmune polyendocrine syndrome. ►APECED, ►autoimmune disease, ►autoimmune polyendocrinopathy

Air Pollution: A probable cause of alterations in the genetic material. It appears that expansion of tandem repeats in the DNA increased about twofold by particulate material in the air compared to the gaseous material (Somers CM et al 2004 Science 304:1008). ►environmental mutagens, ►tandem repeat, ►unequal crossing-over

AKAPs (A kinase anchoring protein): Cytoplasmic proteins, binding to cyclic adenosine 3′,5′ monophosphate (cAMP-dependent protein kinase PKA, calcineurin [phosphatase 2B]) and protein kinase C [PKC] and appears to have a regulatory role as a scaffold for the cellular signaling system. signal transduction, ►T cell, ►condensin; Colledge M, Scott JD 1999 Trends Cell Biol 9:216.

AKI: Adenylate kinase.

A-Kinases: cAMP-dependent protein phosphorylating enzymes; the phosphorylation is dependent on sufficiently high level of cAMP. ►cAMP

Akinesis (akinesia): Lack of movement or poor movement or paralysis. Several types of fetal akinesia are parts of several syndromes. ►Pena-Shokeir syndrome

AKR Mice: A long-inbred albino, specially selected strain of the animals containing the genes *Akv-1* and *Akv-2* that code for ecotropic retroviruses causing thymic lymphosarcoma (leukemia). Ecotropic viruses replicate only in cells from what they have been isolated originally. AKR strains have relatively short life span, are sensitive to ionizing radiation and highly susceptible to the carcinogenic effect, but resistant to the teratogenic effect of ethylnitrosourea. ►replicase, ►ecotropic retrovirus, ►ENU

AKT Oncogene (PKB, serine/threonine protein kinase B): Isolated from thymomas (cancer of the thymus) of AKR mice transformed by an ecotropic virus. In the mouse genome, it is located in chromosome 12. A homolog of it is found in human chromosome 14q32.3 and it is frequently associated with chromosomal breakage. The Akt protein is a threonine/serine protein kinase (protein kinase B/PKB) and targeted by PI3-kinase-generated signals. Akt is involved in the regulation of cellular proliferation/apoptosis, glycogen synthase kinase (GSK3), endothelial nitric oxide synthase and protein synthesis. The interplay of Akt and Tor is frequently observed in cancer progression (Hay N 2005 Cancer Cell 8:179). AKT is activated by loss of PTEN in several types of tumors. Akt is regulated also by an insulin-like growth factor (IGF) and the nerve growth factor (NGF). AKT2 defect results in insulin resistance and diabetes (George S et al 2004 Science 304:1325). Akt is often called a cell survival kinase, activated by phosphoinosite kinase, PIK and down-regulated by the RAS oncoprotein or by a phosphatase. Akt reduces apoptosis by phosphorylating protein BAD and inhibiting Bc*l* and caspase-9 in human cells. AKT inhibits cytochrome C release from mitochondria and thus inhibits apoptosis even when BAX and BAK are inactive (Majewski N et al. 2004 Mol Cell 16:819). The level of Akt1 was found 68% lower in schizophrenia than in normal tissues (Emamian ES et al 2004 Nature Genet 36:131). Akt regulates NF-κB that promotes the expression of anti-apoptotic genes. When Akt phosphorylates Raf the Raf-MEK-ERK signaling pathway is inhibited and cellular proliferation is initiated. The antiapoptotic PDGF also seems to be under Akt influence. TNF-α may or may not be involved through IKK in the regulation of NF-κB. The apoptotic FAS protein synthesis is apparently limited through blocking the FKK protein by Akt. *Akt1* governs mammary epithelial tumor cell (MEC) polarity, migratory directionality and breast cancer onset induced by ErbB2 in vivo (Ju X et al 2007 Proc Natl Acad Sci USA 104:7438). ►AKR, ►insulin-like growth factor, ►nerve growth factor, ►PKB, ►phosphoinositides, ►ecotropic retrovirus, ►apoptosis, ►glycogen, ►hexokinase, ►GSK3, ►mice, ►oncogenes, ►nitric oxide, ►BAD, ►Bcl, ►BAX, ►BAK, ►caspase, ►NK-κB, ►PDGF, ►IKK, ►FKK, ►PDK, ►ERBB1, ►signal transduction, ►TOR, ►epiloia, ►prostate cancer, ►PML, ►Parkinson disease; Datta SR et al 1999 Genes and Development 13:2905; Madrid LV et al 2001 J Biol Chem 276:18934).

ALA: Aminolevulinic acid, a first compound in the synthesis of porphyrins from glycine and succinyl CoA. ►heme

α-Lactose: Milk sugar is converted into allolactose by the β-galactosidase gene of the *Lac* operon of *E. coli* and the latter then becomes the inducer of the operon. ►*Lac* operon

Aladin (AAAS, triple-A syndrome): A neurological disorder resulting in alacrima (lack of tears), achalasia (failure of the smooth muscles to relax), and adrenal insufficiency because of defect in a WD-repeat family of regulatory proteins encoded at 12q13. ►WD-40

Alagille Syndrome: Autosomal dominant (human chromosome 20p11.2) involving obstruction of the bile duct (cholestasis) and jaundice, lung anomalies (pulmonary stenosis), deformed vertebrae, arterial narrowness, deformed iris, altered eye pigmentation, facial anomalies (see Fig. A38), etc. The biochemical defect is in the Notch-ligand, Jagged-1. In some cases translocations or deletions of the region accompany it.

A

Figure A39. Alagille syndrome. By adulthood prominent chin develops in Alagille syndrome

The multiplicity of the symptoms has been considered as a contiguous gene syndrome. The incidence is $\sim 4 \times 10^{-4}$. ►contiguous gene syndrome, ►face/heart defects, ►cholestasis, ►Byler disease, ►BRIC, ►Fallot's tetralogy, ►Notch; Spinner NB et al 2001 Hum Mutat 17:18.

Aland Island Eye Disease: ►albinism ocular

Alanine: L-alanine [$CH_3CH(NH_2)COOH$] is a non-essential amino acid for mammals. The enantiomorph D-alanine may not be metabolized by some organisms and may even inhibit their growth. β-Alanine [$CH_3CH_2CH_2CO_2COOH$] is synthesized by several microorganisms from aspartate but it occurs only in trace amounts in animal tissues, possibly through the action of intestinal microorganisms; γ-butyric acid [$H_2NCH_2CH_2CH_2COOH$] is structurally related. Its dipeptides with histidine are carnosine, homocarnosine and anserine. ►alaninuria, ►alanine aminotransferase, ►carnosinemia

Alanine Aminotransferase (glutamate-pyruvate transaminase, GPT): Autosomal dominant gene (8q24.2-qter) encodes the enzyme that catalyzes the reversible transamination of pyruvate and α-ketoglutarate to alanine. This enzyme exists in cytosolic and mitochondrial forms. ►amino acid metabolism, alaninuria, ►glutamate pyruvate transaminase, ►alanine

Alanine-Scanning Mutagenesis: ►homologue-scanning mutagenesis

Alaninuria (with microcephaly, dwarfism, enamel hypoplasia and diabetes mellitus): The autosomal recessive condition is accompanied by the clinically demonstrable excessive amounts of alanine, pyruvate and lactate in the blood and urine. Both lactate and alanine are derived from pyruvate. ►alanine aminotransferase, ►amino acid metabolism, ►alanine, ►hypoplasia, ►diabetes

Alarmones: Signal molecules (commonly modified nucleotides such as ppGpp) in response to stress. ppGpp interferes with IF2-dependent initiation complex formation, severely inhibits initiation dipeptide formation, and blocks the initiation step of translation. IF2 has the properties of a cellular metabolic sensor and regulator that oscillates between an active GTP-bound form under conditions allowing active protein syntheses and an inactive ppGpp-bound form when there is a shortage of nutrients (Milon P et al. 2006 Proc Natl Acad. Sci USA 103:13962). ►discriminator region, ►IF2

Albers-Schönberg Disease: ►osteopetrosis type II

Albinism: A pigment-free condition in plants and animals (see Fig. A40). The absence of skin and hair pigmentation in mammals is generally determined by homozygosity of recessive genes controlling melanin synthesis. Melanocytes are the cells specialized for melanin synthesis. During embryonal development melanoblasts, precursor cells of melanocytes move to surface areas. Melanin is synthesized in special cytoplasmic organelles, melanosomes.

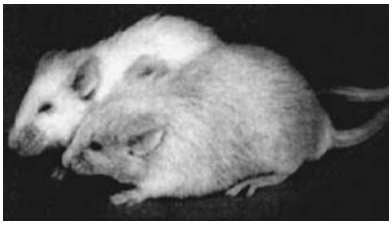

Figure A40. *Tyrosinase* (*Tyr*, chromosome 7–44.0) alleles of mouse (left *c/c*, right *c/c<ch> p/p*). Courtesy of Dr. Paul Szauter, http://www.informatics.jax.org/mgihome/other/citation.shtml)

The precursor of melanin is the amino acid tyrosine and the conversion is catalyzed by the aerobic oxidase, tyrosinase (polyphenol oxydase). In one type of albinism tyrosinase activity in the hair follicle is still present. Albinism may involve the entire melanocyte system of the body or it may be limited to the eye (11q14-q21). In this case, a pigment-specific integral glycoprotein product of the (oculocutaneous) OCA1 gene is specially targeted to the intracellular melanosomes. OCA2 was assigned to 15q11.2-q12. OCA3 is at 6q13-q15. Albinism of the eye may occur in a sectorial manner in females heterozygous for the Xp22.3-p22.2-linked recessive gene (OA1). Albinism of the eye may involve problems of vision, involuntary eye movements (nystagmus), and head nodding. OA2 (Xp11.4-p11–23) males may be partially color blind (protanomalous). Albinism is controlled by numerous single genes.

Figure A41. Cuna Indian Albinos (Courtesy of Dr. C Keeler)

The prevalence of albinism varies from 1/14,000 to 1/60,000 depending on the gene, and the ethnicity of the population; it is generally more frequent among negroids than among caucasoids. Ocular albinism may occur very frequently among some Indian tribes (1/150). Albinism involves hypersensitivity to light and increased susceptibility to some forms of cancer. The absence of hair pigmentation may be locally corrected by gene therapy using the normal tyrosinase gene. Albinism may be a component of complex syndromes and may be associated with deafness, neuropathy and bleeding disorders. Albina condition occurs with very high frequency in progenies of plants exposed to ionizing radiation (see Fig. A41). In plants over 100 genes can cause albinism when mutated. ►Himalayan rabbit, ►piebaldism, ►pigmentation of animals, ►Chédiak-Higashi syndrome, ►Hermansky-Pudlak syndrome, ►xeroderma pigmentosum, ►light-sensitivity diseases, ►color blindness, ►tyrosinase, ►eye color, ►hair color, ►motor proteins, ►oculocutaneous albinism; Toyofuku K et al 2001 Biochem J 355(pt2):259.

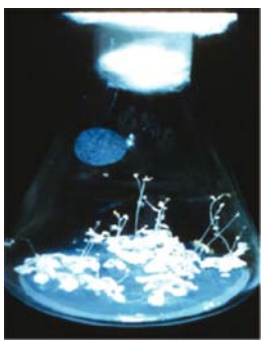

Figure A42. Albina plant

Albino: Animals defective in melanin synthesis. More commonly in plants, *albina* is the designation of leaf-pigment-free individuals (because the Latin word *planta* is of feminine gender).

Albizzin (L-2-amino-ureidopropionic acid): A glutamine analog. ►asparagine synthetase

Albomaculata (or status albomaculatus): A green-yellow-white variegation caused by mutation in extranuclear genes in plants. ►chloroplast genetics

Albright Hereditary Osteodystrophy (pseudohypoparathyroidism, PHP1A, PHP1B, 20q13.2): Autosomal recessive pseudoparathyroidism is based on a defect in a G-protein mutation. The locus actually encodes two G protein subunits, Gs and XLα_s. Gs is expressed from both parents, XLα_s is expressed only from the paternal chromosome. There is a third maternal transcript of the gene that encodes the neurosecretory NESP55 protein. The three transcripts share exons 2 to 11 but have different first exons. The NESP55 coding region is within exon 1 and the rest of the exons remain untranslated. An X-linked dominant form is based on a defect in the parathormone-adenylate cyclase-G_s-protein complex. It displays imprinting. ►hyperparathyroidism, ►parathormone, ►G-protein, ►McCune-Albright syndrome, ►imprinting, ►epigenesis; Bastepe M et al 2005 Nature Genet 37:25.

Albumins: Include different proteins soluble in water and in dilute salt solutions, such as bovine serum albumin (BSA) used in chemical analyses. In the fetal serum of mammals, the predominant protein is the albumin α-fetoprotein, transcribed from two genes in humans, and they have about 35% homology and are immunologically cross-reactive despite their substantial divergence. Both serum albumin and α-fetoprotein, products of the same gene family, are synthesized in the liver and gut. After birth, the production of the latter drops dramatically whereas the former is produced throughout life. Their tissue-specificity of expression resides within 150 bp from the beginning of transcription. The α-fetoprotein gene carries three enhancer elements 6.5, 5 and 2.5 kbp upstream that may increase the level of transcription up to 50-fold. The liver-specificity for the serum albumin gene is controlled by the PE (proximal element), which is most important for promoter activity. It is located between the TATA and CCAAT

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boxes. The distal element (DE I [around −100 base from the initiation of translation] is most important for liver-specificity. There are also DE II [around −116], DE III around about −158]). The PE element (5′-GTTAATGATCTAC-3′) is quite similar to sequences in the promoters of other liver-expressed genes. The PE binding protein is HNF-1 (88 kDa) is also shared by other liver genes, including the hepatitis virus promoter. The binding proteins associated with the DEs do not appear liver-specific inasmuch as they are used by a variety of other genes of ubiquitous expression, or the specificity is modified by so far unknown co-factors. ►serum, ►fetoprotein, ►transcription, ►enhancer, ►promoter, ►TATA box, ►CCAAT box, ►HNF

Alcaptonuria: ►alkaptonuria

Alcohol: An organic molecule formed from hydrocarbons by substituting -OH for H. The simplest representative is ethanol (ethylalcohol, CH_3—CH_2—OH, MW 46.07, boiling point 78.3°C). Ethanol usually contains 5% water; the absolute ethanol is very hygroscopic; for disinfection the 60–80% solutions are most effective. Moderate alcohol consumption may protect against ischemic heart disease. This protection was attributed to modulation of blood lipoproteins, reduced activation of platelets and thrombosis. Protein kinase C(ε) signals may also be involved in the protection at physiological levels of blood alcohol (>10mM). ►ischemia, ►thrombosis, ►protein kinases, ►ethanol

Alcohol Dehydrogenase: ►ADH, ►mutation detection

Alcohol Fermentation: The conversion of sugar into alcohol in the absence of air by glycolysis. ►glycolysis

Alcoholism: A chronic and addictive use of the chemical is a behavioral trait with some hereditary component of the manifestation. Alcoholism may involve fatal or very serious consequences in certain diseases, in pregnancy, and when certain types of medicines or drugs are used. The *fetal alcohol syndrome* includes microcephaly (small head), folded skin at the side of the nose, defective eyelids, upturned nose, etc. In adults, it may cause cirrhosis of the liver leading to further (fatal) complications. The maternal alcohol blocks in the fetus the NMDA glutamate receptors and activates the $GABA_A$ receptors resulting in long-lasting process of neurodegeneration. Unfortunately, no association between alcoholism and any particular gene or chromosomal segment has been firmly established; it is apparently under polygenic control. Alcohol abuse during pregnancy may expose the fetus and the newborn to serious developmental harm (fetal alcohol syndrome, FAS) including physical and mental retardation that may seriously affect lifelong the health and function of the individuals. FAS is an increasingly serious social problem along with other abuses of drugs. About 0.001–0.002 fraction of the children are suffering from it. In mice, the higher alcohol consumption appeared to be associated with defects in the $5\text{-}HT_{1b}$ serotonin receptor and genetic variations (Lys487Glu) of the aldehyde dehydrogenase 1 locus. The (ADH1 and 2) aldehyde dehydrogenases are present in some far-East human populations and may increase the proclivity to alcohol consumption by a factor of 5 to 10. In some other populations low in ADH1 the alcohol consumption is moderate because of the poor tolerance. ADH actually has a protective effect against alcoholism. In *Caenorhabditis,* the neuropeptide Y receptor-like protein allelic variants can account for variations in alcohol tolerance (Davies AG et al 2004 Neuron 42:731). In *Drosophila,* a single inebriation by alcohol may start the development of alcohol tolerance. The tolerance requires the catecholamine octopamine (functional analog of noradrenaline of mammals (see Fig. A43)), and a nuclearly encoded (*Hang*) DNA-binding zinc-finger protein (Scholz H et al 2005 Nature [Lond] 436:845).

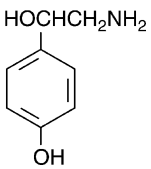

Figure A43. Octopamine

In mice the *Alp1* locus may be responsible for 14% and the *Alcp2* for 18% of the total alcohol preference. Interestingly the former gene is acting only in males and the latter only in females. Other loci-controlling alcohol withdrawal sensitivity (chromosome 1), alcohol-induced hypothermia and amphetamine-induced hyperthermia, and other hyperthermia loci seem to be in chromosome 9 of mouse. These loci do not appear to be controlling general tendencies for substance abuse. Alcohol preference appears to be a quantitative trait with ∼0.39 heritability and ∼60% concordance between monozygotic twins. Sensitivity to the effects of alcohol may be affected by a $GABA_A$ type receptor and mediated by protein kinase Cε. Synuclein-α gene seems to be expressed at more than 2-fold rate in the brain of rats, which prefer alcohol compared to those which do not care for the substance (Liang T et al 2003 Proc Natl Acad Sci USA 100:4690). Moderate alcohol consumption may be beneficial to some individuals but alcohol

consumption in general is undesirable for health and social consequences (Pearson H 2004 Nature [Lond] 428:598). ►Dubowitz syndrome, ►polygenic inheritance, ►teratogenesis, ►serotonin, ►neurotransmitter, ►substance abuse, ►mortality, ►QTL, ►behavior in humans, ►aldehyde dehydrogenase, ►Flyn, ►NMDA, ►GABA, ►glutamate receptor, ►protein kinases, ►addiction, ►synuclein, ►rheumatic fever; Almasy L 2001 Am J Hum Genet 68:128; Sillaber I et al 2002 Science 296:931; Weiss F, Porrino LJ 2002 J Neurosci 22:3332; Yao L et al 2002 Cell 109:733.

Aldehyde Dehydrogenase (ALDH, acetaldehyde dehydrogenase): Form ALDH1 is encoded in human chromosome 9q21. Low level of this form of the enzyme is responsible for poor alcohol tolerance. An ALDH2 functions in the liver and it is encoded in 12q24.2 and ALDH3 is coded in human chromosome 17. Oxidizes also cyclophosphamide-derivative aldophosphamide to non-toxic carboxyphosphamide (see Fig. A44). ►alcohol dehydrogenase, ►cyclophosphamide

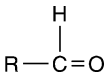

Figure A44. Aldehyde

Aldolase-1 (fructose-1,6-bisphosphate aldolase): The ALDOA isozyme has been mapped to human chromosome 16q22-q24, ALDOB (fructose intolerance) in chromosome 9q22, ALDOC in human chromosome 17cen-q12. There is also a deoxyribose-5-phosphate aldolase but its deficiency is apparently harmless. ALDOA deficiency may be involved in a form of hemolytic anemia (γ-glutamylcysteine synthetase deficiency). ►fructose intolerance, ►anemia

Aldose: A sugar that ends with a carbonyl group (=C=O).

Aldosterone (18-aldo-corticosterone): The main electrolyte-regulating steroid hormone of the kidney cortex. It activates a sodium channel I ATP-dependent manner. steroid hormones, ►aldosteronism, ►ion channel; Gorelik J et al 2005 Proc Natl Acad Sci USA 102:15000.

Aldosteronism (hyperaldosteronism, glucocorticoid-remediable aldosteronism [GRA]): Aldosteronism is controlled by two autosomal dominant genes. It is due to the excessive activity of aldosterone synthase (ADOS) and steroid 11β-hydroxylase (CYP11B2), coded in human chromosome 8q21. These two genes are quite similar in structure and also frequently form somatic recombinants. Their activity results in increased aldosterone production and hypertension. This hyperaldosteronism is suppressible by glucocorticoids and dexamethasone. The chimeric genes are under adrenocorticotropic hormone control. Consequently, aldosterone is secreted and causes water and salt reabsorption and high blood pressure. ►hypertension, ►aldosterone, ►glucocorticoid, ►dexamethasone, ►hypoaldosteronism, ►pseudohypoaldosteronism, ►mineral corticoid syndrome

Aleuron: A protein-rich outer layer of the endosperm of monocotyledonous kernels. There is only a one-cell-thick layer of aleurone in wheat and maize, three-cell-thick layer in barley, and a layer of variable cell-thickness in rice. There are about 250,000 cells in the aleurone in maize and about 100,000 in barley. Aleurone color genes have proven to be very useful chromosomal markers (such as loci *A, C, R, Bz, B* in maize and some of the functional homologs in other cereals). The dominant alleles can be identified already in the seeds of the heterozygotes, and in case of maize, they can be classified on the cob in immobilized condition and in large numbers. ►maize

Alexander's Disease: An autosomal recessive anomaly of lipid metabolism accompanied by a megaencephaly (synonym: macroencephaly), a pathological enlargement of the brain. Astrocyte fibers and small heat-shock proteins may be involved. Defects in NDUFV may be responsible for the symptoms. ►NDUFV; Brenner M et al 2001 Nature Genet 27:117.)

Alfalfa (*Medicago sativa*): A leguminous forage plant (see Fig. A45). Its closest wild relatives are *M. coerulea* (2n = 16) and the somewhat more distant *M. falcata* (2n = 16). *M. sativa* is autotetraploid (2n = 4x = 32). *M. truncatula* (~454–526 bp) has only about half the genome size of *M. sativa;* it is also diploid and its circular chloroplast genome is 124,039 bp. Alfalfa is also called lucerne. By antisense technology, the lignin content of the plant tissue has been reduced and its digestibility improved (Srinivasa Reddy MS et al 2005 Proc Natl Acad Sci USA 102:16573). ►gene index; *M. truncatula* database http://www.tigr.org/tdb/e2k1/mta1/.

Figure A45. *Medicago sativa*

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Alfalfa Mosaic Virus: The genetic material of this virus consists of four RNAs of 1.3, 1.0, 0.7 and 0.34 × 10^6 Da.

Alga: Alga can be prokaryotic such as blue-green algae, or eukaryotic such as *Chlamydomonas reinhardtii, Ch. eugametos, Euglena gracilis*, seaweeds etc.; they are photosynthetic microorganisms. The unicellular red alga *Cyanidioschyzon merolae* has 16,520,305 base pairs in its 20 chromosomes, with at least 5,331 genes. The single mitochondrion is 32,211 bp with 34 protein genes. The single plastid is 149,987 bp encoding 208 intron-less protein genes. (Matsuzaki M et al 2004 Nature [Lond] 428:653). ►*Chlamydomonas*, ►*Euglena*

Algeny: The genetic alteration of an organism by non-natural means such as ►genetic engineering, ►gene therapy, ►genetic surgery, and ►transformation

Algesia: Increased sensitivity to pain.

Alginate: A polymer of mannuronic acid and gulur-onate; it is found in the cell wall of brown algae. ►biofilm; Wong TY et al 2000 Annu Rev Microbiol 54:289.

Algol (algorithmic oriented language): A computer language set by international procedure. ►algorithm

Algorithm: A set of rules and procedures for solving problems in a finite number of sets; usually the repetitive calculation aims to find the greatest common divisor for two members. Computer programs include algorithms.

Algorithm, Genetic: Genetic algorithm uses a computational program to interpret evolutionary changes of mutation, recombination, and selection. ►algorithm, ►darwinism

Alien Addition: Addition of the chromosome(s) of another species to the genome of polyploids without seriously disturbing genic balance, in contrast to the case with diploids, where even small duplications or deletions may become quite deleterious. The procedure of addition involves crossing the higher chromosome number species as pistillate parent with the lower chromosome number pollen donor (see Fig. A46). The F_1 is generally sterile but by doubling their number (with colchicine) may result in a fertile amphiploid. Upon the recurrent back crossing of the amphiploid with the recipient parent, monosomy results for the donor's chromosomes. The F_1 is generally sterile but doubling their number (with colchicine) may result in a fertile amphiploid. After repeated backcrossing in large populations, one may obtain plants with single monosomes for all chromosomes of the donor. These are called single monosomic addition lines. Disomic additions are obtained by selfing such monosomics. These carry an extra pair of chromosomes. The purpose of addition is that occasionally the added chromosome, containing agronomically useful genes, may get substituted for its homoeolog and lead to a substitution line. ►addition line, ►pistillate, ►pollen, ►amphidiploid, ►monosome, ►disomic, ►homoeologue, ►substitution line, ►transchromosomic; Sears ER 1953 Am J Bot 40:168.

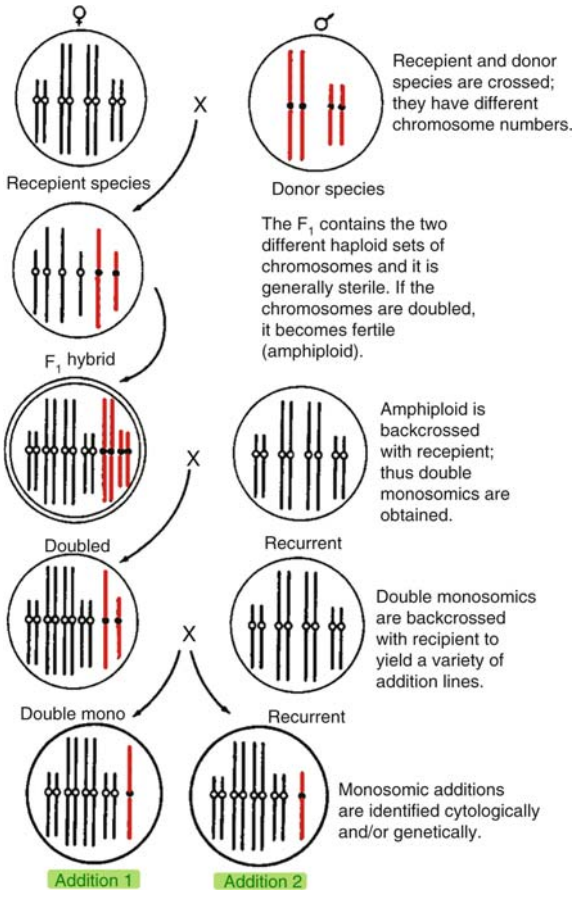

Figure A46. The general scheme for the generation alien addition lines in wheat. The same procedure is applicable to other polyploid plant species

Alien Substitution: Alien Substitution takes place when chromosome(s) of another species replace the own chromosome(s) of a species. Alien substitutions may be obtained from alien addition lines. However, monosomic lines are used most commonly. Monosomic lines can be maintained without too many difficulties in polyploids, because the genomes are better balanced. Monosomic plants produce some eggs that are nullisomic. These recipients are then crossed with a donor species. In the F_1 the chromosome absent in the parent nullisomic will appear as a monosome of

the donor. These monosomic individuals are repeatedly backcrossed (6–8 times) with the recipient, until in some individuals all the chromosomes of the donor are eliminated, except that particular monosome. Selfing this monosomic substitution line results in a disomic substitution that has the same chromosome number as the euploid line from which the nullisomic arose, but one pair of the chromosomes will represent the donor. ►alien addition, ►monosomic, ►nullisomic, ►backcross, ►selfing, ►euploid, ►alien transfer lines, ►chromosome substitution; Sears ER 1972 Stadler Symp 4:23.

Alien Transfer Lines: Alien substitution lines are interesting to the geneticist, but the plant-breeder is rarely satisfied with the substitution of an entire chromosome because the new chromosome may contain, in addition to the desirable gene(s), some that are undesirable. Homoelogous pairing and crossing over, on the other hand can borrow short segments or even single genes from the alien chromosome. This goal can also be achieved by induced translocations, and the resulting line is called a transfer line. ►alien ►substitution, ►alien transfer, ►transchromosomic, ►translocation; Sears ER 1956 Brookhaven Symp Biol 9:1.

AlifoldZ: Consensus structures of aligned sequences can be useful measures in detecting functional RNAs. One method is to test multiple sequence alignments for the existence of an unusually structured and conserved fold. An energy score consisting of free energy and a covariation term significantly improves sensitivity, as compared to a single sequence prediction (Washietl S, Hofacker IL 2004 J Mol Biol 342:19). ►RNAz, ►EvoFold, ►RNA structural

Alignment: Alignment finds nucleotide and amino acid linear sequence matches in nucleic acids and polypeptides, respectively. High alignment scores indicate great similarity between sequences. Free downloads of aligning software are available on the internet. Alignment scores estimates similarities versus dissimilarities in sequences, as well as gaps in the sequence of macromolecules. homology, CLUSTAL W, also BLAST, genomics, PFAM, human–mouse genomes: Schwartz S et al 2003 Genome Res 13:103; Higgins GD et al 2005 Proc Natl Acad Sci USA 102:104511, pairwise sequence alignment: http://genome.cs.mtu.edu/align/align.html, protein sequence alignment: http://compbio.mds.qmw.ac.uk/S4.html, genome alignment, annotation: http://www.bx.psu.edu/, multiple alignment of structure: http://bioinformatics.albany.edu/~dmaps/, binding motif alignment: http://www.benoslab.pitt.edu/stamp/, multiple sequence alignment with medical and microbial relevance: http://genome.lbl.gov/vista/index.shtml, multiple sequence alignment: http://prodata.swmed.edu/compass/compass.php.

AlignACE: AlignACE is a computer program that locates upstream regions of regulons. It helps identify genes in a functional pathway, or genes homologous to known regulons, or a group of genes derived from conserved operons. ►regulon; McGuire AM et al 2000 Genome Res 10:744.

Aliphatic Molecules: The carbon atoms occur in an open chain (non-aromatic) that is bound by single or multiple bonds.

ALK: ►anaplastic lymphoma

Alkaline Chromatography: Is used for the rapid separation of less than 150 bases long DNA probes on Sepharose CL-4B (a beaded [60–14 mm pore size], cross-linked agarose). ►Sepharose

Alkaline Lysis: Alkaline Lysis is a procedure to extract plasmid DNA from bacterial cells, using 0.2 N NaOH and 1% SDS. The plasmids may be further purified by CsCl-ethidium bromide gradient ultracentrifugation, or by polyethylene glycol precipitation at 10,000 rpm. ►SDS

Alkaline Phosphatase: Alkaline Phosphatase cleaves phosphates at a pH optimum about 9; it is present in microorganisms and animal cells but absent from plant tissues. The alkaline phosphatase of *E. coli* is 86-kDA and contains 2 subunits. The human intestinal alkaline phosphatase (ALP1) is encoded in chromosome 2q37, as are the placental enzymes (ALPPP/PLAP); the liver enzyme is coded by ALPL in chromosome 1p36.1-p34. Enzyme levels that are higher or lower than normal may have deleterious consequences. Hypophosphatasia for ALP may be dangerous or even lethal for infants. ►acrodermatitis enteropathica, ►acid phosphatase

Alkaloids: Alkaloids are diverse (more than 2500), mainly heterocyclic, organic compounds containing nitrogen. They are generally alkalic in nature and are secondary metabolites of plants; frequently effecting strong biological activity at higher concentrations (examples are nicotine, caffeine, cocaine, morphine, strychnine, quinine, papaverine, atropine, hyoscyamine, scopolamine codeine, capsaicine, lupinin, etc.). Of particular interest is colchicine (obtained from the lily, *Colchicum autumnale*) that blocks the microtubules of cells, causing the doubling of the chromosome number. Vincristine and vinblastine (from *Vinca rosea*) are antineoplastic drugs. The "animal alkaloid," ptomaine, found in decomposing cadavers, is actually a microbial product. ►nicotine, ►caffeine, ►*Datura* ►alkaloids, ►cocaine, ►morphine,

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►capsaicine, ►lupine, ►colchicine, ►vinblastine; Facchini PJ 2001 Annu Rev Plant Physiol Mol Biol 52:29.

Alkalosis: Alkalosis is the diminished buffering capacity of tissues that leads to higher pH.

Alkane: An alkane is a aliphatic molecule joined by a single covalent bond, e.g., CH_3—CH_3. ►alkene

Alkaptonuria (alcaptonuria, AKU): Alkaptonuria is a recessive metabolic disorder (prevalence about 1/40,000) in which a defect in the enzyme homogentisate 1,2-deoxygenase prevents homogentisic acid from being metabolized into maleyl- and fumaryl-acetoacetic acids. The degradation of the aromatic amino acids normally follows the pathway (see Fig. A47):

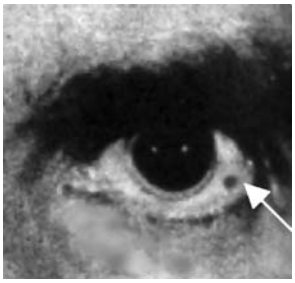

Figure A47. Alkaptonuria

The accumulated homogentisic acid in AKU is excreted in urine and is readily oxidized into a dark compound (see on the cornea: see Fig. A48), alkapton, staining dark already the diapers of affected newborns. Alkapton also causes dark pigmented spots in the connective tissues and bones, and with the ageing of the patient may lead too arthritis. This human hereditary biochemical defect was first recognized in 1859 and its genetic control identified by Sir Archibald Garrod in 1902. The gene (AKU) was located inhuman chromosome 3q21-q23. ►tyrosine, ►phenylketonuria, ►amino acid metabolism, ►tyrosinemia

Alkene: Alkenes are hydrocarbons with one or more double bonds, e.g., H_2C=CH_2. ►alkane

Alkylating Agent: An alkylating agent alkylates other molecules; many chemical mutagens and carcinogens are alkylating agents. The mutationally most effective alkylation site in DNA is the O^6 site of guanine. O^6-alkylguanine can pair with either cytosine, or thymine, resulting in a substitution mutation in case of the latter. The alkyl may be removed from the DNA in *E. coli* by an alkyltransferase enzyme. The acceptor may be a cysteine residue of that protein.

The natural compounds yatakemycin and duocarmycin SA (see Fig. A50) can alkylate nucleosomal DNA in the highly shielded minor groove and are potentially effective anti-tumor agents (Trzupek JD et al 2006 Nature Chem Biol 2:79).

►mutagens-carcinogens, ►mutagenic potency, ►environmental mutagens, ►carcinogen, ►chemical mutagens, ►alkyltransferase; see Fig. A49.

Alkylation: Alkylation is the addition of a CH_3 group (or other member of the alkane series) to a molecule. Alkylation of DNA bases may lead to mutation through mispairing and base substitution. Also, alkylation may lead to disruption of the sugar-phosphate backbone of the DNA through depurination by AP nucleases. Thymine is alkylated at the O^4 position and adenine at the N3 position. ►base pairing, ►hydrogen pairing, ►tautomeric shift, ►AP endonuclease, ►chemical mutagens, ►alkyltransferases, ►methyltransferase; Bautz E, Freese E 1960 Proc Natl Acad Sci USA 46:1585.

Alkyltransferases: Alkyltransferases protect the DNA against alkyl adducts by transferring the methyl or ethyl (alkyl) groups to cysteine and repairing the damage. These enzymes, present in different organisms, display an active site consensus V(I)PCHRV(I). If the level of these enzymes is reduced either by inhibitors, e.g., O^6-benzylguanine, or by mutation, the efficiency of alkylating agents for treatment of cancer increases. DNA repair; Reese JS et al 2001 Oncogene 20:5258.

Allantois: The allantois is a tubular part of the hindgut, later forming the umbilical cord of the fetus and it fuses with the chorion. It also participates in the formation of the placenta. amnion, ►chorion

Allegro: Allegro is a computer program for multipoint linkage, free at allegro@decode.is.

Allele: Alleles are alternative states of a gene (e.g., a^1 and a^2). Hybrids of a^1/a^2 are commonly of mutant phenotype, although they may show incomplete (allelic) complementation. Two alleles are identical if their base sequences are identical, even though one or both of these may be different from the sequence of the wild type. *Non-identical alleles* are still in the same gene (and are non-complementary) yet their expression may be distinguishable. *Homoalleles* are effected in the same codon but a different nucleotide occurs at the same site in each, and therefore the alleles cannot be separated by recombination in a

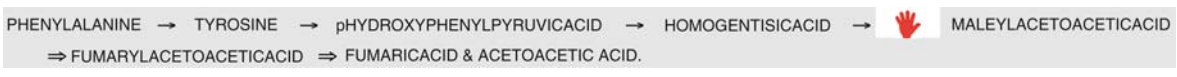

Figure A48. Degradation of aromatic amino acids

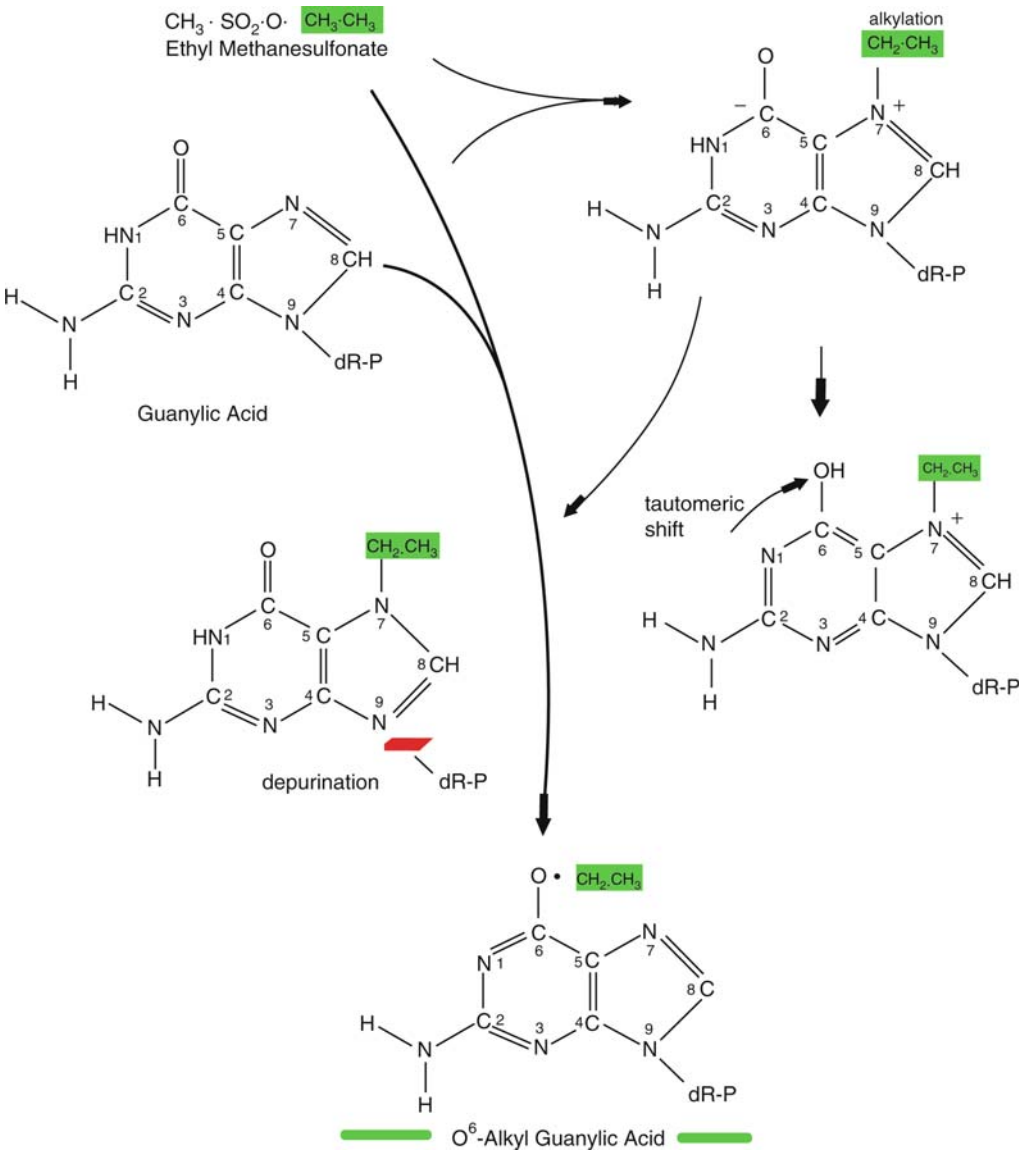

Figure A49. Most common reactions of the alkylating agent, ethylmethane sulfonate with guanine

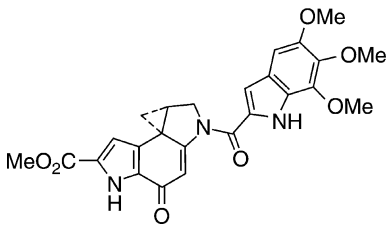

Figure A50. Duocarmycin

heterozygote for the locus. The differences between *heteroalleles* are located at non-identical sites within the codon, or in another codon altogether, and the alleles can therefore be separated by recombination. *Isoalleles* convey wild phenotype, yet under special circumstances can be recognized by appearance. *Multiple alleles* are more than two alternatives alleles of the same locus. *Super alleles* are additional mutations in cis to an allele within a gene that reinforces their expression. *Codominant alleles* both are expressed in the heterozygotes. In some organisms alleles of the *a1* locus are symbolized as *a1-1*, *a1-2*, etc. Molecular geneticists involved in physical mapping of the DNA use this term for any DNA difference (e.g., restriction fragment) that displays Mendelian inheritance and occupies the same chromosomal site (see Fig. A51). Allelic variation is widespread within a species and knowledge of the nature of these alleles is not just important in biology, but may also be relevant in applied fields such as disease susceptibility, forensic identifications, etc. In yeast, by hybridizing two different strains and through conduction microarray analysis, the frequency of such variation (single-feature polymorphism) can be ~1% (Winzeler EA et al 1998

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Science 281:1194; Gresham D et al 2006 Science 311:1932). ►gene symbols, ►RFLP, ►RAPD, ►Mendelian ►segregation, ►coalescent, ►mutation ►age ►of, ►SNIPS; Slatkin M, Rannala B 2000 Annu Rev Genomics Hum Genet 1:225.

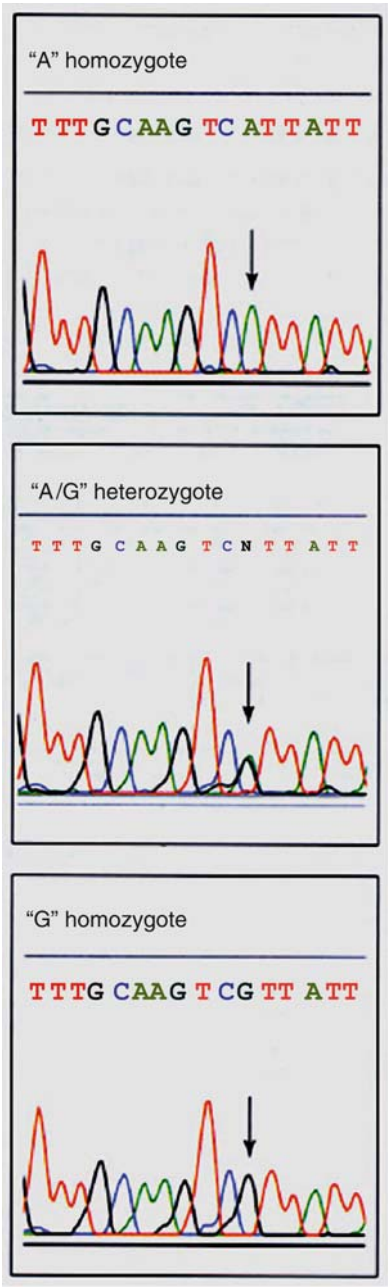

Figure A51. Mutation in a gene results in an allelic change from A (adenine) to G (guanine). Nucleotide substitution is identified by sequencing of the PCR amplified segment of the DNA. In the heterozygote for the site reduced amounts of both A and G is shown. (Courtesy of Amersham Biosciences, GE Healthcare Biodirectory 2005, p. 310.)

Allele Calling: Allele calling refers to the identification of an allele on the basis of chemical/molecular information.

Allele Dropout: When small DNA samples are multiplied too many times during forensic or ancient DNA analysis, certain alleles of a heterozygous individual may be lost to the process. ►forensic ►genetics, ►DNA ►fingerprinting; Gill P et al 2000 Forensic Sci Int 112:17.

Allele-Sharing Methods: Allele-sharing methods detect linkage by examining pedigrees for whether a particular genetic locus (chromosomal fragment) is more common among individuals in a pedigree than expected by random segregation. It is basically a non-parametric method. The probability of allele-sharing may be denoted by Y and the probability that R alleles are shared among 2N = $\binom{2N}{R} Y^{R(1-Y)^{2N-R}}$. For R shared alleles the maximum lod score = Rlog_{10}R + (2N−R)log_{10}(2N−R)−2Nlog_{10}N.

An allele-sharing study of 1,592 DZ twin pairs from two independent Australian cohorts, of which 1,561 pairs were informative for linkage on chromosome 6, and 336 DZ twin pairs from the Netherlands, showed no evidence of excess allele sharing, either at the HLA locus or in the rest of the genome. One Australian group indicated a small yet significant deficit of allele-sharing (Montgomery GW et al 2006 Amer J Hum Genet 79:1052). ►non-►parametric ►tests, ►lod ►score; Nyholt DR 2000 Am J Hum Genet 67:282.

Allele-Specific Probe For Mutation (ASP): In principle, this would detect single base change mutations because under very high stringency of hybridization oligonucleotide probes (ASO) would hybridize only to that sequence, which is exactly matching but not to another that has one base pair substitution. This would also identify heterozygotes because they would hybridize to both types of probes, mutant and normal. This procedure requires high skills but can be semi-automated. ►hybridization, ►mutation ►detection, ►probe, ►SNIP, ►ASO; Prince JA et al 2001 Genome Res 11:152.

Allelic Association: ►linkage, ►disequilibrium

Allelic Combinations: Allelic combinations in gametes (at independent loci) can be predicted by 2n where n is the number of different allelic pairs, and it produces 4n gametic combinations and 3n genotypes. If the number of loci is n and each has a number of alleles, the number of zygotic genotypes at one locus can be calculated as [a × (a + 1)]/2 and for n loci: $\left[\frac{a\times(a+1)}{2}\right]^n$

Thus e.g., for 100 loci, each with three alleles $[(3 \times 4)/2]^{100} \geq 6.53 \times 10^{77}$ zygotic genotypes are

possible. ►multiple alleles, ►gametic array, ►Mendelian segregation

Allelic Complementation: Allelic complementation is partial or incomplete complementation among mutant alleles of a gene, representing different cistrons (see Fig. A52).

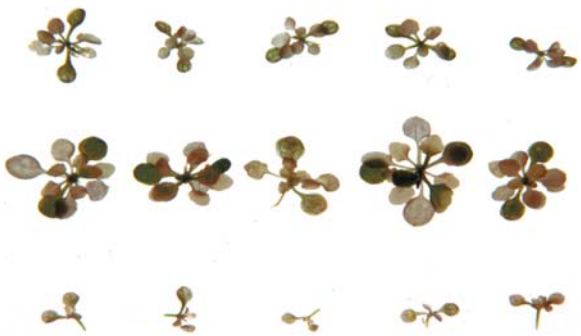

Figure A52. Allelic complementation of *py*^{5} (top row), *py*^{4} (bottom row) temperature-sensitive mutants requiring 2-methyl-4-amino-5-aminomethyl-pyrimidine grown in test tubes. their hybrids are in the middle. (From SL Li and GP Rédei, unpublished)

If the alleles are defective when homozygous, they do not contribute to the synthesis of functional proteins. Each of the two alleles in a heterozygote has another non-overlapping defective polypeptide product. The correct polypeptide chains in the cytoplasm may combine in the heterodimeric or heteropolymeric proteins, and due to right assembly, the function of these proteins may be restored. Since the available correct polypeptide chains are reduced in number relative to that in the wild type, only a reduced number of good protein molecules can be formed. Therefore, allelic complementation is incomplete. The beneficial effect from the non-defective peptide chains may be brought about also by conformation correction, i.e., the conformation of defective chains is brought into line as an effect of the other polypeptide chain, as long as there is no defect at the active site. The extent of allelic complementation can be best determined by in vitro enzyme assays when regulatory genes cannot modify the functions by higher intensity or prolonged transcription of the relevant cistrons. ►step allelomorphism, ►conformation, ►complementation mapping, ►allelism test, ►non-allelic, ►non-complementation; Li SL, Rédei GP 1969 Genetics 62:281.

Allelic Dropout: Allelic dropout occurs during amplification (by PCR) when a microsatellite locus is not replicated by the DNA polymerase. ►PCR; Miller CR et al 2002 Genetics 160:357.

Allelic Exclusion: Allelic exclusion refers to the phenomenon when only one of the two alleles at a locus is expressed or only one type of chain rearrangement is functional. Such conditions are found in immunoglobulins, various receptors, interleukin-2, and imprinted genes. Protein kinase C (PKC) modulates both differentiation and allelic exclusion during thymocyte differentiation. ►immunoglobulins, ►monoallelic ►expression, ►interleukin, ►imprinting, ►PKC, ►thymocytes; Michie AM et al 2001 Proc Natl Acad Sci USA 98:609; Borst P 2002 Cell 109:5; Mostovslavsky R et al 2004 Cell 118:539.

Allelic Fixation: Allelic fixation takes place in a random mating population when one allele completely replaces another. The process depends on the coefficient of selection and the size of the populations (see Fig. A53). The time that has elapsed since the fixation of a beneficial allele is estimated on the basis of nucleotide variation at linked loci. (Przeworski M 2003 Genetics 164:1667).

Allelic Frequencies: Allelic frequencies can be determined on the basis of the Hardy-Weinberg theorem, according to which, the genotypic composition of a random mating population is $p^2 + 2pq + q^2$, where p^2 and q^2 are the frequencies of the homozygous dominants and recessives, respectively. Thus, if we consider a single allelic pair, *A* and *a,* and diploidy, the frequency of the *A* allele = double the number of homozygous dominants plus the number of heterozygotes. The frequency of the *a* allele = double the number of homozygotes plus the heterozygotes, because the homozygotes have two copies of the same allele whereas the heterozygotes have only one of each kind (see Fig. A53).

The frequency of the recessive alleles in an equilibrium population is simply $1 - p$ (= q). The heterozygotes may not be directly recognized in case of dominance, therefore this equation may not be applicable there. However, in case the population is at equilibrium and the mating is at random, the frequency of the recessive alleles is $q = \sqrt{q^2}$. If the size of the homozygous recessive class is very small, the vast majority of recessive alleles occur in the heterozygotes. In case of sex-linkage, the male carries one dose (XY) whereas the female is XX. Thus, males display recessive traits more frequently than do females, who express it only when homozygous. Therefore, if the expression of an X-linked recessive allele is 0.10 in males, in females it is expected to show up at $(0.10)^2 = 0.01$. The frequency of alleles in a population may change by selection, mutation, random drift, and migration. At random mating the total variance of allelic frequency with two alleles of 2n genes is computed from the Weir

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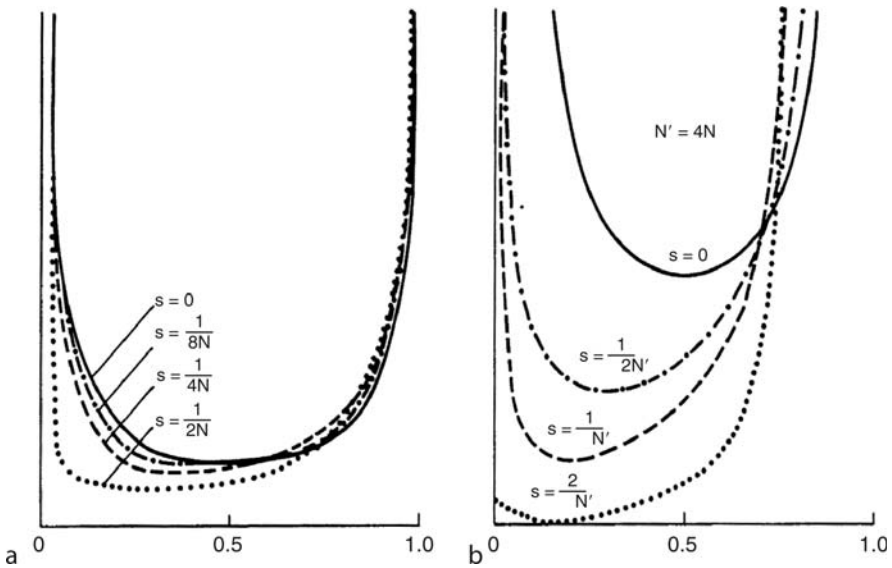

Figure A53. In very small populations only high selection coefficients can bring about changes in allelic distribution (a). When the size of the population increases fourfold, relatively small selection coefficients effectively modify the direction of fixation (b). The ordinate represents allelic densities, the abscissa shows allelic frequencies from loss, (0) to complete fixation (1.0); s = selection coefficient, N = population size. (From Wright S 1931 Genetics 16:97)

formula: $V(p) = \frac{p(1-p)}{2n}[F_{ST}(2n-1)+1$ and $F_{ST} = \frac{\sigma^2-1}{2n-1}$. ►Hardy - Weinberg theorem, ►selection, ►mutation, ►random genetic drift; Hung S-P, Weir BS 2001 Genetics 159:1365, http://info.med.yale.edu/genetics/kkidd; http://alfred.med.yale.edu/alfred/AboutALFRED.asp.

Allelic Interaction: ►overdominance

Allelic Recombination: Allelic recombination takes place between the same sites of the homologous chromosomes. ►ectopic recombination, ►homologous recombination

Allelic Rescue: Allelic rescue is a procedure for cloning a mutant allele. A vector carrying the wild type allele, which has, however, an internal deletion overlapping the mutant site, transforms the mutant cell. When the cellular (gap) repair system fills in the deleted sequences using the mutant template, the plasmid vector carrying a copy of the mutant gene can be isolated, and along with it the gene itself. ►DNA repair, ►transformation, ►marker rescue

Allelism Test: An allelism test is carried out by a complementation test. If two recessive genes are allelic, they fail to complement each other in the F_1 hybrids (i.e., the hybrid is of mutant phenotype). In case the hybrid of two recessive individuals is of wild phenotype (i.e., they complement each other) the two genes are not allelic. Thus, the number of complementation groups reveal the number of different loci. In practice, the term complementation groups is understood as different complementation groups. However, allelic genes at the same multicistronic locus may show partial or allelic complementation. allelic complementation, non-allelic non-complementation; Demerec M, Ozeki H 1959 Genetics 44:269.

Allelomorph: Allelomorph is a historical term for an allele. ►allele

Allelopathy: Allelopathy refers to the release of repellent or toxic compounds by plants to suppress neighboring species or to defend against insects or other parasites. (See Pickett JA et al 2003 Biochem Soc Trans 31 [1]:123)

Allelotyping: Allelotyping is the determination of the spectrum and frequency of allelic variations in a population. Polymorphism may be determined by restriction fragment length, SNIPS, LOH, PCR, etc. genotyping, ►RFLP, ►SNIPS, ►PCR, ►LOH; Girard L et al 2000 Cancer Res 60:4894; Yan H et al 2002 Science 297:1143.

Allergen: An allergen is any substance that causes an allergy. ►allergy, allergenicity assessment: http://bioinformatics.bmc.uu.se/evaller.html.

Allergy: Sensitivity to a particular antigen(s); an allergy is the evidence of an immunological reaction. Common forms are the hay fever after exposure to

pollen (ragweed), drug, food, bacteria, cold, etc. The allergic reaction may be a hereditary property (atopy). In asthma, hay fever, and various other allergic reactions the regulatory *Re* gene is implicated in the decrease of immunoglobulin E level, and in *re/re* individuals it seems to be higher. The frequency of the *re* gene is estimated to be about 0.49. The IgE response in about 60% of the atopy cases is assigned to chromosome 11q13-q12, the site of the high-affinity IgE receptor (FcεRI-β) gene. The IgE response is apparently controlled by IgE receptor (FcεRI) and regulated by interleukin 4 (IL-4). It also appears that the IgG Fc receptor, FcγRIII, affects FcεRI assembly. Ragweed sensitivity is assigned to the HLA complex in human chromosome 6. Elevated levels of immunoglobulin E, controlled by an autosomal dominant gene with incomplete penetrance, have been detected in the neutrophil chemotaxis defect, characterized by chronic eczema, repeated infections by staphylococci and eosinophilia (cytological structures readily stained with eosin stains). Asthma and other allergies are apparently under the control of multiple genetic loci. Allergies may be alleviated by desensitization, which involves exposure to increasing amounts of the allergen in order to regulate IgE production. DNA immunization may stimulate Th1 immunity, either by producing IgG2a and IFN-γ, or by Th2 response along with the production of IgE and IgG and an increase in interleukins (IL-4, -5, -10). Actually Th1 cells antagonize the inflammatory reaction whereas Th2 cells, with the aid of IL-3, IL-5 and GM-CSF, stimulate eosinophils through IL-3, IL-4, IL-6 and IL-9 and regulate mast cells and inflammation. Dendritic cells negatively regulate Th2 cells with the aid of IL-12, and Th2 cells in turn, helped by IL-10, lower the response of dendritic cells to allergens. Bacteria and viruses promote the production of IL-12 and thus stimulate Th1 cells. Th1 cells boost the body's defense against intracellular pathogens (bacteria and viruses) by increased production of IFN-γ and synthesis IgG2a. Th2 cells, IgE, and IgG1 mediate defense against larger extracellular pathogens. The allergens of fungi and other parasites boost the level of Th2 cells and elevate IgE level in the serum. IL-4 and IL-13 enhance IgE production by B-lymphocytes and thus evoke inflammatory responses. The CD23 receptor of IgE may promote or hinder antibody presentation depending on the circumstances. In grass hay fever, $CD4^+CD30^+$ Th2 cells react to the allergen. Glucocorticoids and IL-4 enhance Th2 activity, whereas dihydroepiandrosterol favors Th1 cells. IFNa, IL-12 and TGF-β expand Th1, while IL-10, IL-6 and IL-4 skew the balance toward Th2. Allergen recognition through MHC class II peptides, organ localization, and response to allergens all have clear genetic components. Environmental factors play very important roles as well, considering how the overall incidence of allergy and asthma is on the rise. ►atopy, ►ragweed, ►HLA, ►immunoglobulins, ►asthma, ►anaphylaxis, ►eczema, ►hypersensitive reaction, ►γδT cell, ►interleukin, ►immunization ►genetic, ►$CD4^+$, ►$CD30^+$, ►CD23, ►IFN, ►TGF, ►IL-►10, ►IL-3, IL-5, ►IL-6, ►IL-4, ►IL-12, ►IL-13, ►glucocorticoid, ►histamine, ►interferons; Nature [Lond]) 402[6760] Suppl.; oral allergy vaccine: Ma S, Jevnikar AM 2005 Proc Natl Acad Sci USA 102:17255.

http://www.nlm.nih.gov/medlineplus/allergy.html, allergen prediction: http://www.imtech.res.in/raghava/algpred/.

Alligator (giant lizards): The two most commonly known species are *Alligator mississippiensis*, 2n = 36, *Crocodylus niloticus* 2n = 32.

Allium (onion, garlic): *Allium* is a monocot genus, 2n = 16 or 32, and is well suited for cytological analysis.

Alloantibody (isoantibody): An alloantibody is produced by an individual of a species, against alloantigens within the species. This may be due to preceding transfusions or pregnancies and may cause hyperacute rejection in case of transplantation in another individual of the same species. ►alloantigen

Alloantigen: An alloantigen is a genetically determined antigen variant within the species. It may also be called neoantigen when the epitope appears the first time. Alloantigens are recognized within the same species by lymphocytes with different haplotype. ►antigen, ►epitope, ►lymphocyte, ►haplotype, ►isoallogen, ►alloantibody

Alloantisera: Alloantisera are antibodies that can recognize a certain protein in a different individual.

Allocatalasia: Allocatalasia is characterized by the condition when the catalase activity and stability is normal yet the protein is a different variant. ►catalase

Allocation: Allocation refers to the differential distribution of cellular resources to specific structures and organs in an individual organism.

Allochronic Species: Allochronic species do not exist during the same time period in evolution.

Allocycly: Chromosomal regions, chromosomes, or genomes may show cyclic variation in coiling and heteropycnosis. ►heterochromatin, ►heteropycnosis, ►Lyonization, ►Barr body

Allodiploid: An allodiploid is a polyploid that has chromosome sets (genomes) derived from more than

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one ancestral organism, e.g., hexaploid bread wheat has A, B, and D genomes. ►autotetraploid, ►*Triticum*

Allodynia: Allodynia is pain hypersensitivity evoked by innocuous stimuli. ►pain sensitivity; Tsuda M et al 2003 Nature [Lond] 424:778.

Allogamous: Allogamous individuals do not pollinate the pistils of the same plant, crosspollinating, and are also called exogamous species.

Allogamy: Allogamy is fertilization between gametes from different individual(s). ►autogamy

Allogeneic: Antigenic difference exists between two cells (in a chimera). ►antigen, ►allograft, ►autologous, ►xenogeneic

Allogeneic Inhibition: Allogeneic inhibition is found in mice; in this condition parental cells do not accept a graft from the F1, but the reciprocal graft may be successful. grafting in medicine; Mathew JM et al 2000 Transplantation 70:1752.

Allogenic: ►allogeneic

Allograft: The transplantation of tissues carrying cell surface antigens not present in the recipient leads to a graft that may be rejected and destroyed, and the process itself may harm the recipient. ►HLA, ►graft, ►isograft, ►heterograft, ►complement, ►grafting in medicine, ►xenotransplantation

Allohaploid: An allohaploid is a haploid cell derived from an allodiploid. ►allodiploid

Allolactose: The inducer of the *Lac* operon; it is the intermediate product of lactose (a di-saccharide) digestion by β-galactosidase, and is further converted to galactose and glucose by the same enzyme. ►galactosidase, ►lactose, ►*Lac* operon

Allolysis: ►fratricide

Allometric Development: Allometric development refers to the different growth (development) rate of one part of the body relative to other parts.

Allometry: Allometry is the study of growth of organs in different dimensions of space and time within an individual, or populations, or during evolution (Frankino WA et al 2005 Science 307:718; Kodric-Brown A et al 2006 Proc Natl Acad Sci USA 103:8733).

Allomixis: ►cross fertilization, ►allogamy

Allomone: ►kairomones

Allopatric Speciation: Allopatric speciation is involved in geographic adaptation and sexual isolation of species living in non-identical habitats. ►speciation, ►postzygotic isolation

Allophenic: Originally, allophonic genes refer to those genes that may not be expressed in one cell type but act as gene activators in other tissues. It also refers to the expression of genes in chimeric tissues of an embryo or adult that has been produced through in vitro fusion of two or more genetically different (chimeric) blastomeres. These blastomeres develop upon the fusion of the gametes of two parents, each, and several different blastomeres can be fused, resulting in (tri-, quadri-, hexa-parental, etc.) multi-parental offspring. The fused blastomeres are implanted into the uterus of pseudopregnant animals, who carry the developing mosaic embryos to term. The procedure opposite to the formation of allophenic chimeras is splitting up 8-cell embryos, in two steps, into separate blastomeres and insertion of four such cells into an empty zona pellucida. Subsequently, these "quadruplets" can be transferred into the uterus of a rhesus monkey, which has produced a viable, normal offspring by this procedure (Chan AWS et al 2000 Science 287:317). This type of cloning offers the means for producing progeny identical in both its nuclear and cytoplasmic hereditary components. biparental, chimera, blastomere, photo at multiparental; LoCascio NJ et al 1987 Dev Biol 124:291; Petters RM, Markert CL 1980 J Hered 71:70.

Allophycocyanin: Allophycocyanin is a fluorochrome; it is excited at wavelengths 610 and 640 nm and emits bright red light at 650 nm. It is used in flow cytometry. ►fluorochromes, ►flow cytometry, ►phycobilins

Alloplasmic: An alloplasmic cell is a cell in which the cytoplasm and the nucleus are of different origins. ►nuclear transplantation, ►cell genetics

Allopolyploid: An allopolyploid species contains two or more types of genomes from different species, e.g., *Triticum turgidum* (macaroni wheat), an allotetraploid containing the AABB genomes, *Triticum aestivum* (bread wheat), an allohexaploid with AABBDD genomes, and *Triticum crassum* (a wild grass), a hexaploid DDDDMM. *Nicotiana tabacum* is an allotetraploid (2n = 48) containing the genomes of *N. tomentosiformis* (2n = 24) and *N. sylvestris* (2n = 24). When *N. tabacum* is crossed with either of the parents, the F1 will have 12 bivalent (12″) and 12 univalent (12′) chromosomes. The degree of homology between genomes can cytologically be determined in meiosis on the basis of chromosome pairing and chiasma frequency. Allopolyploids generally acquire during evolution genes that suppress multivalent pairing of chromosomes, therefore the gene segregation pattern resembles that of diploids with more than one pairs of alleles. A duplex autotetraploid may segregate in a range between 35:1 and 19.3:1 (depending on the distance between gene and centromere), while an

allotetraploid is expected to display a 15:1 ratio and an allohexaploid a 63:1 proportion if there are 4 and 6 copies of the genes, respectively. However, some genes (which have only two alleles) in hexaploids may display a 3:1 segregation. ►duplex, ►sesquidiploid, ►allopolyploid segmental, ►autopolyploid

Allopolyploid, Segmental: Here, participating genomes have partial (segmental) homology yet are sufficiently different to cause some sterility. ►allopolyploid

Alloproteins: Alloproteins contain non-natural amino acids. ►genetic ►code, ►peptidomimetics; Kiga D et al 2002 Proc Natl Acad Sci USA 99:9715.

Allopurinol (hydroxypyrazole pyrimidine): Allopurinol is an inhibitor of de novo pyrimidine synthesis and xanthine oxidase activity (see Fig. A54). It is used as a medicine to treat gout and hyperuricemia, but can also cause severe skin disease (epidermal necrolysis). ►xanthine, ►gout, ►uric acid, ►Stevens-Johnson syndrome

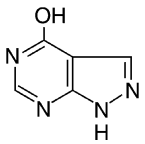

Figure A54. Allopurinol

Alloreactive (allorestrictive): An alloreactive cell is a T cell that recognizes a foreign antigen and mobilizes cellular defense against it, e.g., graft rejection. ►T cell, ►antigen

All-Or-None Trait: Such a trait is either present or absent, and there are no intermediates.

Allospecific: Its specificity is different from the standard normal.

Allostasis: Allostasis is a stage or state of homeostasis beyond the normal range. It may be evoked by environmental stress. homeostasis.

Allostatins: Allostatins are juvenile hormone inhibitors in insects. They have highly conserved six C-terminal amino acids. juvenile hormone.

Allosteric Control: Allosteric control is the modification of the activity of an enzyme by alteration at a site different from the active site by another molecule affecting its conformation without a covalent attachment. ►active ►site, ►conformation, ►intrasteric regulation; Süel GM et al 2003 Nature Struct Biol 10:59; signal transduction models: Changeux J-P, Edelstein SJ 2005 Science 308:1424.

Allosteric Effector: An allosteric effector is a molecule that is involved in bringing about allosteric control. ►allosteric control, ►allostery

Allostery: Allostery is a conformational change in a protein (ribozyme) through the effect of a ligand molecule; the process is often called allosteric shift. ►allosteric ►control; Monod J et al 1963 J Mol Biol 6:306.

Allosyndesis: Allosyndesis is the synapsis between non-entirely homologous chromosomes in an allopolyploid. ►homoeologous chromosomes, ►chromosome pairing

Allotetraploid: ►amphidiploid

Allotopic Expression: Allotopic expression takes place when a gene, which is not organellar (mitochondrial or plastidic by origin), is targeted and expressed in an organelle. ►ectopic expression

Allotype: Allotype refers to the difference in antibody (or antigen) caused presumably by allelic substitution mutation in the same constant region genes. ►isotype, ►immunoglobulins, ►antibody

Allozygote: Allozygote refers to an individual that at one or more loci possesses alleles that were not derived from the same common ancestor, i.e., are not identical by descent. ►inbreeding, ►coancestry, ►autozygous

Allozymes: Allozymes are different forms of an enzyme, occurring due to allelic differences in the genes.

All-Walking Approach: All-walking approach is a program used in the physical mapping of DNA in connection with YACs. The STS (sequence-tagged sites) are derived from the ends of YAC inserts. The three main advantages of this program are: the position of the STS here is defined vis-à-vis cases where the STS is internal; the program identifies chimeric YACs; and uses end-STS YACs that tend to be larger than others. ►YAC, ►STS

Allyl Alcohol: Allyl alcohol is a liquid eye-irritant that permits positive selection of alcohol dehydrogenase mutations because the wild type cells (adh^+) behave in a suicidal manner to convert this compound to acrylaldehyde, as a result of which, only the adh^- cells can survive. ►mutant isolation

Almond (*Prunus amygdalus*): The basic chromosome number x = 7 and 2x to 6x forms are known.

Alopecia: Alopecia is hair loss or baldness caused probably by an autoimmune condition occurring in different forms. In some cases it is accompanied by psychomotor epilepsy (involuntary movements), palm and sole keratosis (callosity), nail dysfunction, and lower mental capacity. In humans it appears as autosomal dominant. A recessive mutation (ACA, [Thr]→GCA, [Ala]) in human chromosome 8p12,

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causing total baldness (alopecia universalis), may be based on a defect in a zinc finger transcription factor. One form is caused by mutation in the Hfh11^{nu} (forkhead/winged helix) transcription factor family. In mice, asebia (rudimentary sebaceous glands) and alopecia may be caused by mutation in two genes: *Scd1* encoding stearoyl-CoA desaturase 1 and *Scd2* coding for stearoyl-CoA desaturase 2. Some cancer chemotherapies induce alopecia, which can be mitigated by topically applied inhibitors of CDK2, such as the analogs of 3-(benzylidene)indolin-2-ones, etoposides, and cyclophosphamide-doxorubicin. ►baldness, ►hair, ►autoimmune disease, ►keratosis, ►zinc finger, ►nude mouse, ►connective tissue disorders, ►hypotrichosis, ►etoposide, ►cyclophosphamide, ►doxorubicin

Alpers Progressive Infantile Poliodystrophy: This condition involves degeneration of the gray matter of the brain and cirrhosis of the liver. POLG (15q25) mutations affecting the catalytic subunit of mitochondrial DNA polymerase-γ A are responsible (Nguyen KV et al 2005 Neurology 65:1493). ►mitochondrial DNA depletion syndromes

Alpert Disease (AFP) AFP is alpha-fetoprotein deficiency, encoded at human chromosome 4q11-q13. ►fetoprotein; Greenberg F et al 1992 Am J Obstet Gynec 167: 509.

Alpert Syndrome 10q26 Alpert Syndrome is acrocephalosyndactylia, a disease characterized by a pointed skull and fused fingers and toes. This autosomal dominant or recessive human disease involves the fibroblast growth factor receptor (FGFR2), which is defective in the Pfeiffer syndrome as well. Its estimated mutation rate is 3–4 × 10^{-6}. ►Pfeiffer syndrome; Moloney DM et al 1995 Nature Genet 13:48.

Alpha Accessory Factor: The alpha accessory factor enhances the affinity of pol α and primase for the DNA template. ►pol α, ►primase, ►Okazaki fragment

Alpha Complex: The translocation complex of chromosomes (see Fig. A55), it transmits only through the female, whereas the beta complex is transmitted only through the male (in *Oenothera*). ►translocation complex, complex heterozygotes; Cleland RE 1972 *Oenothera*: Cytogenetics and Evolution. Academic Press, New York.

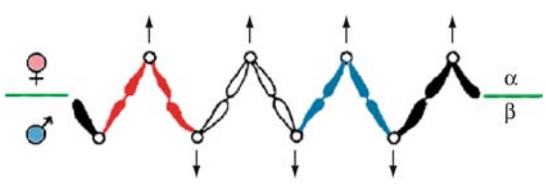

Figure A55. Alternate distribution of a four-translocation complex at anaphase I (α and β)

Alpha-Fetoprotein: ►fetoprotein

Alpha Helix: The alpha helix is a hydrogen-bonded secondary structure of polypeptides, where the polypeptide backbone is tightly wound around the longitudinal axis of peptide bonds and the groups of amino acids protrude along this generally right-handed helical structure (see Fig. A56). Commonly, 3.6 amino acids form each turn. It is often represented as a cylinder as well. protein ►structure, ►pitch

Figure A56. Two representations of alpha helix

Alphameric: Alphameric symbols use alphabetical notations, and possibly other characters, such as numbers.

Alpha Parameter: The alpha parameter provides a combined estimate of the frequency of quadrivalent association (q), meiotic exchange (e), and favorable anaphase distributions (a), and from these it predicts the frequency of double reduction, i.e., the production of *aa* gametes when the parental constitution is *AAAa* (see diagram of chromosome mechanics). In a triplex the cytogenetic constitutions can be represented as shown. The letters W, X, Y and Z stand for the centromeres, the chromatids are symbolized by the gray lines, and the dominant and recessive alleles are numbered from *A1* to *A6* and *a1* to *a2,* respectively (see diagram).

(i) In the absence of recombination the association of chromatids, alleles, and centromeres are: *A1-A2, A3-A4, A5-A6,* and *a1-a2.*

(ii) In case of recombination between gene and centromere the following arrays are formed:

A1-A3, A1-A5, A3-A5. These are the possible recombinant associations of dominant alleles, which were originally attached to different centromeres.

(iii) *A1-a1, A3-a1,* and *A5-a1* are the three possible dominant-recessive recombinant associations, when only one chromatid originally attached to a centromere is considered in the quadrivalent.

The total frequency of the gametes is 1 and the frequency of group (i) is designated as α, and the chance of each of the 4 types of associations within this group is α/4.

The combined frequency of recombinant group (ii) and (iii) associations is 1 − α. Since groups (ii) and (iii) have 3 representatives each, and combined 6, the frequency of each of the recombinant associations is (1 − α)/6.

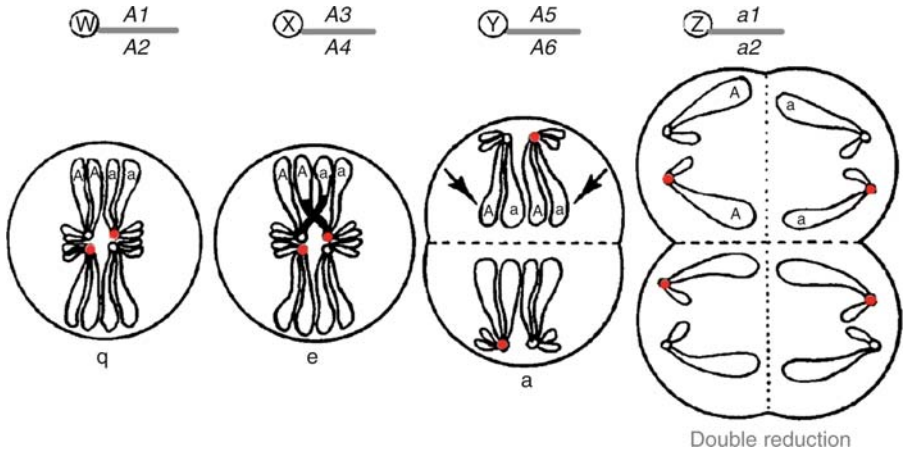

Figure A57. Chromosome mechanics (double reduction) are represented by the diagram; empty arms carry the *A* (dominant) allele

Group (i) has 3 double dominants (*A1-A2, A3-A4*, and *A5-A6*) among 4, each with a frequency of α/4. The combined frequency of the group is 3 × (α/4). Group (ii) also has 3 double dominants (*A1-A3, A1-A5, A3-A5*) with individual frequencies of (1 − α)/6 each, and a combined group frequency of 3 × (1 − α)/6. Thus the total frequency of gametes with a dominant allele in both chromatids is [3 × (α/4)] + [3 × (1 − α)/6] = [3α/4] + [(3 − 3α)]/6. After dividing both the numerator and denominator of the second term by 1.5, we obtain the formula: [3α/4] + [(2 − 2α)/4] = (2 + α)/4 = the frequency of *AA* gametes. The frequency of the *Aa* gametes is obtained similarly Group (iii) has 3 *Aa* gametes with individual frequencies of (1 − α)/6, and their combined frequency upon dividing numerator and denominator by 1.5 becomes 3 × (1 − α)/6 = (3 − 3α)/6 = (2 − 2α)/4. The frequency of the double recessive gametes (*aa*) as shown above is α/4. Thus the total gametic output of the triplex is $\frac{2+\alpha}{4}$ *AA*: $\frac{2-2\alpha}{4}$ *Aa*: α/4 *aa*. The practical meaning of the a parameter is best illustrated by an example. Let us assume that the cytological analysis indicates the value of q = 0.7, e = 0.25, and a = 0.333. Thus a = 0.7 × 0.25 × 0.333 × 0.5 = 0.02914. This value can then be substituted into the formulas in the table (see Table A3).

Accordingly, for the simplex (line 3 at tetrasomy) *AA* becomes α/4 = 0.02914/4 = 0.007285, *Aa* is obtained in frequency 2(1 − α)/4 = 0.48543, and *aa* = (2 + a)/4 = 0.507285. Thus the double dominant gametes are expected to occur at a frequency below 1%, while *Aa* and *aa* at a near equal frequency of around 50%.

The proportion of the double reduction (*aa* gametes) indicates to some extent the relative distance of the gene from the centromere, albeit not in precise units directly convertible to map distance, but approximating it. Theoretically, these calculations are elegant, but unfortunately the determination of the variable components of α requires great experimental skills and very favorable conditions. Therefore the analysis of segregation in polyploids is very difficult. ►autopolyploids, ►centromere ►mapping; Mather K 1935 J Genet 30:53; Mather K 1936 J Genet 32:287.

Alpha Particles: Alpha particles are helium nuclei (contain 2 protons and 2 neutrons) emitted by radioactive decay. They release their excessive energy in a very short track; even in air they move only for a few centimeters. They have minimal penetration in living material, yet are very destructive (can break chromosomes) because of their short track and high ionizing energy.). Mean number of lethal lesions/per cell: α rays: 0.01, γ rays: 0.001, 10 MeVB neutrons: 0.005. ►ionizing radiation, ►linear energy transfer

Alpha Tocopherol (vitamin E): Tocopherols are plant products but are required in mammals for the maintenance of fertility and for the prevention of muscle degeneration. They appear to be antioxidants for unsaturated lipids. Lipid peroxidation may result in cross-linking of proteins and may cause mutation, the appearance of age pigments (lipofuscin), etc. ►unsaturated fatty acids, ►fatty acids

Alphavirus: An alphavirus is a single, negative-strand RNA virus with a 240 molecule basic capsid protein, surrounded by a lipid bilayer of 240 glycoprotein heteromeric envelope. It can infect a variety of cells and its genomic RNA is translated into non-structural proteins to begin the replication of the viral RNA. Although it is a cytocidal virus it may be engineered

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Table A3. Alpha parameter

ZYGOTES	GAMETES			
	TETRASOMY			
	AA	***Aa***	***aa***	DIVISOR
Triplex	2 + α	2(1 - α)	α	4
Duplex	1 + 2-α	4(1 - α)	1 + 2α	6
Simplex	α	2(1 - α)	2 + α	4
	HEXASOMY			
	AAA	***Aaa***	***aaa***	DIVISOR
Pentaplex	3 + α	3 - 2α	α	0	6
Quadruplex	3 + 3α	9 - 5α	3 + 3α	α	15
Triplex	1 + 3α	9 - 3α	9 - 3α	1 + 3α	20
Duplex	α	3 - α	9 - 5α	3 + 3α	15
Simplex	0	α	3 - 2α	3 + α	6

Simplex :	1 *A*
Duplex :	2 *A*
Triplex :	3 *A*
Quadruplex :	4 *A*
Pentaplex :	5 *A*
Nulliplex :	no *A*

The *A* value indicates the number of dominant alleles in the zygotes

The expected gametic frequencies of polyploids. Each term on the corresponding line has to be divided by the *Divisor* • shown at the right column. (After Fisher RA, Mather, K, 1943 Annals of Eugenics 12:1)

into a vector for transient gene therapy or used for vaccination. This group of viruses includes the Sendai virus and the Simliki forest virus. ►Sendai virus

Alphoid DNA: ►α satellite

Alport's Disease: Alport's Disease exists in different forms of which, autosomal dominant, recessive, and X-linked types are described. The phenotypes vary but most common symptoms are inflammation of the kidney(s), and deafness. Most probably the primary defect involves the basement membrane of the kidney glomerules and the Goodpasture antigen leading to kidney failure and hypertension. Bone marrow-derived stem cells may repair basement membrane defects and may prove therapeutically useful for treatment of Alport patients (Sugimoto H et al 2006 Proc Natl Acad Sci USA 103:7321). The basement membrane defect is an Xq22 coded collagen α-chain anomaly. Essentially, the Alport syndrome is the same as the Epstein syndrome. The autosomal dominant Alport syndrome with leukocyte inclusions and macrothrombocytopenia (also called Fechtner syndrome) is assigned to 22q11-q13. ►Goodpasture syndrome, ►collagen, ►basement membrane, ►kidney diseases, ►thrombocytopenia, ►May-Hegglin anomaly, ►stem cells

ALPS-1, ALPS-2 (autoimmune lymphoproliferative syndrome): ALPS-1 (10q24) is caused by malfunction (mutation in Fas or FASL [1q23]) and ALPS-2 by mutation in caspase-10 (2q33-q34). In either case the apoptotic process is interfered with, causing neurodegeneration, tumorigenesis, and other disorders. The disease is rare and occurs in childhood. T cells accumulate but carry no CD4 or CD8 and the immune system turns against the red blood cells or the platelets. ►autoimmune ►diseases, ►FAS, ►FasL, ►apoptosis, ►CD4, ►CD8, ►T cells; Chun HJ et al 2002 Nature [Lond] 419:395.

ALS: ►amyotrophic lateral sclerosis

Alström Syndrome (ALMS, 2p13): The Alstrom Syndrome is an autosomal recessive human defect involving obesity, retinitis pigmentosa, deafness, and diabetes. Its frequency is elevated in some Louisiana and Nova Scotia populations of French origin. The ALMS1 protein contains 4,169 amino acids. ►obesity, ►Bardet-Biedl syndrome

ALT: ALT is a mechanism alternative to telomerase for the maintenance of telomere length integrity. ALT relies on recombination and depends on the Rad52 protein mediating homologous recombination. In order to prevent the restoration of telomere length during cancer therapy, perhaps both telomerase and ALT need to be targeted. ►telomerase; Grobelny JV et al 2001 Hum Mol Genet 10:1953.

AlterMap: The AlterMap is a computer program replacing sections of the Kohara map of *E. coli* with the MapSearch alignments of DNA fragments. ►Kohara map

Alternate Disjunction: Alternative disjunction takes place in a translocation heterozygote when each pole receives a complete set of the genetic material, and consequently the zygote is genetically stable. ►adjacent distribution, ►translocations chromosomal, ►translocation complex

Alternate Paternity: Alternative paternity is the situation where the biological father is different from the legal father. ►paternity exclosure

Alternation of Generations: Alternation of generations refers to the cycles of haploid and diploid generations such as the gametophytic and sporophytic generations of plants. It also refers to the cycles of sexual and asexual generations that coexist in some species. ►life cycles, ►meiosis, ►mitosis, ►apomixis, ►parthenogenesis, ►fission, ►gametophyte, ►sporophyte

Alternative Splicing: Alternative splicing of mRNAs generates different protein molecules from the same genes after eliminating introns (see Fig. A58). Tissue-specific expression of many human genes is based on alternative splicing and the extent of the global operation can be studied by microarrays (Pan Q et al 2004 Mol Cell 16:929). Splicing factors such as the hnRNP and a serine-arginine protein are used to carry out these functions. hnRNP A1 normally favors a distal 5′ splice site, but under the influence of p38 protein kinase signals, splicing may be switched to a proximal 5′ splice site. Typically, alternative splicing occurs in immunoglobulin synthesis (among other mechanisms) and T cell receptors to generate a greater repertory of antibodies from a fewer number of genes (Wang J et al 2002 Science 297:108). A survey of 528 human genes indicated 22% alternative splicing, while others indicated 40–60% alternative splicing. (Modrek B, Lee C 2002 Nature Genet 30:13). (Estimates indicated transcripts between 2.5 and 5.4 per human gene.). The average in human chromosome 12 was 2.89 transcripts per gene but for UBC (ubiquitin C, 12q24.3) 20 transcripts were found for each gene (Scherer SE et al 2006 Nature 440:346). A study of 1% of the human genome indicated that 86% of the genes are alternatively spliced (Harrow J et al 2006 Genome Biol 7[Suppl.1]: S4.1). Also it was found that in 1% of the human genome there are tissue-specific and often unannotated set of exons outside the current boundaries of the annotated genes (Denoeud F et al 2007 Genome Res 17:746). Alternative splicing displays great similarities between the human and mouse genomes (Modrek B, Lee CJ 2003 Nature Genet 34:177). However, Yeo GW et al 2005 (Proc Natl Acad Sci USA 102:2850) found much less correspondence in alternative splicing between humans and mice. The *Drosophila* axon guidance receptor *Dscam* (Down syndrome cell adhesion molecule) gene has the potential to generate 38,000 alternative transcripts (Schmucker D et al 2000 Cell 101:671). Thus alternative splicing requires fewer genes to carry out different functions. Alternative splicing has similar incidence in humans and other higher eukaryotes but it is rare or non-existent in unicellular eukaryotes. In general, about one-third of the alternative splice isoforms contain premature termination codons and although they may persist, eventually they are degraded by nonsense-mediated mRNA decay (Lewis BP et al 2003 Proc Natl Acad Sci USA 100:189). Aberrant alternative splicing is a common cause of human genetic disease (Cáceres JF, Kornblihtt AR 2002 Trends Genet 18:186). Exons duplicated in tandem (occurring in about 10% of eukaryotic genes) may be responsible for alternative splicing. Computational methods identified 245 mammalian genes in which, the exons in the DNA are not linear with the order in the mRNA. Exons in the RNA can be duplicated leading to a potential increase in phenotypic variations (Dixon RJ et al 2005 Nucleic Acids Res 33:5904). Alternative splicing is common in cancer and most of the cDNA sequences (~70%) in databases are derived from cancer cells. Therefore, these do not represent normal conditions (Roy M et al 2005 Nucleic Acids Res 33:5026). In vitro study indicates that in *Drosophila*, exons flanked by long introns have 90-fold higher chances of being alternatively spliced. The length of upstream introns in *Drosophila* is more influential than the length of downstream introns. In humans, the architecture has a similar consequence. (Fox-Walsh KL et al 2005 Proc Natl Acad Sci USA 102:16176). In *Arabidopsis* and rice plants, more than 21% of the genes display over 8% alternative splicing; more than half result in intron retention (Wang B-B, Brendel V 2006 Proc Natl Acad Sci USA 103:7175). ►splicing, ►spliceosome, ►introns, ►mRNA ►surveillance, ►hnRNA, ►p38, ►microarray ►hybridization, ►tissue ►specificity, ►exon ►skipping, ►K_A/K_S, ►DEGEST; Lopez AJ 1998 Annu Rev Genet 32:279; Tollervey D, Caceres JF 2000 Cell 103:703; Standiford DM et al 2001 Genetics 157:259; Modrek B et al 2001 Nucleic Acids Res 29:2850; Hu GK et al 2001 Genome Res

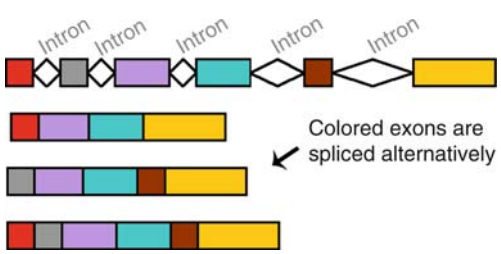

Figure A58. Alternative splicing

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11:1237; Gravely BR 2001 Trends Genet 17:100; Brett D et al 2002 Nature Genet 30:29; Kadener S et al 2002 Proc Natl Acad Sci USA 99:8185; Letunic I et al 2002 Hum Mol Genet 11:1561; Gravely BR 2002 Cell 109:409; Maniatis T, Tasic B 2002 Nature [Lond] 418:236; Zhu J et al 2003 Science 301:836; Matlin AJ et al 2005 Nature Rev Mol Cell Biol 6:386; alternative splicing and protein structure: Wang P et al 2005 Proc Natl Acad Sci USA 102:18920; alternative splicing and evolution: Xing Y, Lee C 2006 Nature Rev Genet 7:499; Biencowe BJ 2006 Cell 126:37, http://cbcg.nersc.gov/asdb; http://isis.bit.uq.edu.au, annotation of alternatively spliced genes: http://genome.ewha.ac.kr/ECgene/, alternative splicing of human genes: http://SpliceInfo.mbc.NCTU.edu.tw; http://prosplicer.mbc.nctu.edu.tw, human alternative splicing database: http://jbirc.jbic.or.jp/h-dbas/, alternative tandem splice sites: http://helios.informatik.uni-freiburg.de/TassDB/; http://www.ebi.ac.uk/asd/; http://hollywood.mit.edu/Login.php, prediction of alternative splicing: http://augustus.gobics.de/; http://t.caspur.it/ASPIC/, alternative splicing in 15 animal species: http://www.bioinformatics.ucla.edu/ASAP2, alternative splicing services: http://bip.umiacs.umd.edu:8080/, alternative splicing for entire transcriptomes and individual genes: http://genome.imim.es/astalavista/.

Altosomes: Altosomes are structurally altered dinucleosomes composed of two histone octamers, and bear an asymmetrically located region of nuclease-accessible DNA. Altosomes can be formed on chromatin that contains the abundant mammalian linker histone H1 and has a unique micrococcal nuclease digestion footprint that helps measure the position and abundance of altosomes on any DNA sequence. Over time, altosomes spontaneously revert to structurally normal but improperly positioned nucleosomes, suggesting a novel mechanism for transcriptional attenuation as well as transcriptional memory, following human SWI/SNF action (Ulyanova NP, Schnitzler GR 2005 Mol Cell Biol 25:11156). ►nucleosome, ►SWI/SNF

Altruistic Behavior: Altruistic behavior is an evolutionary feature in animals where members of the species protect other members, especially the young, even at their own peril. Altruism (helping others without expecting benefits) is genetically controlled; however, cultural inheritance also plays an important role. Human infants as young as 18 months can already show altruism, but chimpanzees at the same development stage are much less motivated for this behavior (Warneken F, Tomasello M 2006 Science 311:1301).

Altruism can promote the survival of the population. Altruism may also be manifested in mating behavior. In a pride of animals some males may refrain from reproduction to allow more powerful kin to mate with available females. Apoptosis involves some elements of altruism of single cells that turn suicidal in order to ensure differentiation of a tissue or defend the organism against mechanical or biological injuries or attacks. ►kin selection, ►inclusive fitness, ►apoptosis, ►behavior genetics, ►aggression, ►group selection, and ►"green beard effect"; Agrawal AF 2001 Proc Roy Soc Lond B Biol Sci 268:1099; Abbot P et al 2001 Proc Natl Acad Sci USA 98:12068; group selection and cooperation: Traulsen A, Nowak MA 2006 Proc Natl Acad Sci USA 103:10952

Alu Family: Alu family refers to 150–300-bp long nucleotide sequence monomers associated head-to-tail, and repeated about 300,000–500,000 times or more in the primate genome. RNA polymerase III transcribes Alu sequences. These nucleotide sequences are cut by the Alu I restriction enzyme (recognition site AG↓CT) and hence the name of these gene families. Members of this family are also considered to be transposable elements, which depend on other elements for transposition. The Alu sequences are specific for the human genomes but homologs appear in other mammals. The Alu sequences appear to have evolved from the 7SL RNA genes throughout the human genome by retrotransposition, to reach the present number of more than one million copies. Several lines of evidence demonstrate that these elements modulate gene expression at the post-transcriptional level (Häsler J, Strub K 2006 Nucleic Acids Res 34:5491; corrigendum: double bond error in Fig 3 [Nucleic Acids Res 35:5491]).

Alu insertional mutations have been identified in the genes involved in antihemophilic factor IX, neurofibromatosis, Apert syndrome, adenomatous polyposis cancer, X-linked immunodeficiency, and breast cancer. It is most likely that many more such sequences will be identified in the completely sequenced human genome. Alu elements may be inserted into RNA transcripts and may convert introns into new exons by a process of *exonization* (Lev-Maor G et al 2003 Science 300:1288). Alu sequences as well as other repeats, by recombination increase the instability of the genome. Alu elements can be used to trace evolutionary paths and human migration (Salem A-H et al 2003 Proc Natl Acad Sci USA 100:12787). ►SINE, ►LINE, ►7SL RNA, ►selfish DNA, ►Myr, ►see the diseases listed under separate entries; Stenger JE et al 2001 Genome Res 11:12, Roy-Engel AM et al 2001 Genetics 159:279;

Batzer MA, Deininger PL 2002 Nature Rev Genet 3:370, Alu in the human genome: McGuire DJ et al 2006 Adv Exp Med Biol: 578:73.

Alu-Equivalent: Alu-equivalent are a group of genomic sequences similar to the Alu family. ►Alu family

Aluminum Tolerance: Aluminum tolerance can be bred into plants by expression of the transgene of *Pseudomonas aeruginosa* citrate synthase. The transgenic plants exude citrate or malate by the roots and lower the pH of the soil. Aluminum induces from the roots of tolerant plants the release of organic acids and chelate Al^{3+} into the rhizosphere; the complexes so formed are less toxic. Several plant genes (QTLs) are involved in the resistance (Hoekenga OA et al 2006 Proc Natl Acad Sci USA 103:9738). Aluminum in alkalic or neutral soil is toxic to many crop plants. The *stop1* mutation (involved in the zinc finger domain in a predicted Cys2His2-type zinc finger protein encoded in chromosome 1 of *Arabidopsis*) had no effect on cadmium, copper, lanthanum, manganese, and sodium chloride sensitivity, but it caused hypersensitivity to Al^{3+} root-toxicity (Iuchi S et al 2007 Proc Natl Acad Sci USA 104:9900). (See Ma JF et al 2001 Trends Plant Sci 6:273)

Alzheimer's Disease (AD, FAD): Is a presenile/senile dementia (loss of memory and ability of judgment as well as general physical impairment) involving the accumulation of amyloid protein plaques in the brain, and resulting in degeneration of neurons and build-up of neurofibril tangles. At an early (prodromal) stage of AD, memory loss is not yet associated with dementia. In this condition there is atrophy in the hippocampus and the region near the hippocampus (parahippocampal region) (Soub TR et al 2006 Proc Natl Acad Sci USA 103:10041). The amyloid fibers form antiparallel β-sheets in a cross arrangement and are bound together between phenylalanine rings and salt bridges that exist between charged pairs (glutamic acid–lysine). These fibers stabilize the structure of the plaques. (Makin OS et al 2005 Proc Natl Acad Sci USA 102:315). Four major genes are responsible for AD. The amyloid-b peptide (Aβ, of 40–42 amino acids) comes from a larger amyloid precursor protein (βAPP) that is synthesized in the normal brain, is processed in a number of ways, and is encoded in chromosome 21q21.3-q22.05 as a rare early onset dominant (AD1). Duplications of 0.58 to 6.37 Mb segments involve increase in deposits of amyloid-β (Rovelet-Lecrux A et al 2006 Nature Genet 38:24). The Aβ-42 fragment has more deleterious effects; its three-dimensional structure has been determined (Lührs T et al 2005 Proc Natl Acad Sci USA 102:17342). The largest protein spans the cell membrane (AD3, 14q24.3). One of the extracellular domains is a protease inhibitor. This domain may be released in normal cells, but in diseased cells the amyloid protein is processed incorrectly. Regulation of K^+ ion channels, calcium homeostasis, and protein kinase C (PKC) gene activation (by bryostatin) promote the solubility and secretion of the amyloid protein APPα obtained from transgenic mouse brain cells. Thus, it may alleviate the human condition as well (Etcheberrygaray R et al 2004 Proc Natl Acad Sci USA 101:11141).

Synaptic acetylcholinesterase (AChE-S) seems to promote fibril formation of insoluble Aβ. The homologous synthetic butyrylcholinesterase (BchE) that has a tryptophan residue in the polar side of the C terminus of the enzyme, co-localizes with AChE and attenuates fibril and tangle formation of amyloids (Diamant S et al 2006 Proc Natl Acad Sci USA 103:8628).

Genes responsible for the amyloid protein synthesis have been cloned and others mapped to human chromosomes 1q31-42 encoding STM2/AD4, a seven-transmembrane integral protein [presenilin 2]), and to chromosome 14q24.3 encoding protein S182/AD3 (presenilin 1), which is 67% homologous to STM2. Human chromosome 19q13.2 encodes (AD2) apolipoprotein E (APOE) that controls the late onset of Alzheimer's disease. In late-onset AD (LOAD) Bace1 protease cleaves APP to generate the N terminus of A42. This protease is more active in patients with LOAD. Some results indicate that compounds antagonizing the apoE/Aβ interaction constitute an effective therapeutic approach for AD (Sadowski MJ et al 2006 Proc Natl Acad Sci USA 103:18787). A Bace-linked leucine-rich repeat transmembrane 3 (*LRRTM3*) neuronal gene promotes APP processing by BACE1 (Majercak J et al 2006 Proc Natl Acad Sci USA 103:17967). Expression of the β-site β-amyloid precursor protein (APP) cleavage enzyme gene *BACE1* is tightly controlled at both the transcriptional and translational levels. A functional hypoxia-responsive element in the *BACE1* gene promoter up-regulates β-secretase cleavage of APP and production of amyloid-β protein, by increasing *BACE1* gene transcription and expression both in vitro and in vivo. Thus, hypoxia facilitates onset of AD (Sun X et al 2006 Proc Natl Acad Sci USA 103:18727). APP overexpression leads to postsynaptic silencing through a selective reduction of AMPA receptor-mediated currents. Aβ likely mediates this effect because expression of mutant APP incapable of producing Aβ was found not to depress transmission (Ting JT et al 2007 Proc Natl Acad Sci USA 104:353).

Homozygosity for the APOE-4 allele (frequency ~16%) increases the chances of onset of the disease

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about 20 times, while a single copy of the APOE-2 (frequency ~7%) only doubles this chance. Chromosome 21q21.3-q22.05 (AD1) encodes βAPP (early onset, dominant) and seems to be involved with the disease. Aβ is the major component of the brain plaques and its ligand is a protein with a relative molecular weight ~50K, identical to RAGE (receptor for advanced glycation endproduct) or AGE/βAPP and for amphoterin controling neurite outgrowth (an inflammatory process). RAGE/AGER receptor (6p21.3) mediates the interaction of Aβ with endothelial cells and neurons, causing oxidative stress. Its interaction with microglia results in cytokine production, chemotaxis and binding movements. A spurious, unconfirmed interaction among AD1/APP, AD2/APOE, A2M (α-macroglobulin, encoded at 12p13.3-p12.3), and a low-density lipoprotein related protein (LRP, encoded at 12q13.1-q13.3) have been reported. The PAR-4/PRKC (prostate apoptosis response) mutations in the gene encoding 342 amino acids, that include a leucine zipper and a death domain, mediate neuronal degeneration and mitochondrial dysfunction in case of defects in presenilin 1. Aβ, in the mitochondria of AD patients, interacts with an alcohol dehydrogenase (ABAD). Reactive oxygen species are leaked consequently and lead to mitochondrial toxicity and impairment of hippocampal function. The latter causes memory impairment (Lustbader JW et al 2004 Science 304:448). Mutations in the control region of the brain mtDNA interfere with mitochondrial replication and transcription in AD (Coscun PE et al 2004 Proc Natl Acad Sci USA 101:10726). Sporadic AD may be associated with the very low-density lipoprotein (VLDL) receptor gene. The sortilin-related protein (SORL1; 11q23.2-q24.2) is a member of both the vacuolar sorting protein-10 domain receptor and the low-density lipoprotein receptor. Inherited variants in the SORL1 neuronal sorting receptor are associated with late-onset AD. These variants occur in at least two different clusters of intronic sequences within the *SORL1* gene (also known as *LR11* or *SORLA*) and may regulate tissue-specific expression of *SORL1*. SORL1 directs trafficking of APP into recycling pathways, and under-expression of SORL1 causes sorting of APP into Aβ-generating compartments and results in AD (Rogaeva E et al 2007 Nature Genet 39:168).

AD is common among individuals with Down's syndrome (that occurs due to chromosome 21 trisomy where βAPP is located). Some psychotropic drugs (drugs affecting the nervous system) may alleviate certain symptoms. The incidence of Alzheimer disease (AD) increases from 0.1% below 70 to double or may even reach 2% after age 80. The risk for first-degree relatives varies from 24 to 50% by age 90. Aberrant aggregation of $A\beta^{42}$ fragments and aging, are slowed when there is a decrease in insulin/insulin-like growth factor-1 signaling. (Cohen E et al 2006 Science 313:1604). The concordance rate of AD among monozygotic twins is 40–50% and among dizygotic twins 10–50%. Genetic screening for the disease is not considered appropriate. In 2005, the estimated number of people afflicted was 4.5 million and by (2050) this number may increase to 11.3–16 million. The sporadic (apparently non-genetic) cases of this disease may be caused by frameshift mutation in the RNA during transcription or after transcription, in the b amyloid precursor and/or in ubiquitin-B. The identification of AD is difficult without an autopsy or biopsy detecting the brain plaques. Biopsies generally reveal shrinkage of gyri in the lobes of the brain involved in processing learning and memory, namely the temporal and the frontal. Pet scans (positron emission tomography) of living brains reveal reduced energy metabolism in these regions in case of AD (Mattson MP 2004 Nature [Lond] 430:631). The aggregation of Aβ can be detected by fluorescence correlation spectroscopy, provided the polymerization is promoted by "seeding" with synthetic Aβ probe in femtoliter samples of the cerebrospinal fluid and Cy2 fluorophore is used. The difference between afflicted and healthy individuals is clear and the procedure may be of potential value for diagnosis. It is highly desirable that AD be detected before the onset of clinical symptoms. Magnetic resonance imaging of the brain of a mouse into whoses basal ganglia or blood stream E,E-1-fluoro-2,5-bis (3-hydroxycarbonyl-4-hydroxy)styrylbenzene (FSB) has been precisely injected, clearly labels the early deposits of amyloids (see Fig. A59). The toxicity of the procedure seems negligible although much improvement is required before it could be used clinically for humans (Higuchi M et al 2005 Nature Neurosci 8:527; this paper is also the source of the formula of FSB adopted).

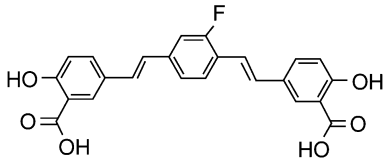
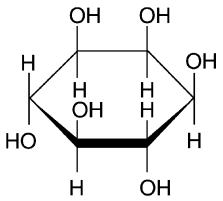


Figure A59. FSB

Mice transgenic for a mutant ($Val^{717}\rightarrow Phe^{717}$) human APP, when immunized with $A\beta^{42,}$ either prevented, or reduced the neuropathological symptoms. Unfortunately this type of vaccination resulted in meningoencephalitis in some patients and clinical trials were halted. Immunotherapy for AD so far has resulted in beneficial as well as undesirable, effects (Monsonego A, Weiner HL 2003 Science 302:834). A non-viral Aβ vaccine in mice is shown to have, beneficial prophylactic effects and ~50% reduction

in amyloids after the onset of amyloid deposition, without serious side effects (Okura Y et al 2006 Proc Natl Acad Sci USA 103:9619).



Cyclohexanehexol
(inositol)

Figure A60. Cyclohexanehexol

The most likely time-course of the development of AD is: mutations in the amyloid and presenilin genes → production of $A\beta^{42}$ fragments → formation of plaques in the brain cortex → hyperphosphorylation of tau, oxidative stress, and the formation of tangled fibers → neuronal dysfunction and neuronal death → mental deterioration. Tau reduction can block Aß- and excitotoxin-induced neuronal dysfunction and may represent an effective strategy for treating AD and related conditions (Robertson ED et al 2007 Science 316:750). There is evidence that the formation of plaques and fibrillar tangle is preceded by the appearance of 2.7 to 4.2 nm diameter soluble oligomers (see Fig. A60). The structure of the oligomers, rather than their amino acid composition, may be responsible for the toxicity (Kayed R et al 2003 Science 300:486). Early in the disease axonal swelling may occur due to deficit in microtubule-associated transport of proteins, organelles and vesicles (Stokin GB et al 2005 Science 307:1283). The hyperphosphorylation of tau, a microtubule-associated protein, is mediated by the cyclin-dependent kinase, Cdk5. Phosphorylation gets enhanced and tau binds less efficiently to microtubules, when the p35 regulatory subunit of Cdk5 is cleaved into a truncated p25 fragment. Also, Cdk5/p25 promotes apoptotic cell death of neurons. AD involves the inflammation of the brain, as well. β-Amyloid seems to stimulate CD40-CD40L interaction causing the activation of microglia. Microglial cells are important players in AD pathogenesis by promoting the degeneration of neurons. Although AD is generally attributed to the accumulation of pathological levels of $A\beta^{1-42}$, it is possible that the other cause of the disease is the lack of clearance of the plaques by the neprilysin-like neutral endopeptidase (NEP) and related enzymes. Insulin-degrading enzyme (IDE, 10q23-q25) in neurons and microglia degrades Aβ. Protein kinase PKCε upregulates endothelin-converting enzyme ECE and reduces the number of amyloid plaques, in transgenic mice (Choi D-S et al 2006 Proc Natl Acad Sci USA 103:8215). In a mouse model, Aβ immunization appears to reduce plaques and fibrils in the brain and improves cognitive functions and memory. In transgenic mice models of AD, oral administration of cyclohexanehexol stereoisomers (before or after the onset of the symptoms), inhibits the aggregation of Aβ amyloid peptides into high molecular weight oligomers, ameliorates cognition, synaptic physiology, and cerebral pathology and reduces early mortality (McLaurin J et al 2006 Nature Med 12:801).

In LOAD the Aβ42 level is elevated by genetic factors in human chromosome 10q (Myers A et al 2002 Am J Med Genet 114:235). Although at the moment there is no cure for AD, some environmental factors may exert beneficial effects. Increased cognitive/mental activity, consumption of a low-calorie diet rich in vitamins C and E, and physical exercise may delay or reduce somewhat the onset of AD. In a mouse model of AD, a diet rich in omega-3-fatty acids was found to protect against synaptic protein loss and memory deficits (Calon F et al 2004 Neuron 43:633). The APP cleavage product by α-secretase is neuroprotective due to the increased expression of transthyretin and an insulin-like growth factor (Stein TD et al 2004 J Neurosci 24:7707). Procedures of blocking the activities of β and γ secretases, chelation of copper and iron in the brain and immunization with Aβ42, are currently being studied. A transgenic mouse model suggests that an "enriched environment," i.e., exercise, elevates the level of the Aβ-degrading endopeptidase, neprilysin, and thus reduces the amyloid burden, selectively upgrading transcripts associated with learning, memory, vasculogenesis, neurogenesis and cell survival (Lazarov O et al 2005 Cell 120:701). A mouse model is available for early-onset behavior and synaptic deficits of AD (Jacobsen JS et al 2006 Proc Natl Acad Sci USA 103:5161). Intracerebral injection of dilute human Aβ or cerebral extract from Alzheimer patients, into an APP transgenic mouse induced β amyloidogenesis depending on the agent used or the recipient host (Meyer-Luehmann M et al 2006 Science 313:1781). This phenomenon bears some similarity to prion action, although this is not very clear.

The nematode *Caenorhabditis elegans* has a single *APP*-related gene, *apl-1*, that is expressed in multiple tissues. Loss of *apl-1* disrupts several developmental processes, including molting and morphogenesis, and results in larval lethality. *Apl-1* lethality can be rescued by neuronal expression of the extracellular domain of APL-1. These data highlight the importance of the extracellular domain of an APP family member and suggest that APL-1 acts in a non-cell-autonomous manner during development. Overexpression of APL-1 also causes several defects, including a high level of larval lethality. Decreased

A

activity of *sel-12*, a *C. elegans* homologue of the human γ-secretase component presenilin 1, partially rescues the lethality associated with APL-1 overexpression, suggesting that SEL-12 activity regulates APL-1 activity either directly or indirectly (Hornsten A et al 2007 Proc Natl Acad Sci USA 104:1971).

Serum response factor (SRF) and myocardin (MYOCD), two interacting transcription factors, orchestrate the vascular smooth muscle cells (VSMC)-differentiated phenotype. SRF-MYOCD overexpression in small cerebral arteries appears to initiate independently of Aβ, a pathogenic pathway mediating arterial hypercontractility, and cerebral blood flow dysregulation, which are both associated with Alzheimer's dementia (Chow N et al 2007 Proc Natl Acad Sci USA 104:823). ►b-amyloid, ►AMPA, ►behavior human, ►prion, ►Creutzfeldt-Jakob disease, ►scrapie, ►encephalopathy, ►sirtuin, ►mental retardation, ►Down's syndrome, ►corticotropin releasing factor,►presenilins, ►memory, ►AGE, ►microglia, ►NF-κB, ►LDL, ►VLDL, ►ERAB, ►frameshift, ►ubiquitin, ►tau, ►excitotoxicity, ►CDK, ►p35, ►secretase, ►statins, ►transthyretin, ►BACE, ►GSK, ►β sheet breaker peptides, ►humanin, ►fluorophore, ►mitochondrial disease in humans, ►microglia, ►CD40, ►CD40 ligand, ►neprilysin, ►endothelin, ►protein kinase, ►tomography, ►sterols, ►macular degeneration; Chapman PF et al 2001 Trends Genet 17:254; Wiltfang J et al 2001 Gerontology 47:65; Selkoe DJ 2001 Physiol Rev 81:741; Baekelandt V et al 2000 Curr Opin Mol Ther 2:540; Selkoe DJ, Podlisny MB 2002 Annu Rev Genomics Hum Genet 3:67, mouse model: Wong PC et al 2002 Nature Neurosci 5:633; Aguzzi A, Haass C 2003 Science 302:814; Cummings JL 2004 New England J Med 351:56, history of Alzheimer disease: Goedert M, Spillantini MG 2006 Science 314:777, potential approaches to treatment: Roberson ED, Mucker L 2006 Science 314:781, http://www.alzforum.org/.

Amacrine Cell: Amacrine cells are retinal neurons with short axons. ►axon, ►neurogenesis, ►retina

Amanitin ($C_{39}H_{54}N_{10}O_{13}S$): ►α-amanitin

Amaranths: Amaranths are subtropical or tropical American seed plants with 2n = 2x = 32.

Amastigote: ►*Trypanosoma*

Amatoxins: Amatoxins are bicyclic octapeptides (e.g., α-amanitin) produced by the fungus *Amanita phalloides.* They inhibit the function of RNA polymerase II (occasionally pol III) of eukaryotes but do not affect the transcriptases of the prokaryotic type, e.g., transcriptases in the cytoplasmic organelles of eukaryotes. ►RNA polymerase, ►RNA replication, ►transcription, ►pol III

Amauris: *Amauris* is an African species of butterfly that is mimicked by the species *Papilo dardanus*. *Amauris* is distasteful to predators; hence the mimicking species improves its survival. ►Batesian mimicry

Amaurosis Congenita (Leber congenital amaurosis, LCA): LCA refers to a group of autosomal recessive conditions of whole or partial blindness caused by a defect of the cornea (keratoconus). About 10% of the visually impaired suffer from LCA. LCA may also be caused by mutations in the photoreceptor guanylate cyclase (RETGC) or the retinal pigment epithelium (RPE), and in genes responsible for phototransduction and photoreceptor maintenance. Autosomal dominant photoreceptor-specific homeodomain gene (CRX), is responsible for cone-rod dystrophy of the retina. Activation of sensory transduction by opsin apoprotein in a light-independent manner may be one of the causes of LCA (Woodruff ML et al 2003 Nature Genet 35:158). LCA has been mapped to human chromosome 17p13.1. Another mutation was mapped to a retinitis pigmentosa locus (RET3C11) at 1q321-q32.1. This locus is called Crumbs Homolog 1 (CRB1) of a *Drosophila* gene. The cause of Type 1 amaurosis is located in chromosome 14 (Heilig R et al 2003 Nature [Lond] 421:601. Chromosome 6q14 encodes the ciliary protein, lebercillin, which interacts with 24 proteins and is associated with LCA (I den Hollander A et al 2007 Nature Genet 39:889). ►eye diseases, ►nephrolithiasis, ►cilia; Seeliger MW et al 2001 Nature Genet 29:70; Cremers FPM et al 2002 Hum Mol Genet 11:1169

Amaurotic Familial Idiocy (AFI): Is the old name for Tay-Sachs disease. ►Tay-Sachs disease, ►Batten disease

Amber: Amber is a fossil tree resin up to millions of years old. It is hardened and resistant to most environmental factors. Frequently it contains microbes, plants or animals, or organic residue in a well preserved state, and thus may provide very valuable information on old organismal specimens, including genetic material. ►ancient DNA

Amber: Amber also refers to a chain-terminator codon (UAG).

Amber Mutation: Amber mutation generates a chain-termination polar effect (the name has nothing to do with function; rather it was named after Felix Bernstein whose German family name translates into amber). ►code genetic, ►polar mutation; Epstein RH et al 1963 Cold Spring Harbor Symp Quant Biol 28:375.

Amber Suppressor: Amber Suppressor is a mutation in the anticodon triplet (3′-AUC-5′) of a tRNA so that

the amber mutation (5′-UAG-3′) may be read as a tyrosine codon and thus the translation not be terminated. *supC*, *supD*, *supE*, *supF*, *supG*, *supU*; Kiga D et al 2001 Eur J Biochem 268:6207.

Ambidextrous: ►handedness

Ambient Signals: The position of a particular cell determines its response to particular environmental stimuli.

Ambiguity In Translation (mistranslation, miscoding): Ambiguity may be brought about by antibiotics, or modification of the tRNA or the ribosomes (16S subunit). Consequently, an amino acid different from the original is incorporated into the nascent polypeptide. It seems the cognate tRNAs have ca. four orders of magnitude higher recognition rate than the non-cognate ones, measured on the basis of GTPase action rate in the EF-Tu-GDP ternary complex. Under normal circumstances, the estimated error per amino acid is 10^{-4}. ►error in aminoacylation, ►RAN, ►protein synthesis, ►EF-TU·GTP; Dong H, Kurland CG 1995 J Mol Biol 248:551; Ardell DH, Sella G 2001 J Mol Evol 53:269; Ogle JM, Ramakrishnan V 2005 Annu Rev Biochem 74:129.

Ambiguity of Restriction Enzymes: Such enzymes can cut more than a single sequence, although with varying efficiency, e.g., Hind I: GTT↓GAC, GTT↓AAC, GTC↓GAC.

Ambisense Virus (e.g., some bunyaviruses, arenaviruses) Ambisense viruses are transcribed into the mRNA, and also into the 5′-end of the RNA genome functioning as mRNA.

AMD: AMD is ARE- (AU-rich sequence) mediated mRNA decay. ►mRNA degradation, ►RNA surveillance, ►non-stop decay, ►RNAi, ►HuR

Ameiotic Recombination: ►parasexual mechanism, ►asexual

Amelia: ►limb defects in humans. ►thalidomide, ►phocomelia

Amelioration of Genes: DNA sequences incorporated into a genome by horizontal transfer, tend to adapt during evolution to the codon usage of recipient organisms. ►transmission, ►codon usage

Amelogenesis Imperfecta (AI): The autosomal dominant forms of this disease (ameloblastin and enamelin encoded within 4q11-q21) lead to softness of the tooth enamel caused by lack of calcium. Calcium deposits in the kidneys and variant symptoms indicate autosomal recessive inheritance as well. Two Xp22.3-p22.1- and Xq22-q28-linked forms are distinguished, one of which, is very similar in phenotype to the autosomal dominant form. The enamel is softer than usual and of normal thickness in one these cases; while in the other, the enamel is hard but very thin. The combined prevalence of the two forms in Sweden is $\sim 1.4 \times 10^{-3}$. Various mouse mutants are available (Masuya H et al 2005 Hum Mol Genet 14:575). (►See entries under tooth; Rajpar MH et al 2001 Hum Mol Genet 10:1673)

Amelogenin Test: Amelogenin test is a forensic and archeological sex typing tissue test. The X chromosome- and the Y chromosome-derived amelogenin sizes are different and thus the test indicates sex of the specimen. In rare instances the AMELY gene (Yp11, Xp22.3-p22.1) is missing from the Y and in such a case, a male sample is indistinguishable from a female sample, unless other markers (e.g., the SRY gene) are involved in the test. Amelogenin is a dental enamel protein. (►SRY, ►sex determination; Buel E et al 1995 J Forensic Sci 40:641).

Amenorrhea: The absence of menstruation that may be caused by physiological factors (obesity or malnourishment, pregnancy), hormonal imbalance, age-related factors, disease-related factors, or genetic causes such as pseudo-hermaphroditism, Turner syndrome, absence of ovaries, uterus or vagina, etc. In the absence of structural deficiencies, selective estrogen-receptor modulating (SERM) drugs may be beneficial. Secondary amenorrhea occurs when menstruation is suspended or ceased after a period of time. In such cases hormone replacement therapy may be indicated. ►hermaphroditism, ►Turner syndrome

Amensalism: A condition in which one organism is inhibited by another, which is unaffected by this relationship.

American Type Culture Collection (ATCC): The ATCC maintains and catalogues microbial stocks, viruses, and cultured cells. http://www.atcc.org/.

Amerind (American Indians): Amerind refers to the ethnically diverse groups of people, which migrated 30–10 thousand years ago in several waves, apparently through the Behring Strait from Asia to North America, and eventually spread South. Anthropological and linguistic studies and DNA (mtDNA, Y chromosome) analysis permits the study of their origin, migration, and diversity. (►mtDNA, ►Y chromosome; Bortolini MC et al 2003 Am J Hum Genet 73:524).

Ames Test: Ames test is a bacterial assay based on backmutation of different histidine-requiring strains of *Salmonella typhimurium* (see Fig. A61). Reversions are capable of detecting various types of base substitutions and frameshift. A single plate generally detects mutations in 100,000 or more cells.

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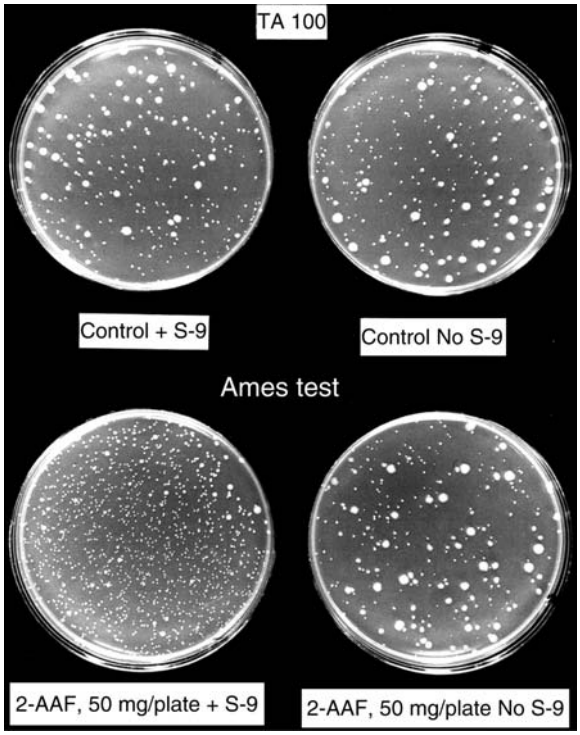

Figure A61. The Ames test with and without the use of the microsomal (S-9) fraction. It is clear that the microsomal enzymes do not affect the frequency of reversions without 2-AAF (2-acetylamino-fluorene). Also 2-AAF without activation is not mutagenic. The S-9 fraction is prepared, usually, from rodent liver homogenate and in its presence, the promutagens can also be assayed. The bacteria lack the activating enzyme component. (Courtesy of Dr. D.M. Zimmer)

In some strains the *his*$^-$ genes are present in multicopy plasmids to enhance the targets of the strains. Bacteria also carry mutations that interfere with genetic repair. The testing medium includes microsomal fractions of mammalian liver that can activate promutagens into ultimate mutagen. Thus the mutagenic effectiveness of a majority of chemicals may be increased by three orders of magnitude. The results of this assay are highly correlated with the carcinogenicity of the compounds being evaluated, yet its administration requires only two days compared with the several months that evaluations of rodent tests need. AMES is also inexpensive and permits the evaluation of a large number of compounds at low cost. ►bioassays in genetic toxicology, reversion studies in *Salmonella* and *E. coli* in ►genetic toxicology, ►microsomes, ►base substitution mutation, ►frameshift mutation, ►activation of mutagens; for statistical evaluations: Kim BS, Margolin BH 1999 Mutation Res 436:113; Maron DM, Ames BN 1983 Mutation Res 113:173, see Fig. A61.

Amethopterin: Amethopterin is an inhibitor of dihydrofolate reductase, an important enzyme in the de novo biosynthetic pathway of purine and pyrimidine nucleotides. Synonymous with methotrexate, amethopterin is used as an antitumor drug and as a selective agent in genetic transformation. It has also been used to treat rheumatoid arthritis and psoriasis. It is extremely toxic in concentrations of 10^{-8} to 10^{-9}, at which it may shut down the biosynthesis of nucleotides (see Fig. A62). It may also cause headaches, rashes, diarrhea, and cirrhosis of the liver. ►aminopterin, ►methotrexate, psoriasis.

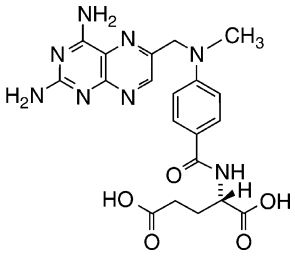

Figure A62. Amethopterin

Amide Bond: An amide bond is formed when a carbonyl group is linked to an amine (see Fig. A63). (See box, ►peptide bond).

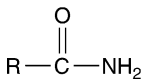

Figure A63. Amide bond

Amidotransferase: Amidotransferase enzymes are involved in charging cognate tRNAs with amino acids and in several other reactions with amid transfer. ►aminoacylation; Ibba M et al 1997 Trends Biochem Sci 22:39.

Amifostin ($C_5H_{15}N_2O_3P$ S): Amifostin is a biological radioprotector. ►radioprotectors

Amiloride ($C_6H_8ClN_7O$): Amiloride is a potassium-sparing diuretic, regulating K^+ and Na^+ balance in the cells. ►ion channels

Amino Acid: An amino acid is the building blocks of a protein. There are approximately 20 naturally occurring amino acids. amino acids.

Amino Acid Activation: ►aminoacylation

Amino Acid Analyzer: The amino acid analyzer is an automated equipment, similar to a high-pressure liquid chromatography apparatus, that separates and

quantifies the amino acid composition of protein digests. ►chromatography

Amino Acid Index: The amino acid index reveals the physico-chemical properties of amino acids and sheds light on proteins. http://www.genome.ad.jp/dbget/aaindex.html.

Amino Acid Metabolism: Amino acids are derived from compounds in the glycolytic-, the citric acid-, and the pentose phosphate pathways. Biosynthetic systems in different evolutionary categories may vary. Bacteria and plants are normally able to synthesize all the 20 primary amino acids, whereas animals depend primarily on diet for the *essential amino acids* (Boudko DY et al 2005 Proc Natl Acad Sci USA 102: 1360). Genetics of microorganisms plays an important role in elucidating ther pathways. Single gene mutations generate special requirement for all amino acids, which can be met by feeding the amino acid or the appropriate precursor. In higher plants, auxotrophy exists only for very few amino acids, probably because amino acids may be synthesized by parallel pathways or functionally duplicated genes. In humans and other mammals, certain genetic defects may affect in different ways all the natural amino acids and many of their derivatives, and thus cause inborn errors of metabolism. ►argininemia, ►citrullinemia, ►ornithine decarboxylase, ►ornithine aminotransferase, ►ornithine transcarbamylase, ►alanine aminotransferase [glutamate-pyruvate transaminase], ►alaninuria, ►aspartate aminotransferase [glutamate oxaloacetate transaminase], ►asparagine synthetase, ►aspartoacylase deficiency, ►cystinuria, ►cystinosis, ►cystathionuria, ►homocystinuria, ►cystin-lysinuria, ►glutamate synthesis, ►glutamate decarboxylase, ►glutamate dehydrogenase, ►glutamate formiminotransferase deficiency, ►glutamate pyruvate transminase, ►glutamate oxaloacetate transminase, ►glutaminase, ►glycine biosynthesis, ►glycinemia, ►methylmalonicaciduria, ►vitamin B_{12} defects, ►histidine operon, ►histidase, ►histidinemia, ►isoleucine–valine biosynthetic pathway, ►isovalericacidemia, ►3-hydroxy-3-methylglutaryl CoA lyase deficiency, ►leucine metabolism, ►methylcrotonyl-glycinemia, ►methylglutaconicaciduria, ►hydroxymethyl-glutaricaciduria, ►lysine biosynthesis, ►hyperlysinemia, ►dibasicaminoaciduria, ►methionine bio-synthesis, ►methionine adenosyl transferase deficiency, ►methionine malabsorption, ►phenylalanine, ►phenylketonuria, ►proline biosynthesis, ►hyperprolinemia, ►serine, ►threonine, ►tryptopham, ►tyrosine, ►alkaptonuria, ►valine, ►hypervalinemia, ►urea cycle, ►sarcosinemia, ►carnosinemia

Amino Acid Regulation: Amino acids and hormones, e.g., insulin, may regulate the translation of a specific amino acid mRNA or global protein synthesis, through an integrated pathway of signals.

Amino Acid Replacements: Amino acid replacements take place by base substitution in the codons, e.g., a glutamic acid (GAA) residue may be replaced by glutamine (CAA), lysine (AAA), glycine (GGA), valine (GTA), alanine, (GCA), aspartic acid (GAT), and so on. The rate of amino acid substitution per site in a protein has been estimated to average 10^{-9}/year during evolution. This average may vary by 3–4 orders of magnitude among different proteins, while the rate of substitution among genes may vary by three orders of magnitude (Wilson AC et al 1977 Annu Rev Biochem 46:573). In the enzyme 3-methyladenine DNA glycosylase (AAG), ~34% of the replacements lead to inactivation (Guo HH et al 2004 Proc Natl Acad Sci USA 101:9205).

In human disease, drastic changes in amino acid substitutions, e.g., deletions versus replacement by a similar amino acid (according to the Grantham classification), generally occur in more severe forms of the disease (Gillard EF et al 1989 Am J Hum Genet, 45:507; Miller MP, Kumar S 2001 Human Mol Genet 10:2319). ►PAM, ►mutation rate; Akanuma S et al 2002 Proc Natl Acad Sci USA 99:13549; Grantham's classification, amino acid replacement in human disease: Vitkup D et al 2003 Genome Biol 4:R72; prediction of substitutions: Ng PC, Henikoff S 2006 Annu Rev Genomics Hum Genet 7:61; http://www.genome.ad.jp/aaindex/; sorting intolerant from tolerant amino acid

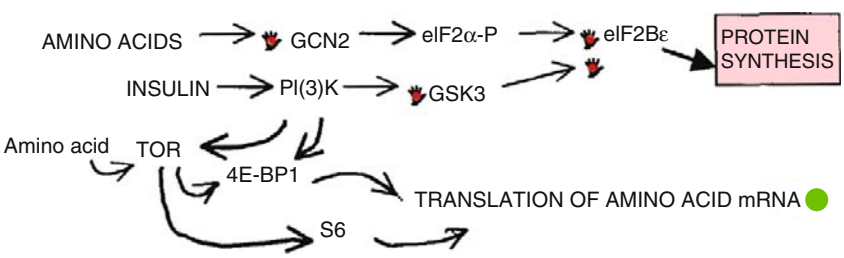

Figure A64. Regulation of Protein and amino acid synthesis under the control of amino acids and insulin

A

substitutions in proteins: http://blocks.fhcrc.org/sift/SIFT.html.

Amino Acid Sequencing: Amino acid sequencing can be carried out in different ways. At present, the most commonly used method deduces the putative amino acid sequence indirectly from the codon sequences in DNA. Direct estimates can be obtained from polypeptides cleaved by proteolytic enzymes (trypsin, chymotrypsin, pepsin, other proteases, and cyanogen bromide) to obtain manageable smaller fragments of proteins. These agents prefer certain points of cleavage, represented by specific amino acids. Direct cleavage also utilizes the chemical breakage of disulphide bonds. This is followed by the Edman degradation, which uses end labeling and removes one amino acid at a time. Eventually, the sequenced fragments must be ordered on the basis of overlapping ends. ►Edman degradation, ►amino acid analyzer, ►sequenator, ►DNA sequencing, ►databases; Rajagopal I, Ahern K 2001 Science 294:2571; key amino acid positions in structurally similar proteins: http://ckaaps.sdsc.edu; sequencing aligning; structure tools: http://toolkit.tuebingen.mpg.de/.

Amino Acid Starvation: ►stringent response, ►stringent control

Amino Acid Substitution: ►amino acid replacement

Amino Acid Symbols in Protein Sequences: These are as follows: alanine A, aspartic acid or asparagine B, cysteine C, aspartic acid D, glutamic acid E, phenylalanine F, glycine G, histidine H, isoleucine I, lysine K, leucine L, methionine M, asparagine N, proline P, glutamine Q, arginine R, serine S, threonine T, valine V, tryptophan W, unknown X, tyrosine Y, glutamic acid or glutamine Z. ►amino acids

Amino Acids: Amino acids are relatively simple yet diverse chemical compounds that all have at least one NH_2 group (see Fig. A65). **R** (see box) can be a *nonpolar aliphatic* group: glycine (Gly), alanine (Ala), valine (Val), leucine (Leu), isoleucine (Ile), proline (Pro), *aromatic:* phenyl alanine (Phe), tyrosine (Tyr), tryptophan (Trp), *polar uncharged:* serine (Ser), threonine (Thr), cysteine (Cys), methionine (Met), asparagine (Asn), glutamine (Gln), *negatively charged:* aspartic acid (Asp), glutamic(Glu), *positively charged:* lysine (Lys), arginine (Arg), histidine (His). The 20 naturally occurring amino acids are known as the building blocks of proteins. Archaea and eubacteria encode, in addition, pyrrolysine (UAG) and selenocysteine (UGA, the latter also in animals). Some amino acids are modified in certain types of proteins. Cysteine and methionine always contain sulphur. In a-amino acids both the amino and carboxyl group(s) are attached to the same C atom. The common natural amino acids in living organisms occur as the L enantiomorphs. The astrocytes in the brain, however, upon glutamate stimulation enzymatically synthesize D-serine, which facilitates synapsis between neurons by stimulation of the NMDA receptors. The amber suppressor, tRNA, aminoacylated with certain unnatural amino acids (fluorotyrosine, branched, and hydrophobic amino acids) can be incorporated into proteins and may be used to study the impact on hydrogen bonding, hydrophobic packing, and protein stability (Mendel D et al 1995 Annu Rev Biophys Biomol Struct 24:435). ►amino acid symbols in protein sequences, ►essential amino acids, ►nonessential amino acids, ►aminoacylation, ►amber suppressor, ►enantiomorph, ►unnatural amino acids, ►NMDA receptor, ►astrocyte, ►selenocysteine, ►pyrrolysine, ►genetic code, ►evolutionary clock

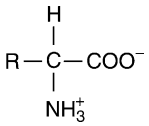

Figure A65. Amino acids general formula

Amino Group: The amino group is derived from ammonia (NH_3) by replacing one of the hydrogens by another atom (H_2N–).

Aminoacidurias: Aminoacidurias are diverse groups of hereditary diseases characterized by the urinal excretion of cystine (in cystinosis), tyrosine (in tyrosinemia), all kinds of amino acids (in fructose intolerance), very large quantities of primarily threonine, tyrosine, and histidine (in Hartnup disease), hypervalinemia. Many diseases of the kidneys show excessive amino acid excretion. Dicarboxylic aminoaciduria is a defect of glutamate/aspartate transport at 9p24. Dibasic aminoaciduria is a defect of cystinuria and the failure of normal transportation of dibasic amino acids at 9q13.1. ►homocystinuria, ►Fanconi renotubular syndrome, ►Hartnup disease, ►neuromuscular diseases, ►Rowley-Rosenberg syndrome, ►blue diaper syndrome, ►iminoglycinuria, ►tyrosinemia

Aminoacylation: An ATP-dependent enzymatic process attaches an amino acid by its NH_2 end to the acceptor arm (CCA-OH) of tRNA. The rate of mischarging is 3×10^{-3} in prokaryotes and may be higher in yeast or higher eukaryotes. Although this reaction requires a protein enzyme, a ribozyme may also be adapted to carry out aminoacylating function in a manner analogous to the ribozyme, peptidyl transferase. Certain aminoacyl-tRNA synthetases have a particular site where the misactivated amino acid tRNA

complex is destroyed to maintain the correct protein structure. Aminoacylation takes place within the eukaryotic nucleus before the correct tRNA is released to the cytosol. A single defective editing domain generates global errors in translation (Bacher JM et al 2005 Proc Natl Acad Sci USA 102:1697). For the crystal structure of an editing domain see Dock-Bergeon AC et al 2004 Mol Cell 16:375. ►tRNA, ►amino acid-tRNA synthetase, ►ribozyme, ►aminoacyl-tRNA synthetase, ►EF-TU·GTP, ►error in aminoacylation, ►operational RNA code, ►suppressor tRNA, ►unnatural amino acids; Rodnina MV, Wintermeyer W 2001 Annu Rev Biochem 70:415; Hendrickson TL et al 2002 Mol Cell 9:353; Fahlman RP et al 2004 Mol Cell 16:799.

Aminoacyl-tRNA: Aminoacyl-tRNA is an amino acid-charged tRNA at the 3′ end. ►tRNA, ►protein synthesis, ►aminoacyl-tRNA synthetase, ►amino acylation

Aminoacyl-tRNA Synthetases: These enzymes carry out the aminoacylation of tRNA (see Fig. A66). First, the amino acid is attached to the α−phosphate group of an ATP molecule. This step is accompanied by the removal of an inorganic pyrophosphate group. The aminoacyl adenylate is then bound to the active site of one of the two types of aminoacyl-tRNA synthaseenzymes. Class I, mainly monomeric (except*), enzymes handle Arg, Cys, Gln, Glu, Ile, Leu, Met,Trp*, Tyr*, and Val. Class II dimeric enzymes are involved with Ala, Asn, Asp, Gly, His, Lys, Phe, Pro, Ser, and Thr (for these abbreviations see amino acids). Class I synthase first attaches the aminoacyl-A to the 2′-OH of the terminal A of the amino arm of tRNA. Subsequently this is shifted to the 3′-OH by transesterification. The class II enzymes bypass the 2′- OH transfer step. Enzymes recognize, among the 40–80 or more tRNAs, the appropriate acid; and this rather complex recognition process is directed by the so-called *second genetic code*. Several sites on the tRNA determine the recognition of the appropriate tRNAs, most importantly by the anticodon. In *Drosophila*, there is a Glutamic acid-Proline tRNA synthetase (GluProRS). The amino-terminal domain is active for Glu, while the C-terminal fragment is functional for Pro. In some bacteria there are three types of glutamyl-tRNA synthetases. Their substrate could be either $tRNA^{Glu}$ and $tRNA^{Gln}$ singly, or both. The three tRNA species have two common elements, the augmented D-helix and the deletion of nucleotide 47 (Salazar JC et al 2003 Proc Natl Acad Sci USA 100:13863).

In some Archaea, e.g., *Methanococcus janaschii*, a single aminoacyl tRNA synthetase, ProCysRS, exists for both proline and cysteine. However, this synthetase never makes $ProtRNA^{Cys}$ or $CystRNA^{Pro}$ (Stathopolous C et al 2000 Science 287:479). In *E. coli* the anticodon is crucial for the recognition of 17 of the 20 amino acids. For many of the isoaccepting tRNAs, the 73 position of the amino acid-accepting arm is very important along with the anticodon. The enzyme also capable of correcting errors in recognition, e.g., isoleucyl-tRNA, cannot entirely prevent valine from attaching to its binding site and may form a valyl-adenylate. This activated valine cannot, however, attach to either $tRNA^{Val}$ or $tRNA^{Ile}$; rather it is hydrolyzed by $tRNA^{Ile}$, so no erroneous valyl-$tRNA^{Ile}$ is formed. Another way to eliminate translational errors is to modify the amino acids attached to the wrong tRNA; thus, rarely can these misacylated tRNA be used for peptide elongation. Actually, misacylation may occur as an intermediate step but the mentioned quality control prevents most of the stated ambiguities and errors. Misacylation of amino acids is subjected to correction by an editing complex of the tRNA (Bishop AC et al 2002 Proc Natl Acad Sci USA 99:585). tRNA-dependent amino acid modifications are the only means for the formation of formylmethionyl-tRNA and others (Asp-$tRNA^{Asn}$, Glu-$tRNA^{Gln}$) in some bacteria, archaea, and organelles. The majority of the aminoacyl-tRNA synthetases either discriminate against the D-enantiomers at activation, or use, e.g., D-Tyr-$tRNA^{Tyr}$ deacylase, to prevent the D form from being incorporated into protein. The elongation factors (EF-Tu, EF-1α) also prefer the L enantiomorphs. The C-terminal domain of the tyrosyl-tRNA synthetase has ∼49% homology with a cytokine (endothelial monocyte-activating polypeptide II [EMAPII]). This cytokine causes phagocytotic cells to express *tissue factor* and TNFα, and migrates to the sites of inflammations. The average error in amino acid incorporation is about 1/3,000 to 1/10,000. Nuclear genes encode the aminoacyl-tRNA synthetases of organelles; however, the enzymes are organelle-specific. Some nuclear genes may encode both types of enzymes by differential transcription and processing. A reactive RNA can also catalyze this reaction, normally catalyzed by aminoacyl-tRNA synthetase. The aminoacyl-tRNA synthetases of higher eukaryotes form multiprotein complexes. Incorporation of unnatural amino acids into protein can be achieved by screening for mutant aminoacyl-tRNA synthetase genes (Link AJ et al 2006 Proc Natl Acad Sci USA 103:10180). arginyl t-RNA synthetase, ►glutamyl-tRNA synthetase, ►histidyl tRNA synthetase, ►leucine t-RNA synthetase, ►threonyl tRNA synthetase, ►methionyl tRNA synthetase, ►tryptophanyl tRNA synthetase, ►valyl tRNA synthetase, ►ribozyme, ►EF-TU.GTP, ►ribosomes, ►protein synthesis, ►tRNA, ►missing genes, ►cytokines, ►EMAPII, ►wobble, ►tmRNA,

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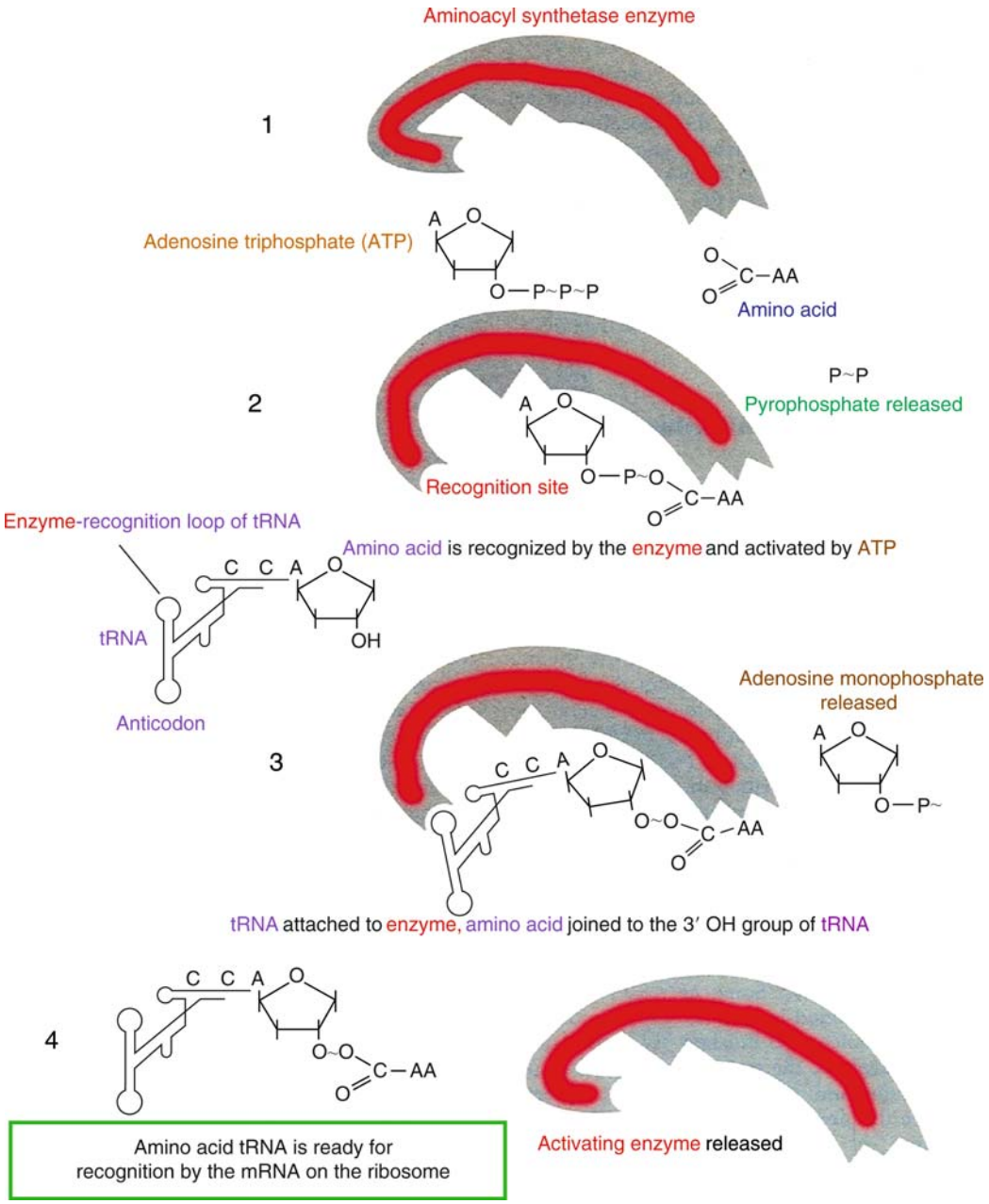

Figure A66. Amino acyl tRNA synthetases

►operational RNA code, ►unnatural amino acids; Jakubowski H, Goldman E 1992 Microbiol Rev 56:412; Carter CW Jr 1993 Annu Rev Biochem 62:715; Ibba M, Söll D 2000 Annu Rev Biochem 69:617; Ribas de Pouplana L, Schimmel P 2001 Cell 98:191; Bishop AC et al 2003 Proc Natl Acad Sci USA 100:490, http://rose.man.poznan.pl/aars/.

Aminobenzyloxymethyl Paper: This is a diazotized (using 1-[(m-nitrobenzyloxy)-methyl] pyridinium chloride [NBPC]) Whatman 540 or other comparable paper, used for Northern blotting. ►Northern blotting

Amino-End: The amino end of a protein marks where the synthesis began on the ribosome. It is commonly a methionine residue, although during processing of the protein the first amino acid(s) may be removed. The amino end of the polypeptide corresponds to the 5′ end of the mRNA. ►amino terminus, ►protein synthesis

Aminoglycoside Phosphotransferases (NPTII, aph(3′)II): NPT II phosphorylates aminoglycoside antibiotics and causes resistance against these antibiotics. The

genes for the two related enzymes were isolated from Tn*5* and Tn*60* bacterial transposons, respectively, and are used as dominant selectable markers (with appropriate promoters) in transformation of animal and plant cells. ►kanamycine resistance, ►geneticin resistance, ►neo^R, ►neomycin phosphotransferase; Wright GD et al 1998 Adv Exp Med Biol 456:27; Boehr DD et al 2001 J Biol Chem 276:23929.

Aminoglycosides: Aminoglycosides form a group of antibiotics in which, a cyclic alcohol occurs in a glycosidic linkage with amino-substituted sugars. They (streptomycin, kanamycin, neomycin, gentamycin, paromomycin, etc.) affect the A site (16S rRNA in the 30S ribosomal subunit) of the prokaryotic/organelle ribosomes, where the codon-anticodon interact, and thus interfere with initiation of translation, fidelity of decoding of the codon, peptidyl transfer, and peptide translocation. Inhibition of eukaryotic ribosome function requires a higher-than-approximately-20-fold concentration of the antibiotic. Resistance,—which is widespread, may be accounted for by the ability of the cells to expel antibiotics, or by enzymatic modification either of the antibiotic or the cellular target. ►ribosome, ►kanamycin, ►neomycin, ►gentamycin, ►A site, ►protein synthesis, ►phenotypic reversion; Ryu H, Rando RR 2001 Bioorg Med Chem 9:2601.

Aminolevulinic Acid: (ALA): ALA is a precursor of porphyrin, required for the production of hemoglobin and chlorophylls (see Fig. A67). The ALA dehydratase (ALAD) is coded in human chromosome 9q34. ►chlorophyll, ►hemoglobin, ►porphyrin

$$H_2NCH_2COCH_2CH_2CO_2H$$

Figure A67. Aminolevulinic acid

Aminopeptidases: Aminopeptidases are generally membrane ectoenzymes involved in the processing of proteins and hormones, in controlling cell adhesion, and in signal transduction.

Aminopterin: Aminopterin inhibits the activity of dihydrofolate reductase at concentrations of 10^{-8} to 10^{-9}. This enzyme is required for the biosynthetic pathway of both pyrimidines and purines, and is also used as a drug in the HAT medium to shut down the de novo synthetic pathway of nucleotides, when thymine-, kinase-, and hypoxanthine-guanine phosphoribosyl transferase mutations are screened for in mammalian cell cultures. ►amethopterin, ►HAT medium, ►DHFR

2-Aminopurine (AP): AP is an adenine analog that may incorporate into DNA in place of adenine, and can form normal hydrogen bonds with thymine. It is prone to mispairing with cytosine, either with a single hydrogen bond in its normal state, or after tautomeric shift with two hydrogen bonds (see Fig. A68). The mispairing may result in a replacement of an AT pair by a GC pair and thus, in mutation. AP may be highly mutagenic in some prokaryotes but not in eukaryotes. base analogs, ►base substitution, ►hydrogen pairing

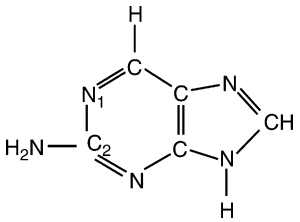

Figure A68. 2-Aminopurine

Aminoterminal: An aminoterminal is the only amino acid in a polypeptide chain with a free α-amino group; it occurs at the end of the chain. ►amino end

Aminotransferase: Aminotransferases are transaminase enzymes that transfer α-amino groups from amino acids to α−keto acids.

3-Amino-1,2,4-Triazole: is a carcinogenic standard (non-mutagenic in the Ames test); it is now a banned herbicide. ►Ames test

Amish: Amish refers to a Mennonite religious group that follow strict and conservative principles and lifestyle. Their communities are relatively isolated from surrounding populations. Actually, the Amish population in the USA in the 1960s, was organized in three approximately equal groups of ~14,000 people. Gene frequencies distinguish the three related groups. Incidence of endogamy and consanguinous marriage is higher, and certain genetically determined conditions more frequent, in these populations. The recessive Ellis-Van Creveld syndrome, pyruvate kinase deficiency, cartilage-hair hypoplasia, limb-girdle muscular dystrophy, and Christmas disease, are relatively common. The Amish brittle hair syndrome (also recessive) involving short stature, somewhat lower intelligence, brittle hair and reduced fertility, and low sulfur content of the nails was first recognized in such a population. ►Ellis-Van Creveld syndrome, ►Christmas disease, ►cartilage-hair hypoplasia, ►endogamy, ►consanguinity, ►ethnicity; McKusick VA 1980 Endeavour 42–52.

Amitochondriate: Amitochondriate organisms lack mitochondria, e.g., some microsporidian eukaryotic parasites of mammals with genomes of less than 3 Mb. More current evidence, however, indicates that these organisms may not be amitochondriate, but merely

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containing mitosomes. ►mitosome, ►hydrogenosome, ►mitochondria

Amitosis: Amitosis refers to nuclear division without the characteristic features of the mitotic apparatus, and involving the small (21 to 1,500 kb) and acentric chromosomes, in the macronucleus of some *Protists*. No mitotic spindle is evident and the nuclear membrane seems intact during the entire division. The distribution of the chromatin is nevertheless, not entirely random. ►mitosis, ►*Paramecia*, ►fission, ►acentric, ►chromatin; Prescott DM 1994 Microbiol Rev 58:233.

Amixis: Amixis is the term fungal genetics uses for apomixis. ►apomixis

Aml1: AML1 is an acute myeloid leukemia oncogene, a DNA-binding protein, encoded in human chromosome 21q22. ►leukemias

Ammonification: Ammonification refers to the release of ammonia upon decomposition of compounds such as amino acids.

Ammunition: Ammunition refers to gene tagging with non-autonomous P elements of *Drosophila*, which remains in place even after the removal of the helper (complete) element. ►hybrid dysgenesis, ►smart ammunition

Amniocentesis: Amniocentesis is a prenatal diagnosis of the genetic constitution of a fetus by withdrawing fluid or cells from the abdomen (amniotic sac) of a pregnant woman. This procedure is applicable after about 16 weeks of the pregnancy by which time the amount of the amniotic fluid is sufficient. The tests can be cytological, enzymological, immunological, or molecular, and may involve cell cultures to amplify the material. Amniocentesis can also be used for genetic counseling. Normally it entails minimal risk to either the fetus or the mother, yet should be used only in cases when it is warranted by other parts of the diagnoses. Newer procedures are aimed at the very frequency ($\sim 10^{-6}$) of fetal cells, or at fetal DNA in maternal blood. ►risk, ►counseling genetic, ►prenatal diagnosis, ►PCR, ►polymerase chain reaction, ►maternal contamination; Trent RJ (ed) 1995 Handbook of prenatal diagnosis, Cambridge University Press, New York; Special Advances in Fetal Evaluation; http://www.healthscout.com/ency/1/541/main.html.

Amnion: Amnion is the strong membrane enveloping the mammalian fetus. It contains the amniotic fluid that protects the fetus during the entire pregnancy. A similar membrane is found in other animals too. The amnion is the layer closest to the embryo, followed by the allantoic mesoderm, while the chorion is the outer layer. ►chorion, ►allantois

Amoeba: Amoebas are free-living or parasitic single-cell eukaryotes (see Fig. A69). Some amoebas crawl by forming pseudopodia (leg-like extensions of the single). *Amoeba dubia* has a genome size (bp) of 6.7×10^{11} in n = several hundred chromosomes. ►nuclear transplantation

Figure A69. Ameoba

Amorph Allele: Amorph alleles are inactive; they may also be deletions. ►allele

Amova: AMOVA refers to the analysis of molecular variance. ►ANOVA; Excoffier L et al 1992 Genetics 131:479.

Amoxicillin: Amoxicillin is an inhibitor of cell wall-crosslinking transpeptidase; thus it enhances the effect of β-lactam antibiotics (see Fig. A70). ►clavulanate

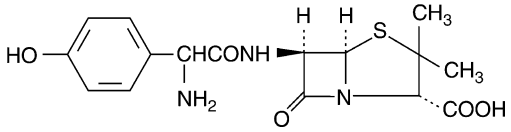

Figure A70. Amoxicillin

Amp (ampicillin, 6-[D(-)a aminophenylacetamid]-penicillinic acid): AMP is a member of the penicillin family antibiotics. The Amp^R genes are common in genetic vectors (see Fig. A71). ►antibiotics, ►vectors genetic

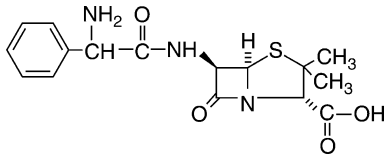

Figure A71. Ampicillin

AMP: AMP refers to adenosine 5′-monophosphate (adenylic acid); when additional 2 phosphates are added to AMP, ATP is formed. ►cAMP

AMPA (α-amino-3-hydroxy-5-methyl-4-isoxozolpropionate): AMPA is a member of the glutamate receptor family of proteins and it mediates the excitatory synaptic transmissions in the brain and the spinal cord. It also controls post-synaptic influx of Ca^{2+}, further

regulating synapse. The AMPA receptors are built from four variable subunits having large extracellular amino ends, three transmembrane domains, and an intracellular COOH end. PDZ domains mediate the cell targeting. AMPA channels are linked to elevated Ca^{2+} influx and to progressive decline and degeneration of spinal motor neurons. The channels may also be involved in the sporadic development of amyotrophic lateral sclerosis, when aided by Cu^{2+} /Zn^{2+} superoxide dismutase (Kuner R et al 2005 Proc Natl Acad Sci USA 102:5826). The GRIP (glutamate receptor interacting protein) contains seven PDZ domains, interacts with C end, and links AMPA to other proteins. ►synaps, ►excitatory neurotransmitters, ►PDZ domains, ►NMDA, ►MAGUK, ►kainate, ►superoxide dismutase, ►amyotrophic lateral sclerosis, ►fragile X; Posser RA 2001 J Neurosci 21:7815; structure, conformation of AMPA receptors: Nakagawa T et al 2005 Nature [Lond] 433:545; Tomita S et al 2005 Nature [Lond] 435:1052; Nicoll RA et al 2006 Science 311:1253.

5´-AMP-Activated Protein Kinase: This kinase regulates energy balance (Kahn BB et al 2005 Cell Metabolism 1:15).

Ampere (A): Ampere is a electric unit. 1 A = 1 C/sec. 1C (Coulomb) = 1 As (Amperesecond). ►Volt, ►Watt

Amphibolic Path: The amphibolic path of metabolism involves both anabolic and catabolic reactions.

Amphid: Amphid is a chemoreceptor in nematodes, e.g., in *Caenorhabditis*. ►*Caenorhabditis*

Amphidiploid: A cell that contains 2 genomes from at least two different species; it is obtained by doubling the number of chromosomes of amphiploids. ►amphiploid, ►chromosome doubling; Kashkush K et al 2002 Genetics 160:1651.

Amphigamy: In the usual type of fertilization the gametic nuclei fuse. ►dikaryon

Amphihaploid: Amphihaploid refers to the haploid cell of an amphidiploid, an allohaploid. ►haploid, ►amphidiploid, ►allohaploid

Amphimeric Genomes: In amphimeric genomes, the inverted repeats are separated by wide sequences. They may be generated in the mitochondrial DNA of yeast. Their origin appears to be due to illegitimate recombination between a pair of short inverted repeats. In amplified genomes they are relatively common, and are presumably advantageous for DNA replication. (See Royko E, Goursot R 1999 Curr Genet 35:14)

Amphimixis: Amphimixis is another term for sexual reproduction. ►apomixis

Amphipathic: An amphipathic compound has both a charged and neutral face (e.g., some proteins forming amphipathic helix), structures that have hydrophilic (polar) and hydrophobic (non-polar) surfaces, e.g., lipids. Generally, molecular surfaces tend to be hydrophilic whereas the inner residues are hydrophobic.

Amphiphile: Amphiphile refers to a nanomolecule with a peptide and a hydrocarbon tail. Amino acid sequences inserted into the peptide, may stimulate neural growth, tend to form connections with neighboring neurons, and can possibly repair neural cord injury when inserted into a defective spinal cord. ►nanotechnology, amphiphile for bone regeneration: Hosseinkhani H et al 2007 Tissue Eng 13:11.

Amphiphysin: Amphiphysin is a nerve protein of the synaptic vesicle bound to synaptotagmin, clathrin, and dynamin. It also participates in general endocytosis and in membrane remodeling. ►synaptotagmin, ►BIN1, ►endocytosis; Peter BJ et al 2004 Science 303:495.

Amphiploid: An amphiploid cell contains at least two genomes from more than one species. ►amphidiploid, ►allopolyploid

Amphiprotic: An amphiprotic compound can donate or accept protons and thus can behave as a weak acid or alkali, e.g., water or amino acids. ►proton, ►amino acids

Amphiregulin: Amphiregulin is a regulator with both positive and negative effects. It regulates the proliferation of keratocytes and some fibroblasts, and inhibits the proliferation of various tumor cells. It competes for the epidermal growth factor (EGF) receptor, is required for normal implantation of blastocytes and is regulated by progesterone. Amphiregulin is the unique EGF family member, which is transcriptionally induced by estrogen in the mammary glands of sexually maturing (pubertal) mice at the time of exponential expansion of the ductal system (Ciarloni L et al 2007 Proc Natl Acad Sci USA 104:5455). ►EGFR, ►keratosis, ►progesterone, ►embryogenesis; Akatsu N et al 2001 Biochem Biophys Res Commun 281:1051.

Amphistomatous: Amphistomatous leaves bear stomata on both surfaces. ►stoma

Amphithallism: Amphithallism refers to homoheteromixis, i.e., both self-fertilization and outcrossing; it occurs in fungi.

Amphitropic Molecule: An amphitropic molecule carries out different functions at different sites.

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Ampholine: Ampholine is an ampholyte used in polyacrylamide, agarose, and dextran gels, for density gradient stabilization in analytical and preparative electrofocusing. ►isoelectric focusing

Ampholyte: Ampholyte is an amphoteric electrolyte. ►amphoteric, ►electrolyte

Amphoteric: An amphoteric substance has dual, opposing characteristics, such as behaving both as an acid and a base.

AMPHOTERINE: ►Alzheimer's Disease

Amphotropic Retrovirus (polytropic retrovirus) The polytropic retrovirus replicates both in the cells from where it was isolated, as well as in other types of cells. ►ecotropic and xenotropic retroviruses

Ampicillin: Ampicillin is an antibiotic that binds to the bacterial cell membranes and inhibits the synthesis of the cell wall. The ampicillin resistance gene (*amp*^{r}) codes for a β-lactamase enzyme that detoxifies this antibiotic; the *Amp*^{r} gene is used also as marker for insertional inactivation and concomitant ampicillin susceptibility. ►antibiotics, ►insertional mutation, ►pBR322, ►amp, ►β-lactamase, ►see formula at AMP

AMPK: AMPK refers to 5′-AMP-activated protein kinase.

Amplicon: Amplicon is a DNA fragment produced by polymerase chain reaction (PCR) amplification. It also refers to the amount of DNA present in an amplified gene, a chromosomal segment, or a reduced size viral construct used for genetic transformation. ►PCR

Ampliconic Region: The ampliconic region covers about half the extent of the euchromatin region of the Y chromosome and includes large palindromes. Gene conversion is frequent in these tracts. (See Rozen S et al 2003 Nature [Lond] 423:873; ►euchromatin, ►palindrome, ►gene conversion, ►Y chromosome

Amplification: Amplification is the temporary synthesis of extra, functional copies of some genes, in vivo or in vitro, by some forms of the polymerase chain reaction. Bacteriophage l can be amplified by a series of nitrocellulose filter transfers after in situ hybridization. The addition of chloramphenicol (10–20 μg/mL) to pBR322 and pBR327 may amplify plasmid yield, if the synthesis of protein is not completely prevented. Cosmid libraries may be amplified by starting on solid plates followed by liquid cultures. Replica-plating can amplify animal cell cultures. Approximately 5×10^4 colonies can be accommodated on a 138-mm filter, and this way about 30 filters are required to obtain a representative library of overlapping fragments. DNA amplification can occur in a *genetically programmed and predetermined* manner in eukaryotes. For example, in the ovarian follicle of *Drosophila*, large quantities of an egg-shell protein is needed during oogenesis. The need is met by a disproportionately favorable replication of the chorion gene clusters in the X-chromosome and chromosome 3. DNA replication is initiated bidirectionally at a replicational origin, and generates multiple copies of the genes needed. The replication tapers off after a distance and the flanking regions are amplified less and less in proportion to the distance from the origin. Similar programmed amplification takes place in the ribosomal genes of amphibia during intense periods of protein synthesis in embryogenesis. The approximately 500–600 genomic copies of rRNA genes may thus be increased by a factor of 1000. The replication of detached DNA sequences follows a rolling circle type process, and the new DNAs (in about 100 rDNA repeats) are separately localized in micronuclei. The replicates of these nuclei are structurally similar, indicating that they are the clonal products of a single replicating unit; but the new micronuclei generated in different cells may not be the same as judged by the differences in length in the intergenic spacers. Ribosomal DNA amplification takes place during the amitotic divisions of the protozoon, *Tetrahymena*. Here again, the macronuclear rDNA copies may be selectively amplified in the 10^4 range, whereas the micronuclear DNA contains only a single rDNA gene. A *genetically non-programmed amplification* takes place in several mutant cell lines to correct mutational defects. Producing multiple copies of gene-controlling low-efficiency enzymes may compensate for enzyme deficiencies. Transfection of ADA genes to mammalian cells may be amplified in the presence of dCF (see adenosine deaminase). Mammalian cells can be amplified if they are co-transfected with the *dhfr* (conveying methotrexate resistance) gene and other desired sequences. In the presence of methotrexate, the *dhfr* genes, as well as the flanking DNA, may be amplified (1000) fold. The amplified DNA, in stable lines, is integrated into the chromosome in *homogeneously stained regions* (HSRs). In unstable cell lines, *dhfr* occurs in autonomously replicating elements, called double-minute chromosomes (DMs), which have no centromeres and can be maintained only in cultures that contain methotrexate. Amplification may generate fragile sites in the chromosomes by integration of DMs sequences. Hypoxia may be a factor inducing such integration. Some general features of amplification are: (i) expansion of a particular locus and flanking regions, or the generation of small supernumerary chromosomes called double minutes that

contain the critical gene, (ii) possible rearrangements of the amplified unit (iii) the amplified sequences are not all identical and may change, but these changes are somewhat unusual because a larger number of copies may be altered simultaneously in an identical manner. In vivo amplification of genes during evolution may account for the presence of gene families. Some amplified genes, in which production of a larger number of copies was no longer advantageous, may have acquired new functions without entirely losing their structural similarity to the ancestral sequences. Other members of the amplified group lost their function(s) through deletions and mutations and became pseudogenes. Carcinogenesis commonly involves amplification of some oncogenes and genes involved with the cell cycle (cyclins). Fragile sites in some chromosomes aid amplification. ►PCR, ►MDA, ►nitrocellulose filter, ►in situ hybridization, ►chloramphenicol, ►pBR322, ►cosmid library, ►oogenesis, ►chorion, ►bidirectional replication, ►rolling circle, ►micronucleus, ►ADA, ►HSR, ►methotrexate, ►fragile sites, ►pseudogene, ►unequal crossing over, ►DM chromosome, ►adaptive amplification, ►breakage–bridge–fusion cycles, ►translocation heterozygote; Romero D, Palacios R 1997 Annu Rev Genet 31:91; Monni O et al 2001 Proc Natl Acad Sci USA 98:5711; Dean FB et al 2002 Proc Natl Acad Sci USA 99:5261; Tower J 2004 Annu Rev Genet 38:273.

Amplification Control Elements: Amplification of genes in chromosome 3 and the X-chromosome of *Drosophila*, are determined by DNA sequences measuring less than 5 kbp, which normally occur in the vicinity of the genes that are amplified under natural conditions of the genome (e.g., the chorion protein gene). If these control elements are isolated, inserted into genetic vectors (P-elements), and reintroduced at random sites into the *Drosophila* genome, they may amplify other sequences in their new neighborhood. ►amplification, ►hybrid dysgenesis

Amplified Fragment Length Polymorphism: ►AFLP

Amplitaq: Amplitaq is a taq DNA polymerase, a single polypeptide chain enzyme with minimal secondary structure. It is isolated from the bacterium *Thermus aquaticus*. Its temperature optimum is about 75 °C but it can withstand ≤95 °C without great loss of activity. It lacks intrinsic nuclease function but has a polymerization-dependent 5′ → 3′ exonuclease activity. It is a preferred enzyme for PCR. ►PCR, ►DNA polymerase, ►exonuclease, ►Taq DNA polymerase

Amplitype: ►DNA fingerprinting

Amputations: ►ADAM complex, ►limb defects

Amsterdam Criteria: Amsterdam criteria were established in (1990) at a meeting in Amsterdam for ascertaining the hereditary nature of non-polyposis colorectal cancer. The criteria are: 1. at least three family members, of which two are first degree relatives, are affected, 2. at least two generations are represented, and 3. at least one family member is below age 50 at the time of onset. ►hereditary non-polyposis colorectal cancer, relatedness, degree of, http://www.medscape.com/viewarticle/468147_4.

Amusia: Amusia is a deficit of music perception caused by a genetic or acquired brain anomaly. It may not affect any other brain function or intelligence. In some case it is associated with limitation of prosody, rhythm and pitch of speech. ►musical talent

AMV Oncogen (*v-amv*): ►MYB

α-Amylase: α-amylase hydrolyzes α-1–4 glucosidic linkages of amylose, amylopectin, and other carbohydrates and yields maltose, α-dextrin, and maltotriose. β-Amylase hydrolyzes starch into maltose. The human AMY genes are located in chromosome 1p21.

Amyloid Angiopathy: ►amyloidosis type VI

Amyloidosis: Amyloidosis involves extracellular deposition of variable amounts of amyloids. Amyloids are special fibrous glycoproteins of connective tissues, and are caused by protein misfolding. Some of the familial nephropathies (kidney diseases), heart diseases, and neoplasias involve amyloidosis. Heparanase overproduction digests heparans that are also essential for amyloid deposition (Li JP et al 2005 Proc Natl Acad Sci USA 102:6473). Genetically these are inhomogeneous groups of diseases mainly with dominant, but some with recessive, patterns of inheritance. Amyloidosis in some aging individuals manifests symptoms similar to the symptoms of Alzheimer's disease. The dominant genes were mapped to the same region of chromosome 21 as the genes behind AD, and also to 20p12, the site of the prion gene. The Swedish and Portuguese Amyloidosis I is a dominant polyneuropathy encoded near the centromere in the long arm of human chromosome 18. The Finnish Amyloidosis type V is apparently due to an autosomal dominant defect in gelsolin. The Icelandic Amyloidosis type VI involves high incidence of hemorrhages due to accumulation of amyloids. The afflicted individuals (dominant) are low in cystein proteinase inhibitor, cystatin C, encoded in the region of human chromosome 20q13. The Ohio type Amyloidosis VII involves ocular and mental affliction. The German Amyloidosis type VIII is a visceral and renal disease. Amyloidosis IX is a skin disorder. The familial British dementia is a dominant, late onset brain degenerative

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condition caused by the BRI gene in human chromosome 13q14. There are recessive amyloidoses affecting the gingiva (gum), eyelids, cornea (eyeball), and mental health. Amyloid formation may occur in a number of pathogenic conditions, but can also occur as a rather general feature of polypeptide chains. Under some conditions, there may be a cycle of dissociation re-association. (Carulla N et al 2005 Nature [Lond] 436:554) The gelatinous drop-like corneal dystrophy (GDLD, human chromosome 1p) is an amyloidosis caused by mutation in a gastrointestinal tumor-associated antigen. The small molecules of transthyretin (thyroxin-binding prealbumin) interfere with the misfolding of the protein, and may be considered for therapeutic use. Some mutations in the human lysozyme promote fibril and plaque formation, but a heavy chain domain of the camelid antibody raised against the wild type lysozyme may inhibit this deleterious aggregation (Dumoulin M et al 2003 Nature [Lond] 424:783). ►cold hypersensitivity, ►Mediterranean fever, ►β-amyloid, ►Alzheimer disease, ►scrapie, ►prion, ►encephalopathies, ►gelsolin, ►amyotrophic lateral sclerosis, ►sterols; Pepys MB et al 2002 Nature [Lond] 417:254; Hammarström P et al 2003 Science 299:713.

Amyloids: Amyloids are fibrillar poorly soluble/insoluble proteins forming β sheets, e.g., apolipoproteins. Positional scanning mutagenesis reveals tolerant and restrictive sites in the peptide for fibril formation. Mutations that accelerate β-sheet polymerization do not necessarily increase amyloid formation. Some abundant mutant fibrils polymerize slowly, and some amino acid combinations disrupt aggregating capabilities (López de la Plaz M, Serrano L 2004 Proc Natl Acad Sci USA 101:87). Potent inhibitors of amyloid aggregation may involve synthetic molecules that can bind to chaperones (of the FK506 family), and can interact with amyloids by their increased size, required for interaction with proteins (Gestwicki JE et al 2004 Science 306:865). Proteoglycan-amyloid complexes are protected from proteolysis. Several neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, prions) are caused by amyloid formation. Recent information indicates that it is not fibrillar amyloids, but rather their globular aggregation, which form ion channel-like structures, that act as the major pathological agents (Quist A 2005 Proc Natl Acad Sci USA 102:10427). According to the *amyloid stretch hypothesis* the tendency to form amyloids is localized in short stretches of the proteins in question (Esteras-Chopo A et al 2005 Proc Natl Acad Sci USA 102:16672). In addition, atomic structures, common to various amyloid proteins, have been determined (Sawaya MR et al 2007 Nature [Lond] 447:453).

Certain starch-like substances are also called amyloids. The amyloid Pml17 of melanosomes, promotes the polymerization of smaller molecules into melanin. Melanins, unlike many amyloid proteins, are beneficial molecules important in protecting against ultraviolet light and other oxidative damage. Pml17 protects cells against adverse effects of excessive melanin (Fowler DM et al 2006 PLoS Biol 4(1):e6). ►amyloidosis, ►Alzheimer's disease, ►proteoglycan, ►β sheet, ►protein structure, ►FK506, ►chaperone, ►homolog-scanning mutagenesis, ►melanin, ►glaucoma

Amylopectin: Amylopectin is normally a minor variant of common starch. While starch (amylose) is an unbranched chain of D-glucose units of α1–4 glycosidic linkages, amylopectin contains, in addition, at every 24 to 30 residues branch points in α-1–6 linkages (see Fig. A72).

Amylose is synthesized by an active granule-bound starch synthase; starch-branching enzymes SBEI and SBEII synthesize amylopectin. In monocots there are two isoforms of SBEII (a and b). In maize, deficiency of SBEIIb is the consequence of the *ae* (amylose extender) gene. Increased amounts of amylose vis-a-vis those of amylopectin lead to dietary and health-related advantages. Transgenic technology (RNAi) Can help reduce SBE enzyme levels, resulting in more than 70% amylose in wheat. (Regina A et al 2006 Proc Natl Acad Sci USA 103:3546). Cereal grains commonly contain amylose as the principal storage polysaccharide, but recessive mutations may cause the predominance of amylopectin (dextrin). Several genes of maize (*ae, du*) may substantially increase the amylose content relative to that of amylopectin.

These two types of starches are easily distinguished in situ by a drop of iodine solution (I_2 0.12 g + KI 0.4 g in 100 mL H_2O); amylose stains blue-black, while amylopectin appears red-brown. The amylose content of corn is desirable also to the film and fiber-manufacturing industry.

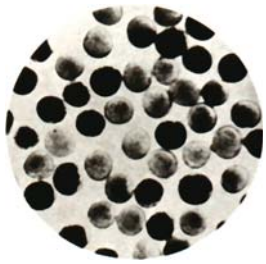

Figure A72. Stained sorghum pollen displays segregation for starch and amylopectin. (Courtesy of Dr. JR Quinby. See Karper RE (1933) J Hered 24:257)

Amyloplasts: Amyloplasts are plastids whose primary function is starch storage.

Amylose: ▶amylopectin

Amyotrophic Lateral Sclerosis (ALS, Lou Gehrig disease): ALS is characterized by the hardening of the lateral columns of the spinal cord with concomitant muscular atrophy. This may spread and may cause death in a few years after onset. According to a mouse model, it is probably caused by a defect in the enzyme Cu/Zinc Superoxide Dismutase (SOD) in about 20% of the familial cases. The expression of mSOD1G93A results in activated and neurotoxic microglia, and suggests that the lack of mSOD1G93A expression in microglia may contribute to motor neuron protection (Beers DR et al 2006 Proc Natl Acad Sci USA 103:16021). SOD breaks down superoxide radicals (highly reactive compounds) to less reactive products; it may also form other types of free radicals. Under normal conditions, SOD exists in a dimerized state. Mutations may either destabilize the precursor monomers, or weaken the dimer interface, or both. In any case, the difference between various abnormal foldings of the protein leads to differing severity of the disease (Lindberg MJ et al 2005 Proc Natl Acad Sci USA 102:9754). In ALS, frontotemporal lobe degeneration occurs in the brain, displaying tau and synuclein inclusions. Ubiquitin is also present and cleaves the C-terminal fragment of the TDP-43/TARDP protein that is detectable in the hippocampus, neocortex, and the spinal cord (Neumann M et al 2006 Science 314:130).

Not all cases of SOD dismutase apoprotein mutations are involved in reduced stability (Rodriguez JA et al 2005 Proc Natl Acad Sci USA 1032:10516). Aggregation of the molecules results in ALS. SOD1 apparently causes neural death by acting on caspases that mediate apoptosis. The *Bcl-1* gene inhibiting apoptosis prolongs the life of mice affected by SOD. A subsequent study found, however, that neither the elimination, nor elevation of SOD activity in mice influenced the expression of ALS. Current research indicates that Zinc-deficient SOD, plays a role in nitric oxide-dependent apoptosis of some motor neurons. The SOD transgene effect can be restrained by N-benzyloxycarbonyl-Val-Asp-fluoromethyl-ketone (zVAD-fmk), an inhibitor of caspases. This, in turn delays the onset of ALS in mice, and increases life expectancy. Mutations in SOD1 may cause aberrant decrease of *S*-nitrosothiol level and may be remedied by *S*-nitrosocysteine (Schonhoff CM et al 2006 Proc Natl Acad Sci USA 103:2404).

In G37R *SOD1* mice, administration of repeated injections of adjuvant/SOD1 mouse mutant with a final booster injection before symptoms manifested at 6 months of age, were effective in delaying disease onset and extending the life span by >4 weeks. Western blot analysis with a monoclonal antibody specific to mutant *SOD1* forms provided evidence of clearance of *SOD1* species in the spinal cord of vaccinated animals. This vaccination failed to confer significant protection in G93A *SOD1* mice that showed extreme and excessive expression of mutant *SOD1*. Nonetheless, a passive immunization, in which an intraventricular infusion of purified anti-human *SOD1* antibody was administered through an osmotic minipump, succeeded in alleviating disease symptoms and in prolonging the life span of G93A *SOD1* mice (Urushitani M et al 2007 Proc Natl Acad Sci USA 104:2495). Adult motor neurons collected by laser microdissection from mice expressing dismutase active ALS-linked mutants were found to undergo an age-dependent mRNA change that developed presymptomatically. in This change occurs due to the dysregulation of the D/L-serine biosynthetic pathway, previously linked to both excitotoxic and neurotrophic effects. An unexpected dysregulation, common to motor neurons expressing mutants that were either dismutase active, or inactive, comprised of the induction of neuronally derived components of the classic complement system, and the regenerative/injury response (Lobsiger CS et al 2007 Proc Natl Acad Sci USA 104:7319).

The gene leading to ALS symptoms is a dominant "gain-of-function" mutation within the area 21q22.1-q22.2 (SOD1, Cu/Zn superoxide dismutase). The syndrome, in different forms, occurs at a frequency of about 1×10^{-5}. About 10% of the cases are hereditary and 90% are sporadic. It is also called LGD after baseball infielder Henry Louis (Lou) Gehrig. Gehrig, who was elected to the US National Hall of Fame in 1939, suffered from this condition. ALS is sometimes associated with phenotypes like those in Parkinson's disease and Alzheimer's disease. This form may be caused or aggravated by nutritional factors (neurotoxins in the food, low calcium and magnesium uptake). Other dominant loci were assigned to 18q21 and 16q12.1-q12.2. The dominant juvenile form (ALS4) has been mapped to 9q34; a similar gene is located at 15q15-q22. A recessive autosomal type of ALS, with an early onset between the ages of 3 and 20, is assigned to human chromosome 2q33. The protein encoded, alsin, may directly affect motor neuron degeneration and may signal to GEFs. Copaxone (Cop-1), a synthetic copolymer of tyrosine, glutamate, alanine and lysine, may protect motor neurons against acute and chronic degeneration (Kipnis J, Schwartz M 2002 Trends Mol Med, 8:319). Retrograde transport of insulin growth factor 1 with the aid of adeno-associated vector, from axon terminal receptors to motor neurons of the spinal cord, appears very beneficial in animal models

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(Kaspar BK et al 2003 Science 3001:839). VEGF mutations may increase the risk of developing ALS; in a mouse model a single injection of VEGF-expressing vector improved the host's condition and prolonged its survival (Azzouz M et al 2004 Nature [Lond] 429:413). It appears that mRNA editing in the GluR2 subunit of the AMPA receptor in the motor neurons may be critical for the disease (Kawahara Y et al 2004 Nature [Lond] 427:801). The pancreatic ribonuclease A family protein ANG (angiogenesis, 124 amino acid residues encoded at 14q11.2) can mutate at several sites. In addition to the catalytic center, it has a site for translocation to the nucleolus. ANG and VEGF variations in hypoxia-inducible genes increase ALS susceptibility, particularly in Irish and Scottish populations (Greenway MJ et al 2006 Nature Genet 38:411). Molecular evidence suggests common pathogenesis for sporadic and familial ALS, but no evidence suggests this commonality between ALS and normal or disease-affected tissues from other neurodegenerative diseases, including Alzheimer's, Parkinson's, and Huntington's diseases, and spinal muscular atrophy, a non-ALS motor neuron disease. This fact permits the use of ALS as a biomarker (Gruzman A et al 2007 Proc Natl Acad Sci USA 104:12524). ►neuromuscular diseases, ►Alzheimer disease, ►Parkinson disease, ►tau, ►apoptosis, ►filament, ►SOD, ►gain-of-function, ►hypoxia, ►GEF, ►VEGF, ►dynein, ►VEGF, ►AMPA, ►TARDP; Julien J-P 2001 Cell 104:581; Yang Y et al 2001 Nature Genet 29:160; Giess R et al 2002 Am J Hum Genet 70:1277; SOD mutations: Selverstone J et al 2005 Annu Rev Biochem 74:563.

Amyotrophy, Hereditary, Neuralgic (HNA, 17q25): Amyotrophy is a recurrent muscle weakness affecting the neck and arms; it occurs due to defects in cervical and thoracic spinal nerves. It is generally triggered by stress, such as infection, immunization, or labor at childbirth. The mutation apparently occurs in the septin gene (SEPT9) involved in the formation of the cytoskeleton, in cell division, and in tumorigenesis. (See Kuhlenbäumer G et al 2005 Nature Genet 37:1044; Parsonage-Turner syndrome, Guillain-Barré syndrome)

Anabasine (neonicotine): Anabasine is an alkaloid occurring in chenopods and solanaceous plants; it is highly toxic (LDlo orally 5 mg/kg for humans). ►LDlo

Anabolic Steroids: Anabolic steroids are androgens that promote protein synthesis, general growth, and the development of muscles and bones. Some synthetic forms (methyltestosterone, oxymetholone, norethandrolone) show higher anabolic than testosterone-related activity and are used illegally by athletes to boost performance; literally, these steroids are "body builders." Some androgenic and anabolic steroids are used as drugs in the treatment of impotence, anemias, and bone marrow aplasia. These compounds may cause liver adenomas that in rare cases may become cancerous. ►steroid hormones, ►adenoma, ►impotence, ►anemia, ►aplasia, ►steroid doping

Anabolism: Anabolism comprises the energy-requiring synthetic processes of cellular metabolism.

Anaerob: Anaerobs are organisms that live without atmospheric (free) oxygen.

Anaerobic: Anaerobic a processes take place in the absence of (air) oxygen.

Anagenesis: Anagenesis is an evolutionary change within a line of descent. ►cladogenesis

Analbuminemia: Analbuminemia is a human chromosome 4 recessive absence or reduction of albumin from the blood serum. It does not lead to very serious ailments, although fatigue, mild anemia, and mild diarrhea may be associated with it. ►albumins

Analgesic: An analgesic is a medication that alleviates pain without inducing loss of consciousness. Endocannabinoids mediate analgesic action; stress can mediate the response (Hohmann AG et al 2005 Nature [Lond] 435:1108). TRPM8 cold receptor and its central downstream mediators are elements of endogenous-cooling-induced analgesia, and they represent a novel analgesic pathway that can be exploited in chronic sensitized pain of nerves in rats (Proudfoot CJ et al 2006 Current Biol 16:1591). ►nociceptor, ►cannabinoid

Analogous Genes: Analogous genes have similar function without common evolutionary descent. ►homologous genes

Analogue (analog): Analogue is a chemical counterpart to a natural compound, but it may or may not function in metabolism. It may even block the function of a normal metabolite or enzyme.

Analogy: Analogy is a similarity not based on common origin. ►homology, ►convergent evolution

Analysis of Variance: Analysis of variance is a statistical method that detects the components of variance. It is used for the evaluation of differences between experimental data from different treatments. The square root of the quotient of the sum of squares of the variants and the mean square of the error variance is equal to *t*, and the corresponding probability, at each degree of freedom, can be read from a *t*-distribution table. The results are usually presented in a table form such as shown (see Table A4).

Table A4. Analysis of variance

Variance Source	Degree of Freedom	Sum of Squares (SS)	Mean Square (MS)	Mean Square Ratio (MSR)
Between Groups	k−1	SSB	SSB/(k−1)	$\frac{SSB/(k1)}{SSW/(Nk)}$
Within Groups	N−k	SSW	SSW/(N−k)	
Total	N−1			

The MSR (mean square root) permits testing the significance of the data, also with the aid of an F table. Analysis of variance is also used in calculating heritability by intraclass correlation. ►variance intraclass correlation, ►F distribution, ►*t-distribution*; Sokal RR, Rohlf FJ 1969 Biometry, Freeman, San Francisco, California.

Analyte: An analyte is a substance subjected to analysis. It frequently reveals the basis (by deficiency or overproduction) of a genetically determined disease.

Anandamide (*N*-arachidonoylethanolamine): Anandamide is an endocannabinoid and vanilloid receptor that plays different roles in healthy and cancerous cells. It is a ligand for G proteins. It is produced at higher levels in the uterus before implantation of embryo, and is regulated to lower levels afterwards. G protein, ►cannabinoid, ►vanillin; Wang H et al 2003 Proc Natl Acad Sci USA 100:14914; biosynthetic pathway: Liu J et al 2006 Proc Natl Acad Sci USA 103:13345.

Anaphase: During *mitosis*, the centromere of the chromosomes splits at anaphase; this is what enables spindle fibers to pull the two identical chromatids towards opposite poles. This process ensures the daughter cells are identical. In *meiotic* anaphase I, the centromere does not split and the chromatids are held together as they move toward the poles. Thus, it is the means for the reduction of chromosome number. Anaphase II of meiosis essentially resembles anaphase in mitosis. Microtubules and special motor proteins mediate the movement of chromosomes. The molecular mechanism of the process is only partly known. In yeast, the *MAD* (mitotic arrest deficient) and *BUB* (budding inhibited by benzimidazole) gene products seem to be the sensors of those kinetochores, which have not yet tackled the spindle fibers. Before the sister-chromatids can separate, the anaphase-promoting complex (APC) degrades the inhibitors of the process (Pds1/Cut2). Proteins Cdc20/Slpl and Hct1/Cdh1 digest other inhibitory proteins (Clb2 and Ase1). ►meiosis, ►mitosis, ►microtubules, ►motor protein, ►APC, ►cell cycle, ►spindle, ►sister chromatid cohesion, ►cohesin, ►separins; Nasmyth K 2005 Cell 120:739.

Anaphase-Promoting Complex: ►APC

Anaphora: Originally anaphora is a rhetorical device of repeating a word or phrase in successive clause(s) or sentences. In science writing, the name of a compound, gene, or protein is generally referred to, after first instance, with the word "it" or with a previously given abbreviation.

Anaphylactic Shock: Anaphylactic shock refers to immediate hypersensitivity to specific antigens or haptens, resulting in dangerous loss of respiratory function. ►anaphylatoxins, ►anaphylaxis

Anaphylatoxins: Anaphylatoxins are fragments released during activation of the serum complement C proteins of antibodies. C3a, C4a, and C5a (each ∼10 kDa) anaphylatoxins are proteolytically cleaved from the corresponding complement components. These activation peptides are called anaphylatoxins because they may elicit reactions similar to anaphylactic shock (violent reaction to antibodies and/or haptens that may be fatal). These fragments enhance vascular permeability, cause contraction of the smooth muscles, and trigger the release of histamine, other vasoactive amines, and lysosomal enzymes. ►antibody, ►complement, ►histamine, ►lysozymes; Gerard C, Gerard NP 1994 Annu Rev Immunol 12:775; Sunyer JO et al 2005 Vet Immunol Immunopathol 108:77.

Anaphylaxis: Anaphylaxis is a rapid serological (antigen-antibody) reaction of an organism to a foreign protein. Either the crystalline fragment of the antibody (Fc), or its complement is involved. Prior sensitization may turn the reaction quite violent and even lead to death. Anaphylaxis may be treated with adrenaline. ►immune system, ►antibody, ►complement, ►allergy

Anaplasia: Anaplasia is another term for dedifferentiation.

Anaplasma marginale: *Anaplasma marginale* causes tick-borne rickettsia of livestock. The genome of the sequenced strain has 1,197,687 bp. ►rickettsia; Brayton KA et al 2005 Proc Natl Acad Sci USA 102:844.

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Anaplastic Lymphoma (large-cell non-Hodgkin lymphoma): Anaplastic lymphoma is a lymphoma in children, and is caused by a 2p23:5q35 chromosomal translocation fusing a protein tyrosine kinase gene, ALK, to the nucleolar phosphoprotein genes (NPM, nucleophosmin). The resulting anomaly affects the small intestine, testis, and brain, but not the lymphocytes. ALK is related to the insulin receptor tyrosine kinases and may eventually cause malignancies. Translocations involving 1q21-q23, the site of the IgG Fc receptor (FcγRIIB), are also responsible for this malignant lymphoma. ►leukemias, ►lymphoma, ►Duncan syndrome, ►Hodgkin disease, ►antibody, ►immunoglobulins; Pulford K et al 2001 Curr Opin Hematol 8(4):231.

Anaplerosis: Anaplerosis is biological repair or replacement.

Anastomosis: Anastomosis refers to formation of a reticulate arrangement, fusion between vessels.

Anastral Spindle: Anastral spindle is a mitotic spindle without asters, such as in higher plants. ►aster

Anatomy: Anatomy is the biological discipline dealing with body structure. For functional anatomy see: http://bodymap.jp/.

Anautogenous Control: The organism requires an external factor for the completion of a developmental process, e.g., the mosquito *Aedes aegypti* requires a meal of blood to activate its reproductive cycle. ►autogenous, ►mosquito

Ancestral: Ancestral is a trait inherited from a remote forebear or derived from a precursor molecule. Modern ancestry inferences are based on multilocus genotypes and allelic frequencies. Various statistical tools make inferences meaningful (Rosenberg NA et al 2003 Am J Hum Genet 73:1402).

Ancestral inheritance as a theory based on the false assumptions of a non-particulate genetic material, was developed by Francis Galton (1897), but lost meaning after Mendelism.

Ancestral Repeats (AR): The origin of ancestral repeats predates the separation of two species, e.g., mice and humans. ARs can be exploited for the estimation of neutral substitutions in the genomes.

Ancestry Markers: Ancestry markers can provide information on the descent of a population or an individual, because certain alleles occur in characteristic frequencies in some populations.

Anchor Cell: An anchor cell is a gonadal cell of *Caenorhabditis* that in the vulval opening induces the development of its neighboring cell. ►*Caenorhabditis*, organizer, ►morphogenesis

Anchor Locus: Anchor locus is a gene with well-known map position and can be used as a reference point for mapping new genes. ►anchoring

Anchor Residues: Anchor residues are amino acids of those peptides that attach to MHC molecules. ►MHC

Anchorage Dependence: Normal mammalian cells grow in culture in a monolayer attached to a solid surface; cancer cells are not contact-inhibited and pile upon each other. It appears that the suppression of cyclin E-CDK2 activity is required for cell anchorage. In transformed fibroblasts, the cyclin E-CDK2 complex is active regardless of anchorage. The surface of the cell substrate has an impact on differentiation, development, regeneration, and disease of cells (Discher DE et al 2005 Science 310:1139). ►CATR1, ►AIG, ►cyclins, ►cancer cells, ►anoikis, ►CAM, ►RGD, ►tissue engineering

Anchored Periplasmic Expression (APEx): APEx permits the isolation of ligand-binding proteins from combinatorial libraries anchored to the inner periplasmic face of *E. coli*. The procedure serves the same purpose as phage display, but the larger bacterial (or yeast) cells allow screening by flow cytometry of labeled proteins and antibodies. ►periplasma, ►phage display; Harvey BR et al 2004 Proc Natl Acad SCI. USA 101:9193.

Anchoring: DNA fragments obtained during the initial stages of physical mapping must be tied together by contigs. Large capacity YACs are used for the establishment of contigs. These YACs must be corelated with molecular markers (anchors) along the length of the chromosome. RFLPs, RAPDs, STSs, and even the recombination maps obtained by strictly genetic methods may be used as anchors. The relative position of two YACs is revealed when a YAC is found to bridge two anchors to each of which, one of the two YACs each is attached (see Fig. A73).

Anchoring may provide the means for corelating genetic linkage maps with physical maps that are based on nucleotide sequencing. The principle of the procedure is diagrammed. (See also Matallana E et al 1992 In: Koncz C et al (eds) Methods in Arabidopsis Research, World Scientific, Singapore, p. 144)

Ancient DNA: DNA from ancient bones, older than 50,000–100,000 years or even more, may still be analyzed. Clear family lines between parents and children could be ascertained among bone samples collected from cemeteries in Mongolia that are older than (2000) years. This was done on the basis of the autosomal short tandem repeat of mtDNA and Y chromosomal DNA (Keyser-Tracqui C et al 2003 Am J Hum Genet 73:247). Obtained from hair and wool,

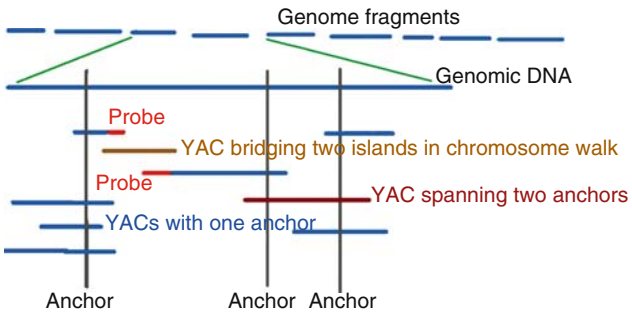

Figure A73. Anchoring

mtDNA has been successfully analyzed in samples ranging from 100– to 9,400 years old (Gilbert MTP et al 2004 Current Biol 14:R463). From the more-than-40,000-years-old Australian remains of the now extinct cave bear (*Ursus spelaeus*), 26,861 bp sequences of its genome have been sequenced. This revealed the extinct species' evolutionary relationship to the extant bear species (Noonan JP et al 2005 Science 309:597).

Samples preserved in amber may last longer. Mitochondrial DNA extracted 80 million years and amplified by PCR has shown sequences different from all known sequences. The validity of reports on very old DNA samples have thus seriously been questioned and contamination may not be ruled out. The condition of preservation is critical in DNA analysis. Often, the washed fossil bones stored in museums do not permit any DNA amplification; all recently excavated bones, however, are shown to yield authentic aurochs sequences. During the 57 years when the aurochs bones were stored in a collection, at least as much amplifiable DNA was lost as during the previous 3,200 years of burial (Pruvost M et al 2007 Proc Natl Acad Sci USA 104:739). It is very important that the greatest caution is exercised to avoid contamination during PCR analysis. It is advisable to test not just the sample but its immediate environment and the reagents themselves, and verify that the sample conforms to that of a species. Fragments that are too long are suspicious. Statistical tests have been developed for compensation for the miscoding (C→U, G→A) changes due to degradation and contamination with DNA of more recent origin (Helgason A et al 2007 J Mol Evol 65:92). In case a protein is present, the high ratio between D and L aspartic acid indicates that most likely the DNA has been degraded. The purposes of the analysis of ancient DNA are to obtain information on individuals and groups and to assess evolutionary relations. The mtDNA (~17,000 bp) of two kinds of moa birds extinct for 400 years has been fully recovered. Analysis of ancient DNA has some limitations yet it may be the only means of inquiry into some problems of speciation, history of pathogens, human evolution, and migration. Some of the problems encountered with degradation of ancient fossil samples (~2,000–10,000 years old) of animal and human bones have been overcome by using crystal aggregates, which preserve DNA much better than they preserve entire bone samples. Sodium hypochlorite washing also removes all contaminations of recent DNA samples. Using these techniques, fossils yielded upon PCR procedures longer sequences of intact DNA (Salamon M et al 2005 Proc Natl Acad Sci USA 102:13783). Cross-linking is a more important cause of deterioration of ancient DNA than single- or double-strand breaks (Hansen AJ et al 2006 Genetics 173:1175). Ancient DNA can shed some light on the diet of ancient animals and humans, domestication of plants and animals, etc. (Pääbo S et al 2004 Annu Rev Genet 38:645). Ancient mitochondrial DNA may show C/G→T/A transitions upon amplification (Stiller M et al 2006 Proc Natl Acad Sci USA 103:13578), yet new methods facilitate to some extent, the reconstruction of at least the mtDNA. ►ancient organisms, ►Neanderthal people, ►mammoth, ►PCR, ►ice man, ►mummies, ►coproscopy, ►Romanovs, ►hominidae, ►out of Africa; Hoftreiter M et al 2001 Nature Rev Genet 2:353; Lambert DM et al 2002 Science 295:2270; Gilbert MTP et al 2003 Am J Hum Genet 72:32; Jones M 2002 The Molecule Hunt. Arcade Publishing, New York)

Ancient Organisms: Extinct species recognized as paleontological relics are difficult to study even by the most modern research techniques because the organic material has decayed. A 25–40 million-years-old bacterial spore, discovered in the digestive tract of an extinct bee species, preserved in amber, was reported to be revived. It was found that its 16S ribosomal RNA was quite similar to that of the living *Bacillus sphericus*. Actually, the calculated rate of nucleotide substitution in the 16S RNA encoding DNA segment appeared to be 1.8 to 2.4 × 10^{-9} per site per year. Although the isolation of the spore from

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the amber was carried out with extreme caution, some questions regarding possible contamination may be raised and newer studies failed to confirm DNA in amber. More recently (in 2000), 250 million-years-old spore-forming bacilli have been revived, and the authenticity of their age confirmed (Science 308:603). ►ancient ►DNA, ►mummies, ►ice ►man, ►amber, ►mammoth; Hoftreiter M et al 2001 Nature Rev Genet, 2:353.

Ancient RNA: Ancient RNA is retrieved from extinct or very old specimens. ►ancient organisms

ANCOVA: ANCOVA is the abbreviation for analysis of covariance. ►correlation

Ancylostoma: ►AcAP, ►hookworm

Andalusian Fowl: The Andalusian fowl is frequently used as an example for co-dominant segregation. When a black fowl is crossed with a white fowl, in the F_2 1 black: 2 blue: 1 white individuals are found; the "blue" has black and white (white-splashed) feathers (see Fig. A74). ►codominance

Figure A74. Andalusian fowl

Andersen's Disease 3p12: Andersen's disease is an autosomal recessive deficiency of amylotrans glucosidase(s) that causes liver, heart, and muscular disease because of the defect in glycogen storage. ►glycogen storage disease [►Type IV].

Andersen's Syndrome (KCJN2, 17q23): Andersen's syndrome is a periodic paralysis accompanied by heart arryhthmia and deformations. The basic defect is in an inwardly rectifying potassium channel (KCNJ2). ►ion channels; Plaster NM et al 2001 Cell 105:511.

Anderson's Disease: Anderson's disease involves lipid transport defects of the intestines and the retention of chylomicrons. ►lipids, ►chylomicron

Anderson-Fabry Disease: Anderso-Fabry disease is a human X-chromosome linked deficiency of α-galactosidase resulting in angiokeratoma (red or pink skin or mucous membrane lesions caused by dilation of veins). The relevant gene is 12 kb with 7 exons encoding a 427 amino acid protein. ►galactosidase-β, angiokeratoma.

ANDi (inserted DNA [in reverse]): ANDi was the name given to the first transgenic (rhesus) monkey.

Androdioecy: Androdioecy is the phenomenon in which male and hermaphrodite flowers are found in separate plants like in some maples, ash trees, and others. This breeding system also occurs in *Caenorhabditis elegans*, fresh water shrimps (*Eulimnada texana*), and other invertebrates. The only vertebrate capable of self-fertilization (see Fig. A75), killifish (*Kryptolebias marmoratus*), can display androdioecy and extensive outcrossing (Mackiewicz M et al 2006 Proc Natl Acad Sci USA 103:9924). ►hermaphrodite, ►dioecy; Wolf DE et al 2001 Genetics 159:1243.

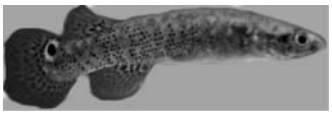

Figure A75. Killifish

Androecium: Androecium is the male part of a flower (the stamens). ►stamen

Androgen: Androgen refers to a hormone that promotes virility, but is also present in lower concentrations in females. Androgens are formed by hydroxylation of progesterone. The most important androsterone is testosterone. Androgen has important roles in the development of the male and in prostate cancer. ►animal hormones, ►testosterone, ►estrogen, ►FGF, ►aromatase, ►steroid hormones, probasin, ►sex differences, ►prostate cancer; Cifuentes E et al 2004 Proc Natl Acad Sci USA 101:464.

Androgen Receptor: Androgen receptors in muscle cells are activated by a 205-kDa actin-binding protein, supervillin. ►hormone response elements (HRE), ►Kennedy disease, ►gynecomastia,►testicular feminization, h►istone demethylation; Reid KJ et al 2001 J Biol Chem 276:2943; Ting H-J et al 2002 Proc Natl Acad Sci USA 99:661.

Androgen-Insensitivity (Xq11-q12): Androgen insensitivity is caused by a defect in the dihydrotestosterone receptor. ►testicular feminization, ►Kennedy disease, ►Reifenstein syndrome

Androgenesis: Androgenesis is the development of the male gamete into a paternal haploid or diploid embryo under natural conditions; it can be obtained by in vitro culturing and regeneration of plants from microspores. In vitro androgenesis can be *direct* when the microspores develop directly into plantlets, or *indirect* when the microspores form first a callus,

which then t regenerates plantlets. Androgenesis may also arise when all the chromosomes of the female are lost in a fertilized egg, and only male chromosomes remain. Androgenesis occurs in both plants and animals. ►apomixis, ►embryo culture, ►anther culture, ►microspore culture, ►hydatidiform mole, ►gynogenesis, ►hemiclonal, ►hybridogenetic; Kermicle JL 1969 Science 166:1422; Corley-Smith GE et al 1996 Genetics 142:1265.

Androgenital Syndrome: ►pseudohermaphroditism

Androgenote: An androgenote is a diploid embryo with only the paternal sets of chromosomes. ►androgenesis

Androgenous: Androgenous describes a pseudo- or true hermaphroditic stage in mammals or plants. ►hermaphrodite

Andromerogony: Andromerogony is the development of an egg (or its part) containing only the male pronucleus; the egg's own nucleus was removed prior to fusion with the male nucleus. ►androgenesis, ►pronucleus

Andropause: Andropause is the period of decline of the free testosterone level in human males after its peak at age 30, yet at 60 the testosterone level is still comparable to that at 20. Muscle strength may be increased by replacement therapy but impotence is usually not cured. ►menopause

Androsome: An androsome is a chromosome, which normally occurs only in males. ►sex chromosomes

Androstanes: Androstanes are androstanol and androstenol steroids.

Androstanol (5α-androstan-3α-ol): Androstanol is a mammalian pheromone, inhibitory to constitutive CAR-β. ►CAR-β, ►androstane, ►androstenol

Androstenol (5α-androst-16-en-3α-ol) Androstenol is a mammalian pheromone, inhibitory to constitutive CAR-β. ►CAR-β, ►androstane, ►androstanol

ANE Genes: ANE genes stand for annotated non-expressed genes. ►annotation, ►AE genes, ►NAE genes

Anemia: Anemia is a reduction of the red blood cells and hemoglobin below the normal level. It occurs when the production of erythrocytes does not keep up with losses. Several human diseases involve anemia, including some that are hereditary, such as thalassemias, sickle cell anemia, glucose-6-phosphate dehydrogenase deficiency, etc. Some anemias appear under autosomal dominant, autosomal recessive, or X-linked control. ►Cooley's anemia, ►Fanconi's anemia, ►elliptocytosis, ►hemolytic anemia, ►sickle cell anemia, ►pyruvate kinase deficiency, ►pyrimidine 5-nucleotidase deficiency, ►glutathione synthetase deficiency, ►thalassemia, ►siderocyte anemia, ►transcobalamine deficiency, ►magaloblastic anemia, ►atransferrinemia, ►aceruloplasminemia,►hemochromatosis, ►diphosphoglycerate mutase deficiency, ►adenylate kinase deficiency, ►IRE

Anemophily: Anemophily is pollination by wind.

Anencephaly (spina bifida): Anencephaly is a perinatal disorder of fetuses and newborns where the brain is absent (cerebrum and cerebellum); many of the afflicted die before birth, 1/16 of all cases survive birth but rarely live beyond a week. Anencephaly may be due to a recessive mutation but some cases can be attributed to non-genetic causes. Its prevalence is less than 1/1000. Prenatal test may be carried out if family history indicates genetic causes. Microhydranencephaly maps to 16p13.3-p12.1. Porencephaly is encoded in human chromosome 13q34. ►neural tube defects, ►prenatal diagnosis, ►genetic screening, ►MSAPF, ►Arnold-Chiari malformation, ►hydrocephalus MDM2

Anergy: Anergy is a lymphocyte's non-responsiveness to an antigen because, e.g., a slightly modified peptide-MHC is attached to the T cell receptor, or some inducive factors are not functioning adequately. Anergized $CD4^+$ T cells are not completely idle but have some regulatory function. ►T cell, ►HLA, ►MHC; Jooss K et al 2001 Proc Natl Acad Sci USA 98:8738; Schwartz RH 2003 Annu Rev Immunol 21:305.

Anesthetics: Anesthetics numb the nerve receptors; they generally affect the ligand-gated ion channels, and lipids and proteins in cell membranes. In mammals, stomatin and degenerin, and in *Caenorhabditis* the product of the *UNC-1* gene, may affect the critical ion channels. ►ion channels, ►stomatin, ►degenerin; Humphrey JA et al 2002 Hum Mol Genet 11:1241.

Aneugamy: In case of aneugamy the chromosome number of the two gametes involved in fertilization is different. ►anisogamy, ►isogamy, ►heterogametic, ►homogametic

Aneuhaploid: is a haploid, which has incomplete set(s) of chromosomes. ►aneuploidy, ►haploid

Aneuploidy: Chromosome numbers in case of aneuploidy are either more or less than $2n \pm 1$ or ± 2 or ± 3, etc. Aneuploids are trisomics or monosomics, single or multiple (see Fig. A76).

Aneuploidy is frequent in cultured cells and in cancer cells. Hamerton (1971), after surveying 1291 spontaneous human abortions, found 5%

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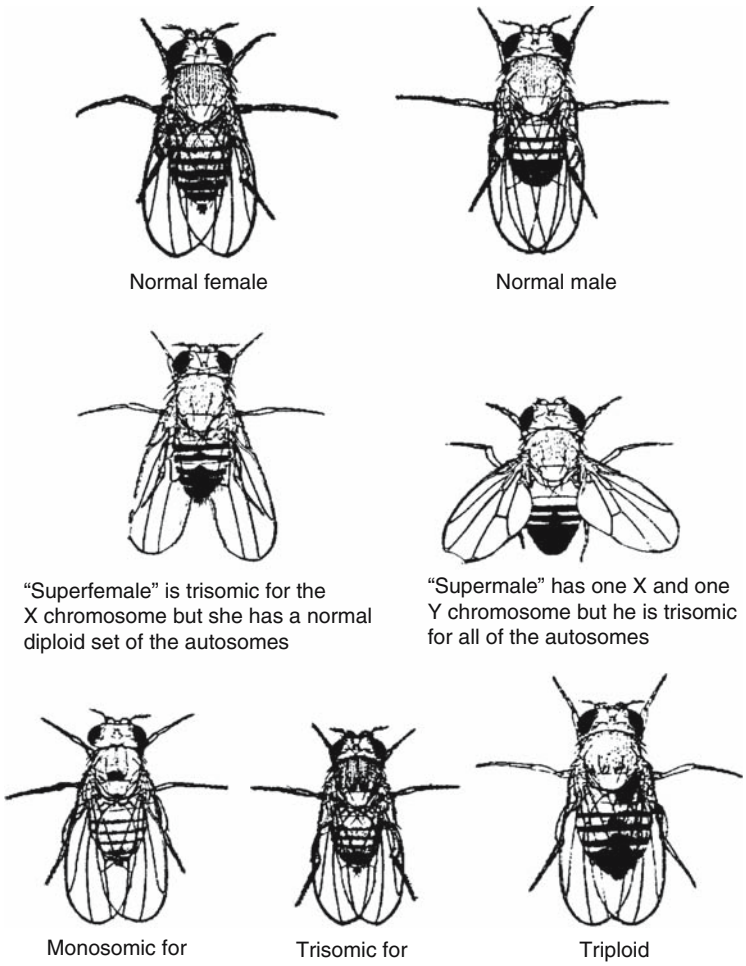

Figure A76. Normal female, normal male and various aneuploids of *Drosophila*. (From Morgan TH et al 1925 Bibl Genet 2:3)

monosomics, 11.9% trisomics, 4.1% triploids, and 1.2% tetraploids (note that the triploids and tetraploids are polyploids but not aneuploids, whose frequency is included only for comparison.). Among live human births chromosomal anomalies are close to 1%. Aneuploids are usually very deleterious yet sex-chromosomal aneuploidy e.g., Turner syndrome XO, Klinefelter syndrome XXY, etc. are not generally lethal in humans or other animals. In the 47 XXY individuals the anomaly in the majority of cases is due to nondisjunction of the XY bivalent. This high frequency may be attributed to the fact that usually even under normal conditions only a single chiasma occurs between the X and the Y (in the pseudoautosomal region), and if this chiasma fails to materialize, nondisjunction takes place. A clinical test based on cytology and quantitative fluorescent polymerase chain reaction on X, Y, 21, 13, and 18 chromosomes is commercially available to test human aneuploidy. Monosomics (2n−1) have been very skillfully exploited for mapping genes to chromosomes in polyploid plants (wheat, oats, etc.).

Microarray hybridization profiles reveal aneuploidy without cytological analysis because the expressions of large tracts of genes are detectable. Aneuploidy may lead to cancerous growth. Increased rate of aneuploidy drives an elevated level of spontaneous lymphomas and lung tumors in aged animals. Remarkably, however, in examples of chemically- or genetically-induced tumor formation, an increased rate of aneuploidy is a more effective inhibitor than initiator of tumorigenesis, probably because the aneuploid cells have diminished selective value. These findings reveal the additional role of aneuploidy and chromosomal instability in preventing tumorigenesis (Weaver BAA et al 2007 Cancer Cell 11:25). A cause of aneuploidy is probably the abnormal organization of the centrosome of animals. Animal histones are deacetylated during meiosis in the female, and it has been suggested that decreased

deacetylation can be a cause of aneuploidy and embryonic death in mice (Akyama T et al 2006 Proc Natl Acad Sci USA 103:7339). (See ►illustration, ►hypoploid, ►hyperploid, ►triploid, ►pentaploid, ►monosomic analysis, ►MSAFP, ►pseudoautosomal, ►chiasma, ►microarray hybridization, ►centrosome, ►polymerase chain reaction, ►mosaic variegated aneuploidy; Jacobs PA, Hassold TJ 1995 Adv Genet 33:101; Hassold T, Hunt P 2001 Nature Rev Genet 2:280; Yuan L et al 2002 Science 296:1115; cancer: Rajagopalan H, Lengauer C 2004 Nature [Lond] 432:338)

Aneurysm: Aneurysm refers to the formation of small sacs of blood caused by the dilation of veins. Both abdominal aneurysms (more common in females) and brain aneurysms are under autosomal dominant control. Aortic aneurysm (15q21) is a heart disease involving fibrillin. Apparent linkage to 5q22-q31, 7q11 and 14q22 have also been reported. Thoracic aneurysm/aortic dissection (splitting of the arterial wall resulting in hemorrhage, TAAD) and patent ductus arteriosus is located to human chromosome 16p12.2-p13.3. It is caused by mutation in myosin 11-heavy chain (Zhu L et al 2006 Nature Genet 38:343). ►collagen, ►fibrillin, ►patent ductus, ►myosin, ►Marfan syndrome, ►Loeys-Dietz syndrome; Onda H et al 2001 Am J Hum Genet 69:804.

Aneusomatic: Aneusomatic describes the condition in which the somatic chromosome number varies among cells because of the presence of supernumerary chromosomes and because of their frequent somatic nondisjunction. Aneusomy is one of the most common causes of cancer. ►supernumerary chromosomes, ►nondisjunction, ►aneuploidy; Fabarius A et al 2002 Proc Natl Acad Sci USA 99:6778.

Aneusomy, Segmental: ►contiguous gene syndrome

Angelman Syndrome (Happy Puppet Syndrome): Angelman syndrome is apparently an autosomal recessive human defect with somewhat irregular inheritance. Cytologically and molecularly detectable deletion in the 15q11-q13 region (similar to the Prader-Willi syndrome) has been observed. The unusual feature of this condition is that it is transmitted only through the mother whereas, in the Prader-Willi syndrome the transmission is via the father, the gene on the maternal chromosome being inactive. Imprinting has been suggested for the phenomenon. It has been suggested that in the female germline the so-named BD RNA transcripts induce methylation in the promoter of snRNP genes. Affected individuals have motor function defects (see Fig. A77), mental retardation, epilepsy, speech defect or absence, and a frequently protruding tongue accompanied by excessive laughter (hence the name HPS). It appears that the syndrome is effected by abnormal ubiquitin-mediated degradation of a brain ligase (UBE3A, Xq28) of the E6-AP class. ►disomic, ►Prader-Willi syndrome, ►mental retardation, ►imprinting, ►epigenesis, ►head/face/brain defects, ►snRNP, ►ubiquitin, ►Ube3, ►E3, ►imprinting box, ►Rett syndrome; Jiang Y-H et al 1999 Am J Hum Genet 65:1.

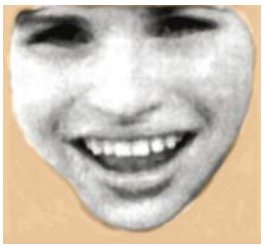

Figure A77. Angelman syndrome

Angina Pectoris: Angina pectoris is characterized by spasmic chest pain that may radiate to the arms (primarily the left) and breathing difficulties. It is caused by arterial ischemia and heart disease. It is a symptom also of several hereditary syndromes. ►ischemia

Angioectasis: Angioectasis is the excessive dilation of blood vessels.

Angioedema: Angioedema is the dilation of the subcutaneous capillary veins leading to skin, respiratory tract, and gastrointestinal fluid accumulations. The hereditary dominant form has been attributed to mutations in a serpin gene or to complement inhibitory factor deficiency (C1-INH). The condition may be haplo-insufficient. ►serpin, ►complement, ►haplo-insufficient

Angiogenesis: Angiogenesis refers to the formation of blood vessels and chronic inflammation. The vascular endothelial growth factor and its two receptors Flt-1 and Flk-1/KDR are required in rodents for angiogenesis. Vasculogenesis factor (VEGF) peptide hormones, secreted by tumors, increase blood supply and ensure neoplasias and their further growth. There are two angiogenesis pathways. Actually some pro-angiogenesis factors (FGF family) can eventually restore blood supply even after blocking VEGF receptors (Casanovas O et al 2005 Cancer Cell 8:299). The fibroblast growth factor- or tumor necrosis factor-α initiated path depends on integrin $\alpha_v\beta_3$, whereas angiogenesis initiated by vascular endothelial growth factor, transforming growth factor-α, or phorbol ester uses the $\alpha_v\beta_5$ path.

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Disruption of the matrix metalloproteinase 2 binding to integrin inhibits angiogenesis, and it may be relevant to tumor control. The tumor necrosis factor-α induced angiogenesis uses the B61 cytokine-inducible ligand for the Eck protein tyrosine kinase receptor (RPTK).

VEGF dynamically regulates tumor endothelial expression of Delta-like ligand 4 (Dll4), which was shown to be essential to normal embryonic vascular development. Blocking of Dll4 resulted in markedly increased tumor vascularization, associated with enhanced angiogenic sprouting and branching. Paradoxically, this increased vascularization was non-productive—as shown by poor perfusion and increased hypoxia, and most importantly, by decreased tumor growth—even for tumors resistant to anti-VEGF therapy. Thus, VEGF-induced Dll4 acts as a negative regulator of tumor angiogenesis; its blockade results in a striking uncoupling of tumor growth from vessel density, and may offer a novel therapeutic approach even for tumors resistant to anti-VEGF therapies (Noguera-Troise I et al 2006 Nature [Lond] 444:1032).

Angiogenesis also promotes the proliferation of tumors, but the process can be restricted by the antibiotic minocycline, AGM, interferon α/β/γ, angiostatin, endostatin, interferons, etc. Antiangiogenic therapy may destroy the vasculature of the solid tumors and neutralize VEGF signaling. Normalization can occur by recruiting pericytes (flexible cells, which wrap around the pre-capillary vessels and stabilize them transiently). The normalization is mediated by angiopoietin-1 and metalloproteinases, and provides an opportunity for radiation and chemotherapy (Lin M Ii, Sessa WC 2004 Cancer Cell 6:529).

The combined action of the three classes of angiostatic compounds, each targeting different aspects of the angiogenic process, was tested using a VEGF aptamer chemically identical to Macugen, recently approved for the treatment of neovascular eye diseases. The small-molecules $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrin antagonists targeted the extracellular matrix-mediated endothelial cell survival. To block endothelial intracellular adhesion and lumen formation, T2-TrpRS (T2) was used. This is a proteolytic fragment of tryptophan tRNA synthetase that exhibits angiostatic activity, which is linked to its ability to block vascular endothelial-cadherin-mediated adhesion. The combination angiostatic therapy significantly reduced the compensatory upregulation possible in case a component of the blocking system had been used. The synergistic antiangiogenic activity appeared effective for the treatment of neovascular disease (Dorrell MI et al 2007 Proc Natl Acad Sci USA 104:967).

Tilted (or oblique-oriented) peptides are short peptides known to destabilize membranes and lipid cores. They are characterized by an asymmetric distribution of hydrophobic residues along the axis when helical, and are antiangiogenic. 16-kDa fragments of the members of the human prolactin/growth hormone (PRL/GH) family are potent angiogenesis inhibitors. All these fragments possess a 14-amino acid sequence having the characteristics of a tilted peptide. Tilted human peptides induce endothelial cell apoptosis, inhibit endothelial cell proliferation, and inhibit capillary formation both in vitro and in vivo. These antiangiogenic effects are abolished when the peptides' hydrophobicity gradient is altered by mutation. Well-known tilted peptides of simian immunodeficiency virus gp32 and Alzheimer's disease amyloid peptide are also angiogenesis inhibitors (Nguyen N-Q-N et al 2006 Proc Natl Acad Sci USA 103:14319).

Promoters of angiogenesis include cytokines (EGF, TGF, TNF), various carbohydrates, angiogenin, and several other molecules. The ligands of the Tie receptors, Angi1 and Angi 4, regulate angiogenesis positively, whereas Angi3 is a negative regulator. MicroRNA (miR-17–92) is an important factor for adenocarcinomas because it regulates vascular endothelial growth factor (VEGF). miR-17–92 represses anti-angiogenic factors thrombospondin-1 and connective tissue growth factor (CTGF), which are upregulated by KRAS and cMyc protooncogenes and are involved in tumorigenesis (Dews M et al 2006 Nature Genet 38:1060).

Gene *ING4* is known to control angiogenesis. In the presence of the *ING4* gene transcript, angiogenic vasculature is repressed (see Fig. A78) relative to the control, whereas when the transcript is reduced by antisense RNA (*as-ANG4*) angiogenesis and glioma growth are enhanced. ING4 physically interacts with RelA subunit of NF-κB. These images were obtained from human glioblastoma (U87MG) grafted into the brain of a mouse. Several new drugs are now available to fight angiogenesis, such as Avastin, an antibody that blocks VEGF, and Sutent and Sorafenib that block angiogenesis indirectly by inhibiting tyrosine kinases and appear effective against cancer.

Although inhibition of angiogenesis deprives tumors of the blood supply essential for proliferation, it also hinders the targeted delivery of therapeutic chemicals; furthermore hypoxia-inducible factor (HIF1-α) accumulates and leads to an increase in metastasis. A nanoparticle has been designed to target tumors, to overcome these problems. The outer envelope of the nanocell releases temporally an anti-angiogenesis agent combretastatin at first, and then a doxorubicin-PGLA (poly-(1-lactic-co-glycolic) acid, a biodegradable, non-bioactive polymer)

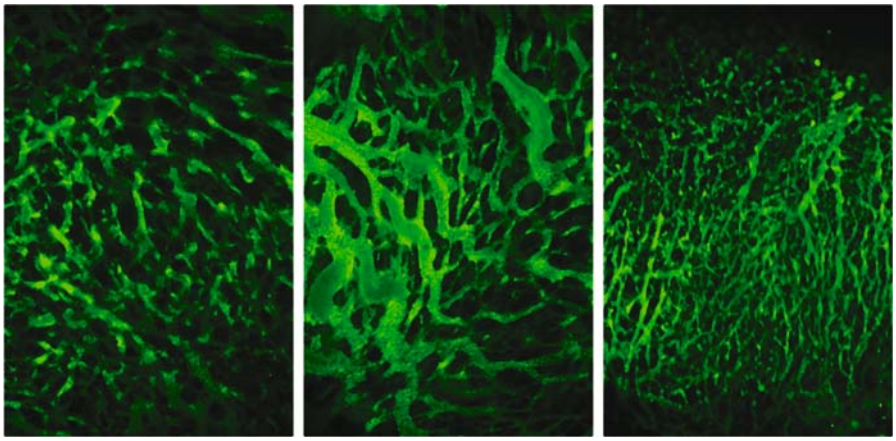

Figure A78. Angiogenesis. (Courtesy of Dr. Igor Gardatsev; see also Garkatse, I. *et al*. 2004 Nature [Lond] 428, 328)

conjugate is slowly released inside the tumor. The nanocell prefers tumor cells. This targeted approach hurts the tumor, and also comparatively reduces toxicity for normal cells (Sengupta S et al 2005 Nature [Lond] 436:568).

►tumor, ►cancer, ►glioma, ►VEGF [vascular endothelial growth factor], ►wound healing, ►fibroblast growth factor [FGF], ►Flk, ►Flt, ►angiopoietin, ►integrin, ►phorbol esters, ►metalloproteinases, ►tumor necrosis factor [TNF], ►neuropilin, ►neutrophil, ►angiostatin, ►Avastin, ►endostatin, ►hemangioblast,►CXCR, ►leptin, ►EGF, ►TGF, ►TNF, ►PTEN, ►Id proteins, ►maspin, ►NF-κB, ►HIF, ►doxorubicin, ►PLGA, ►combretastin, ►KRAS, ►MYC, ►thrombospondin, ►connective tissue growth factor; Carmeliet P, Jain RK 2000 Nature [Lond] 407:249; Folkman J 2001 Proc Natl Acad Sci USA 98:398; Kuo CJ et al 2001 Proc Natl Acad Sci USA 98:4605; Jones N et al 2001 Nature Rev Mol Cell Biol 2:257; Isner JM 2002 Nature [Lond] 415:234; Grunewald M et al 2006 Cell 124:175; antiangiogenic therapies; Kerbel RS 2006 Science 312:1171, http://angiodb.snu.ac.kr.

Angiogenins: Angiogenins are RNases stimulating blood vessel formation. ►ribonucleases

Angiokeratoma: Angiokeratoma is a recessive X-chromosome linked skin disease involving dilation of the small veins, warty growth, and thickening of the epidermis primarily on fingers, toes, and the scrotum. ►Anderson-Fabry disease, ►Kanzaki disease, ►fucosidosis

Angioma: Angioma is a tumor of the blood or lymph vessels or a neoplasia, which forms blood and lymph vessels. Many forms exist in humans; they are controlled by dominant genes at chromosomes 7q11.2-q21 (CCM1), 7p15-p13 (CCM2), and 3q25.2-q27 (CCM3). The CCM1 locus encodes RAP1A interacting KRIT1 protein. ►hemangioma, ►RAP1

Angioneurotic Edema: Angioneurotic edema is a dominant chromosome 11q11-q13.1 deficiency of complement C1 inhibitor, causing edema of the air passageway. The reduced level of the inhibitor leads to excesses of the C4 and C2 kinin fragments. Angioneurotic edema is a hereditary disease. ►complement, ►angioedema, ►kinin

Angioplasty: Angioplasty corrects narrowed blood vessels. One procedure involves inflation of a balloon inside an artery to break up plaque(s) in order to restore free blood flow.

Angiopoietin: Angipoietin-1 is a blood-vessel differentiation factor that promotes tissue vascularization. Angiopoietin-2 is an antagonist of angiogenesis. ►VEGF, ►angiogenesis

Angiosperm: Angiosperms are plants that bear seeds within an ovary; the majority of higher plants belong to this taxonomic category. Fossil evidence points to their presence in the Jurassic period (137–190 Mya). ►Mya, ►geological time periods

Angiostatin: Angiostatin is a 38-kDa protein with some homology to plasminogen. It is an anticancer agent with the twin advantages that it can deprive cancer cells from developing new blood vessels and that resistance mutations against it (common to most anticancer drugs) have not yet been observed. The therapeutic effectiveness in the cure of human cancer has not been completely accepted, although some positive results have been obtained, especially in combination with radiation treatment. Angiostatin

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may act by inhibiting endothelial ATP synthase, possibly required for supplying the energy for tumorigenesis. ►endostatin, ►cancer, ►angiogenesis, ►plasminogen, ►cancer therapy; Moser TL et al 2001 Proc Natl Acad Sci USA 98:6656.

Angiotensin: Asp - Arg - Val - Tyr - -Ile - His - Pro - Phe peptides stimulate the smooth muscles of the blood vessels, reduce the blood flow through the kidneys and decrease the excretion of fluid and salts, increase the secretion of aldosterone, and stimulate the reabsorption of sodium. These peptides are known as angiotensins. They are involved in the hereditary disorders of adrenocortical steroid biogenesis (see Fig. A79). Angiotensin I receptor AT_1 mediates the enhancer (higher blood pressure) and angiotensin II receptor AT has the opposite (depressor) effect. The drugs Lisinopril and Losartan, frequently prescribed against high blood pressure, are inhibitors of the ACE enzyme and reduce hypertension. Angiotensin II cell surface receptor is directly stimulated by the Jak/STAT signal transduction pathway. The angiotensin converting enzyme (ACE, 17q23) is a dipeptidyl carboxypeptidase (kininase) that catalyzes the conversion of angiotensin I to angiotensin II. ACE2 was located to human Xp22; angiotensinogen (AGT) is at 1q42-q43. aldosterone, ►hypertension, ►ecclampsia, ►signal transduction, ►tachykinin, ►pseudoaldosteronism, ►angiostatin, ►SARS, ►BBB, ►DCP1, ►rennin, ►Marfan syndrome, Zhu X et al 2001 Am J Hum Genet 68:1139; Morimoto S et al 2002 Physiol Genomics 9:113, review: Keidar S et al 2007 Cardiovasc Res 73:463.

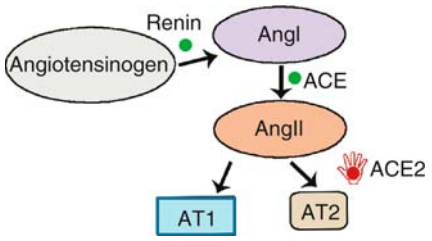

Figure A79. Renin protease cleaves angiotensinogen into the inactive decameric angiotensin I (AngI) and the angiotensin converting enzyme (ACE) cleaves it into the active octamer angiotensin II (AngII). This can promote hypertension and renal Na reabsorption. ACE2 inactivates AngII and protects against acute lung injury by receptor AT1 with the aid of AT2. Imai, Y. et al. 2005 Nature 436:112; Danilczyk, U. et al. 2006 Nature 444: 1088

Ångström (Å): Angstrom is a unit in measurement. 1 Å = 1/10 nanometer (nm).

Angular Transformation (arcsine transformation): Angular transformation is used with percentages and proportions. In a binomial distribution the variance is a function of the mean. The arcsine transformation prevents that $\theta = \text{arcsine } \sqrt{p}$, where p is a proportion which stands for an angle whose sine is the given quantity. The transformation stretches out both ends of a distribution of percentages and compresses the middle. It may be usefully applied to genetic data when the figures fall outside the 30% and 70% ranges. ►arcsine, sine.

Anhidrosis: Anhidrosis is reduction or lack of sweating. An X-linked hypo- or anhidrotic ectodermal dysplasia is caused by mutation in a transmembrane protein. Ectodermal dysplasia is a part of about 150 syndromes. ►ectodermal dysplasia, ►pain-insensitivity

Anhidrotic Ectodermal Dysplasia: ectodermal dysplasia.

Anhydride: An anhydride is a compound that results from a condensation reaction where water was eliminated (between carboxyl and phosphate groups).

Animal Genetics: ►individual animal species, ►OMIA, ►breeding value, ►heritability, ►QTL, ►GOBASE; Fadiel A et al 2005 Nucleic Acids Res 33:6308.

Animal Genome Size: http://www.genomesize.com.

Animal Hormones: Hormones are the first chemical messengers secreted by certain tissues to be carried by the bloodstream to the specific sites of action where regulatory functions are enacted. Hormones regulate either the synthesis or activity of enzymes, or affect membrane transport in cooperation with the second messengers, cyclic adenosine monophosphate and cGMP. There are of three major types of hormones, which are detailed as follows. *PEPTIDE HORMONES*: secreted by the hypophysis of the pituitary gland, are somatotropin (general growth hormone, GH), corticotropin (adrenocorticotropin, ACTH in the kidneys), thyrotropin (thyroid-stimulating hormone, TSH), follitropin (FSH, in gonads), lutrotropin (luteinizing hormone, LH, in gonads), and prolactin (in mammary glands). Secreted by the neurohypophysis are: oxytocin (controls uterine contractions and milk production), vasopressin (antidiuretic hormone that controls water reabsorption of the kidneys and blood pressure).Secreted by the middle section of the hypophysis are Melanotropins (control melanin pigments). The pancreas secretes insulin (controls carbohydrate, fatty acid, and cholesterol metabolism), and glucagon (stimulates glucose production by the liver). The ovary produces relaxin (controls pelvic ligaments, the uteral cervix, thereby labor), the thyroid gland is the source of parathyrin (involved in calcium and phosphorus metabolism), the kidneys release

erythropoietin (a glucoprotein involved in erythrocyte production by the bone marrow), and renin (causes constriction of the blood vessels). The digestive tract secretes gastrin (promotes digestive enzymes), enterogastrone (controls the gastric secretion), cholecystokinin (regulates gall bladder), secretin (controls pancreatic fluids and bile production), and pancreozymin (of duodenal origin, stimulates pancreatic functions). *AMINO ACID HORMONES*: thyroxin and triiodothyronin are secreted by the thyroid gland and affect many functions in the body. The kidney tissues secrete epinephrine (adrenaline) and norepinephrine (triiodothyronin) that regulate blood pressure and heart rate, while the pineal gland (a cone-shaped epithelial body at the base of the brain) produces melatonin, which affects the pigment producing melanophore cells. The nerve cells produce serotonin (5-hydroxytryptamine) affecting contraction of the blood vessels and nerve function. Serotonin controls the central nervous system and therefore, alertness, sleep, mood, aggressiveness, etc. *STEROID HORMONES*: are produced in the testes (testosterone, regulates male reproductive capacities), in the ovaries (estrogen [estradiol-17β], involved in female reproductive functions), in the corpus luteum of the ovary. Progesterone is produced in the Schwann cells of the peripheral nervous system. It functions during menstrual cycles, pregnancy, and in myelin formation. In the kidney cortex cortisol (corticosterone) is synthesized affecting glucose utilization and glucose levels in the blood. Although estrogen is typically a female hormone, yet extremely high concentrations occur in the fluids of the testis, and it is important for male fertility. Progesterone is necessary for the maintenance of pregnancy. It binds to the oxytocin receptor (OTR) and prevents uterine contractions. *EICOSANOID (HORMONELIKE) SUBSTANCES*: include prostaglandins (trigger smooth muscle contraction, control fever and inflammations), leukotrienes (secreted by the white blood cells and affect hypersensitivity reactions and pulmonary functions), and thromboxanes (produced by the blood platelets and other cells, involved in blood clotting, blood vessel constriction, etc.) A large number of other hormones also exist, and perform important functions. ►hormones, ►hormone receptors, ►hormone response elements, ►opiocortin, ►oxytocin

Animal Host Cells: Host cells are used for genetic transformation. *Xenopus* oocytes are well suited for such studies because they can propagate foreign genes in appropriate vectors quite efficiently. Similarly, COS cells of mice and other somatic cells have been used effectively. Recently available techniques for the transformation of animal zygotes and embryos have enabled that genetic information be added or replaced in the germline, and transmitted to the sexual progeny. ►transformation of animal cells, ►COS, ►vectors genetic, ►germline

Animal Models: Certain biological phenomena cannot be studied in humans because mutants are not available and cannot be produced or manipulated effectively. In such cases animals such as *Caenorhabditis, Drosophila*, and mice are used for the experimentation (in behavioral genetics, neurobiology, various diseases, etc.). Animal models may have an important role in improving the techniques of gene therapy. The "shiverer" deletion in mice, resulting in convulsions because of the loss of a gene coding for a myelin protein, has been genetically cured by transfection of the wild type allele into the gamete. Similarly, the size of mice could be genetically increased by transformation using the rat somatotropin (RGH, growth hormone) gene fused to and regulated by a metallothionein promoter. The following monogenic human genetic disorders have models in mouse [abbreviations h. chr. = human chromosome, m. chr. mouse chromosome]: *adenomatous polyposis* (protrusive growth in the mucous membranes, h. chr. 5q21-q22, mouse homolog Apc^{Min}, chr. 18), *androgen insensitivity* (sterility, h. chr. Xq11.2-q12, mouse gene AR^{Tfm}, m. chr. X), *X-linked agammaglobulinemia* (deficiency of γ globulin in blood, h. chr. Xq21.33-q22, mouse gene Btk^{Xid}, m. chr. X), *Duchenne muscular dystrophy* (an early muscular disability), h. chr. Xp21.3-p21.2, mouse Dmd^{mdx}, m. chr. X), *Greig cephalopolysyndactily* (multiple fusion of digits, h. chr. 7p13, mouse gene $Gli3^{Xt}$ m. chr. 13), *mucopolysaccharidosis type VII* (a type of lysosomal storage disease, h. chr. 7q22, mouse gene Gus^{mps}, m. chr. 5), α–*thalassemia* (defect in the hemoglobin α chain, h. chr. 16p13.3, mouse gene Hba^{th}, m. chr. 11), *β-thalassemia* (defect in the β−chain of hemoglobin, h. chr. 11p15.5, mouse gene Hbb^{th}, m. chr. 7), *piebaldism* (color patches on the body, h. chr. 4p11-q22, mouse gene Kit^{W}, m. chr. 5), *ornithine transcarbamylase* (defect in the transfer of a carbamoyl group, H_2N - C = O, from ornithine to citrulline, h. chr. Xp21.1, mouse gene Otc^{Spf}, m. chr. X), *tyrosinase-positive type II* (occulocutaneous albinism, h. chr. 15q11-q12, mouse gene p^{p}, m. chr. 7), *phenylketonuria* (phenylalanine hydroxylase deficiency, h. chr. 12q22-q24.2, mouse gene Pah^{enu2}, m. chr. 10), *Waardenburg syndrome type 1* (h. chr. 2q35-q37, mouse gene $Pax3^{Sp}$, m. chr. 1), *aniridia* (absence of the iris, h. chr. 11p13, mouse gene $Pax6^{Sey}$ m. chr. 2), *pituitary hormone deficiency* (h. chr. 3q, mouse gene $Pit1^{dw}$, m. chr. 16), *Pelizaeus-Merzbacher disease* (central brain sclerosis, h. chr. Xq21.33-q22, mouse gene Plp^{jlp}, m. chr. X),

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Charcot-Marie-Tooth disease type 1A (a progressive neuropathic muscular atrophy, h. chr. 17p12-p11.2, mouse gene *Pmp22*^{Tr}, m. chr. 11), *retinitis pigmentosa* (sclerosis and pigmentation of the retina, h. chr. 6p21.2-cen, mouse gene *RD2*^{Rd2}, m. chr. 17), *gonadal dysgenesis* (underdeveloped germ cells in the testes) h. chr. Y11.2-pter, mouse gene *Sry*$^{Sxr'}$, m. chr. Y), *tyrosinase negative oculocutaneous albinism* albinism, h. chr. 11q14-q21, mouse gene *Tyr*^{c}, m. chr. 7. By disruption of hexosaminidase α subunit, a model for the Tay-Sachs disease has been generated in mice. Interestingly, these animals suffered no obvious behavioral or neurological deficit. Disrupting the hexoseaminidase β subunit (Sandhoff disease model) resulted in massive depletion of spinal cord axons and neuronal storage of ganglioside G_{M2}. The two latter examples indicate possible complications with animal models (see Fig. A80).

Mouse polygenic disorders with similarities to human conditions [human problem - mouse strain]: alcoholism and opiate drug addictions - C57BL/6J, asthma - A/J, atherosclerosis - C57BL, audiogenic (sound-induced) seizures - DBA, cleft palate (fissure in the mouth) - A, deafness - LP, dental disease - C57BL, BALB/c, diabetes - NOD, epilepsy - EL, SWXL-4, granulosa cell tumors in the ovary - SWR, germ cell tumors in the ovary - LT, germ cell tumors in the testes - 129, hemolytic.

Anemia - NZB, hepatitis - BALB/c, Hodgkin disease (pre-B cell lymphoma - SJL, hypertension - MA/My, kidney adenocarcinoma -BALB/c Cd, leprosy (*Mycobacterium leprae*) - BALB/c, leukemia - AKR/J, C58/J, P/J, lung tumors - A, Ma/My, measles - BALB/c, osteoporosis - DBA, polygenic obesity - NZB, NZW, pulmonary tumors - A/J, rheumatoid arthritis - MRL/Mp, spina bifida (defect of the bones of the spinal cord) - CT, systemic lupus erythematosus (a skin degeneration) - NZB, NZW, whooping cough - BALB/c. Some of the diseases (e.g., various types of cancer) occur sporadically because of mutations occurring during the course of the development of animals/humans. The introduction of a functional oncogene into the germline or into the soma line of a person cannot appropriately represent the conditions emerging in sporadic cases. Usually in cancer the sporadic occurrence of mutation is predominant. Normal cells generally surround the mutation in the soma and through bystander effect these may modify the expression of the mutant cell and its clonal derivatives, unlike the cases when the mutation has occurred in the male/female germline before fertilization. The former condition can be simulated in a genetic model, if, e.g., through recombination between one of the wild type RAS oncogene and its mutant a potentially proliferative allele is activated. The construction of such a model may be represented graphically.

Despite their usefulness for the study of human diseases, animal models may not always represent completely the human condition. For instance, mice deficient for both copies of the insulin receptor are born with normal weight but die from ketoacidosis soon after birth. The analogous null mutant humans are small at birth but rarely develop ketoacidosis. Human mutants of PPARγ Pro467Leu develop extreme insulin resistance, diabetes mellitus, and hypertension. Mice with the same mutation are also hypertensive but display normal insulin-sensitivity and glucose homeostasis (O'Rahilly S et al 2005 Science 307:370). (See terms and diseases under separate entries).

Animal Pole: The animal pole is the dorsal end of the (animal) egg opposite the lower end, the vegetal pole, and the site of the entry of the sperm. After the entry,

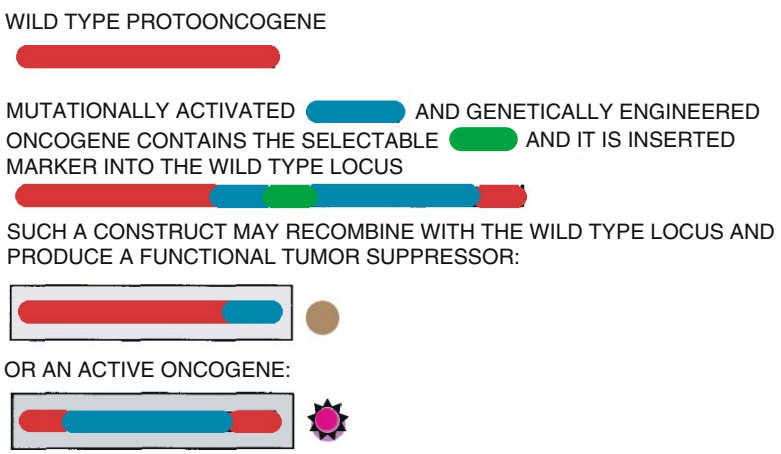

Figure A80. A genetic construct simulating the sporadic occurrence of oncogenic mutations. (See Johnson L et al (2001) Nature (Lond] 410:1111)

the egg cortex rotates slightly and in some species at the side opposite the entry a *gray crescent* is formed. ►vegetal pole

Animal Species Hybrids: The most familiar examples are the hybrids of the mare (*Equus caballus*, 2n = 64) and the jackass (*Equus asinus*, 2n = 62), and the stallion and the she-ass (see Fig. A81).

Figure A81. Hybrid of the male Grant's zebra and the female black Arabian ass, gloucester zoo. (From Gray, A.P. Mammalian Hybrids. Commonwealth Agric. Bureau. Farnham Roal, Slough, UK)

Hybrid males do not produce viable sperm although they may show normal libido. The females may have a uterus and ovulate but there is no proven case of fertility. Zebras (2n = 44) also may form hybrids with both donkeys and horses. Buffalo (*Bison bison*, 2n = 60) may be crossed reciprocally with cattle (*Bos taurus*, 2n = 60) but their offspring (cattalo) has reduced fertility. The domesticated pig (*Sus crofa*, 2n = 38) forms fertile hybrids with several wild pigs with the same number of chromosomes. The sheep (*Ovis aries,* 2n = 54) interbreeds with the wild mouflons but the sheep x goat (*Capra hircus,* 2n = 60) hybrid embryo rarely survives. Some monkeys can be interbred but primates are generally sexually isolated.

There is no sexual barrier among various human races, indicating close relationship, but no hybrids are known between humans and other species. These general rules do not hold for somatic cell hybrids because human cells can be fused with rodent or plant cells but they cannot be regenerated or even maintained successfully for indefinite periods of time. somatic cell hybrids, ►goat ►x sheep hybrids, ►transformation genetics

Animal Transformation Vectors: Most commonly used transformation vectors in animals are Simian virus 40 (SV40) and Bovine papilloma virus (BPV) based vectors. The BPV vectors can be used for the synthesis of large amounts of proteins specified by the gene(s) carried by the expression vectors. In addition, the BPV vectors can be maintained for long periods of time in cell cultures and may yield 10 mg of specific protein(s) per liter of culture/24 hr. The SV40 vectors can also be used for gene amplification in COS cells. Both these vectors can serve as shuttles between animal and prokaryotic cells. ►BPV and SV40 ►constructs, ►adenovirus, ►adenoassociated virus, ►retroviral vectors, ►lentivirus, ►vaccinia virus, ►COS cells, ►gene therapy

Animal Viruses: Animal viruses include viruses found in both invertebrates and vertebrates. The Rhabdoviridae and the Bunyoviridae may also infect plants. The double-stranded DNA viruses that may have be *enveloped* include Baculoviridae, Poxviridae, Herpesviridae, Hepadnaviridae, and Polydnaviridae. Double-stranded DNA viruses *without envelope* comprise Iridoviridae, Adenoviridae, and Papovaviridae. Parvoviridae have single-stranded DNA and do not have an envelope. The single-stranded RNA and *enveloped* group includes the Togaviridae, Bunyaviridae, Rhabdoviridae, Coronaviridae, Paramixoviridae, Toroviridae, Orthomyxoviridae, Arenaviridae, Flaviviridae, Retroviridae, and Filoviridae. The single-stranded RNA and *non-enveloped* viruses are: Picornaviridae, Tetraviridae, Nodaviridae, and Caliciviridae. The double-stranded RNA and *non-enveloped* viruses are Reoviridae and Birnaviridae. Their genetic material varies in size from 5 kb in the Parvoviridae to 375 kbp in the Poxviridae. The Polydnaviridae may have several copies of double-stranded circular DNAs. The Papovaviridae have only a single double-stranded DNA genetic material. The others may have two or more segments of linear nucleic acid genetic material. ►viruses, http://www.ncbi.nlm.nih.gov/ICTVdb/ictvdb.htm.

Animal Welfare: Animal welfare is a serious societal concern that seeks to balance the interest and need of medical research with the humane treatment of animals. Among the goals are Refinement, Reduction, and Replacement of animals as much as possible in experiments. The idea is to limit their use to the minimal and most indispensable experimentation that is in the best interest of humans as well as animals.

Animalcules: The pioneer microscopist Anthony Leuwenhoek (17th century) believed he could see small encapsulated animals in the sperm of various animals and this apparent observation supported his view that inheritance travels only through the sperm and the females serve only as incubators. His observations lead

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to the notion of preformation, rather than epigenesis (see Fig. A82). ►preformation, ►epigenesis, ►sperm

Figure A82. Animalcule

Animation: The condition of being alive and maintaining at least limited metabolic activity (suspended animation). Nitric oxide may favor *Drosophila* survival under hypoxia. ►hypoxia, ►nitric oxide; Teodoro RO, O'Farrell PH 2003 EMBO J 22:580)

Anion Exchange Resin: A polymer with cationic groups, the anion exchange resin traps anionic groups and thus can be used in chromatographic separation.

Anions: Anions are negatively charged ions.

Aniridia: Aniridia refers to the absence or reduction of the iris of the eye (see Fig. A83). It is frequently accompanied by cataract (opacity of the eye[s]), glaucoma (increased intraocular pressure causing deformation of the optic disk), nystagmus (involuntary movement of the eyeball), etc.

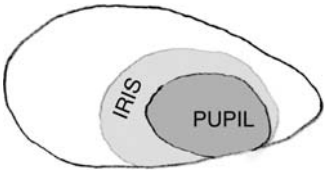

Figure A83. Hypoplasic iris and enlarged excentric pupil in adult aniridia

The condition is caused by dominant defects in human chromosomes 2 and 11. In a sample population from Michigan, the rate of mutation was 4×10^{-6}. Aniridia may involve Wilms tumors and genital abnormalities due a deletion in human chromosome 11p13 (PAX6). Aniridia may be haplo-insufficient. The *Drosophila* locus *eyeless* and the mouse *Sey/Pax-6* are the corresponding homologs. ►Wilms tumor, ►WAGR, ►deletion, ►eyeless, ►haplo-insufficient

Anisogamy: the gametes are not identical, e.g., male and female (+ or −) are distinguishable. ►isogamy

Anisomycin: Anisomycin is an antibiotic isolated from *Streptomyces griseolus*. It inhibits peptidyl transferase during protein synthesis on the ribosomes. It also inhibits pathogenic fungi (e.g., mildew) in plants and it was found to be useful against infection by various species of the parasitic flagellate, *Trichomonas*, causing inflammation of the gums, diarrhea, vaginal discharge, and irritation in humans and animals (particularly poultry and pigeons). ►antibiotics, ►protein synthesis

Anisotropic: Anisotropic describes the condition in which the material varies in different directions, responds differently to external effects depending on direction.

Anj1: A heat and other stress-inducible membrane-associated chaperone of higher plants. The Cys-Ala-Gln-Gln C-terminus may be subject to farnesylation. ►heat-shock proteins, ►chaperones, ►DnaK, ►prenylation

Ankyloblepharon: Ankyloblepharon describes fused eyelids. ►Hay-Wells syndrome

Ankylosing Spondylitis (AS): AS is an autosomal dominant rheumatism-type disease with reduced penetration. The greatest susceptibility to AS is associated with MHC (HLA B27), but spurious or fair linkage was observed with chromosomes 1p, 2q, 6p, 9q, 10q, 16q and 19q. The onset of AS occurs after age 20. ►HLA, ►immunodeficiency, ►connective tissue disorders,►autoimmune disease, ►penetrance; Laval SH et al 2001 Am J Hum Genet 68:918.

Ankyrin: Ankyrins are protein motifs capable of binding fibrous proteins (e.g., spectrin) of the cytoskeleton, and thus may be involved in some polar transports within the cell. Several ankyrin and ankyrin-like proteins are encoded in different human chromosomes (8p11.2, 4q25-q27, 10q21, etc.). Ankyrin B mutations may be involved in type 4 LQT cardiac arrhythmia. Ankyrin repeats may form superhelical spirals and have spring-like function in *Drosophila* hairs and bristles, among others (Lee G et al 2006 Nature [Lond] 440:246). ►LQT, ►cytoskeleton, ►spectrin, ►elliptocytosis, ►poikilocytosis, ►IκB, ►spherocytosis, ►tankyrase, ►*Wolbachia*; Hayashi T, Su T-S 2001 Proc Natl Acad Sci USA 98:491.

Anlage: Anlagen are a group of cells of the embryo that initiate specific biological structures. ►primordium

Annealing: Annealing is the formation of double-stranded nucleic acid when two complementary single stranded chains meet (nucleic acid hybridization, attachment of a primer). Used to estimate DNA complexity, the process identifies the presence of homologous sequences in the genome with the help

of radioactively labeled or fluorescent homologous and heterologous probes. ►c_0t curve, ►probe, ►chromosome painting, ►FISH, ►DNA hybridization, ►primer

Annexins: Annexins are proteins composed of four or eight conserved 70-amino acid domains with variations mainly at the amino end. In mammals, there are at least 10 annexins; others exist in lower eukaryotes. Annexins bind to negatively charged phospholipids in the membranes. Annexins V and VI form voltage-regulated ion channels for different cations, whereas VII is specific for Ca^{2+}. Annexin V can reveal apoptosis in imaging technology. Annexins II may assist exo- and endocytosis. An annexin-like protein may be involved in mitigating H_2O_2 stress. Annexin 7 (ANX7, 10q21) is a tumor suppressor. ►ion channels, ►endocytosis, ►exocytosis, ►imaging; Bandorowicz-Pikula J et al 2001 Bioessays 23:170.

Annotation of the Genome: The identification of the function of open-reading frames and other elements. This is also called *one-dimensional annotation*. When the annotation extends also to the interaction of components identified in one dimension, *two-dimensional annotation* results. *Three-dimensional annotation* identifies the spatial positions within the chromosome and *four-dimensional annotation* considers the genome changes during adaptive evolution (Reed JL et al 2006 Nat. Rev Genet 7:130). During recent years many of the early sequenced genomes required re-annotation because the original procedures were loaded with substantial errors (Haas BJ et al 2005 BMC Biology 3:7).

In microbial genomes, when an annotated gene is linked to an unclassified one either by genetic linkage in a related species or microarray profile or protein-protein interaction, there is a high probability that they are members of the same functional category. Silencing the expression of a gene may also reveal its function. The expansion of annotations will be the task of the proteome projects. Comparative sequencing of many (16) eutherian mammals may greatly facilitate the identification of evolutionarily preserved sequences (Margulies EH et al 2005 Proc Natl Acad Sci USA 102:4795). A precisely annotated human genome is of great significance for medicine (Bentley DR 2004 Nature [Lond] 429:440; Cobb JP et al 2005 Proc Natl Acad Sci USA 102:4801). and for basic research (http://www.ncbi.nlm.nih.gov/projects/CCDS). ►proteome, ►gene prediction, ►DAS, ►silencer, ►insertional inactivation, ►RNAi, ►degron, ►RefSeq, ►VEGA, ►genome annotation, ►Recon; Marcotte EM et al 1999 Science 285:751; Mount SM 2000 Am J Hum Genet 67:788; Karlin S et al 2001 Nature [Lond] 411:259; Auburg S, Rouze P 2001 Plant Physiol Biochem 39:181; Stein L 2001 Nature Rev Genet 2:493; Yanai I et al 2001 Proc Natl Acad Sci USA 98:7940; Gaasterland T, Oprea M 2001 Curr Opin Struct Biol 11:377; Ashurst JL, Collins JE 2003 Annu Rev Genomics Hum Genet 4:69; Miller W et al 2004 Annu Rev Genomics Hum Genet 5:15; noncoding RNA: Griffith-Jones S 2007 Annu Rev Genomics Hum Genet 8:279, http://gen100.imb-jena.de/~baumgart/rummage/register.html, annotations for 130 genomes available by 2004: http://cbcsrv.watson.ibm.com/Annotations/home.html; http://vega.sanger.ac.uk/; http://www.sanger.ac.uk/HGP/havana/hawk.shtml/; http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene, Argo Genome Browser, released every 6–8weeks and displays annotation tracks from FASTA, GenBank, GFF, BLAST and Genscan files: http://www.broad.mit.edu/annotation/ago; http://pedant.gsf.de, genome browser for 32 species: http://genome.ucsc.edu/, condensation of large gene lists into gene functional groups, convert between gene/protein identifiers, visualize many-genes-to-many-terms relationships, cluster redundant and heterogeneous terms into groups, search for interesting and related genes or terms, dynamically view genes from their lists on bio-pathways: http://david.niaid.nih.gov, automatic annotation: http://www.genome.jp/kegg/kaas/.

Annulus (a ring): For example, specialized cells in a sporangium involved in opening.

Anodontia: ►tooth agenesis, ►hypodontia, ►Rieger syndrome

Anoikis: Anoikis is the loss of cell anchorage to a substrate that may lead to apoptosis and may be the requisite for metastasis. Some cell lines resistant to anoikis display increased metastasis because the probability of apoptosis is reduced. Rac GTP-ase may protect against anoikis. Neurotrophic tyrosine receptor kinase receptor (TrkB) suppresses anoikis and promotes metastasis (Douma S et al 2004 Nature [Lond] 430:1034). ►apoptosis, ►metastasis, ►anchorage dependence, ►receptor tyrosine kinase Coniglio S et al 2001 J Biol Chem 276:28113.

Anomalous Genetic Ratios: Genetic ratios that are caused by many different mechanisms. Defective chromosomes or chromosomes carrying deleterious genes are transmitted at lower than normal frequencies and reduce the expression (transmission) of the genes residing in that chromosome (conversely the other allele may appear in excess). Monosomy and trisomy also modify segregation ratios. The genetic ratios may be altered by preferential segregation of certain chromosomes in meiosis. Similarly, segregation distorter genes can cause dysfunction of the sperm carrying them. Meiotic drive in a population

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can work against the more fit alleles. ►Mendelian segregation, ►chromosomal breakage, ►aneuploidy, ►deletion, ►segregation distorter, ►gametophyte factor, ►certation, ►meiotic drive, ►preferential segregation, ►monosomic analysis, ►trisomic analysis, ►gene conversion, ►drift genetic, ►penetrance, ►Muller's ratchet

Anomalous Killer Cell (AK): A T cell grown in the presence of IL-2 and which acquires natural killer cell (NK)-like properties. ►killer cell, ►*Paramecium*

Anomer: Stereoisomers of sugar, differing only in the configuration of the carbonyl residue, e.g., α-D-(+)-glucose and β-D(+)-glucose.

Anonychia/Hyponychia Congenita: A human chromosome 20p13 recessive condition involving no or incomplete finger and toenail development controlled by R-spondin 4 (encoding a receptor of Frizzled in the Wnt pathway. (Blaydon DC et al 2006 Nature Genet 38:1245). ►wingless

Anonymous DNA Segment: Mapped DNA fragment without known gene content.

Anonymous Gene: A mapped gene without information about its molecular mechanisms but known to affect the expression of a quantitative response such as a behavioral trait. If it displays two allelic states it can be used for (DNA) mapping. ►behavior, ►behavior genetics

Anonymous Probe: A DNA probe with no known gene(s) and unknown function. Nevertheless, it provides information on the presence of sequences homologous to it and thus may be useful for taxonomic or evolutionary studies. ►physical mapping, ►microsatellites

***Anopheles* Mosquito**: The host and vector of the protozoan *Plasmodium falciparum*, the cause of malaria. *Anopheles gambiae* (278,244,063 bp) carries one major and two minor genes that control the formation of melanin-rich capsules in the midgut, thus disarming the *Plasmodium*. *Plasmodium* resistance in *Anopheles* is regulated by a leucine-rich repeat protein, similar to the role of leucine-rich repeats in plant and animal resistance to pathogens (Riehle MM et al 2006 Science 312:577). *Anopheles* control may be a major objective of fighting malaria. ►thalassemia, ►sickle cell anemia, ►*Wolbachia*, ►leucine-rich repeats, Atkinson PW, Michel K 2002 Genesis 32:42, ►*Aedes aegypti*, *Anopheles gambiae* genome sequence: Holt RH et al 2002 Science 298:129, systematics: Krzywinski J, Besansky NJ 2003 Annu Rev Entomol 48:11, *Anopheles* database: http://www.anobase.org/.

Anophthalmia: Anophthalmia is the lack of rudimentary eyes. It is caused by deletions or chromosome breakage at 3q27, the location of the SOX2 transcription factor gene involved in the control in eye, eye lens and the nervous system. Terminal deletion of chromosome 6p also causes anophthalmia among many craniofacial abnormalities (Bogani D et al 2005 Proc Natl Acad Sci USA 102:12477). The Pax6 may also be involved. ►eye diseases; ►eyeless; Fantes J et al 2003 Nature Genet 33:461.

Anophthalmos: An autosomal recessive bilateral defect in the formation of the optic pit. It has been reported also as an Xq27-encoded fusion of the eyelids and other complications. ►microphthalmos, ►eye diseases

Anorexia: Lack of appetite or *anorexia nervosa* is a psychological disturbance of adolescents (primarily females) caused by an abnormal fear of gaining weight and therefore refusal to eat. It is characterized by habitual self-induced vomiting, unnecessary use of laxatives leading to emaciation, irregular or lack of ovulation, reduced interest in sex, and other anomalies. Medical treatment may be required. Ciliary neurotrophic factor (CNTF) shows anorectic effect by overcoming leptin resistance through activation of hypothalamic neurons. This effect of CNTF could be abolished by knocking out pro-opiomelanocortin-specific glycoprotein 130 (gp130) in mice (Janoschek R et al 2006 Proc Natl Acad Sci USA 103:10707). The melanocyte-stimulating hormone, α-MSH, and analogs may be responsible for anorexia and weight loss. Oleyethanolamide may be a regulator of feeding. Susceptibility loci appear to be in chromosomes 1, 2 and 13. ►obesity, ►leptin, ►bulimia, ►ciliary neurotrophic factor, ►melanocyte stimulating hormone; Rodríguez de Fonseca F et al 2001 Nature [Lond] 414:209; Adan RA, Vink T 2001 Eur Neuropsychopharmacol 11[6]:483; Devlin B et al 2002 Hum Mol Genet 11:689.

Anosmia: Anosmia is the inability to smell.

ANOVA: Abbreviation for analysis of variance. ►analysis of variance, ►AMOVA

Anoxia: Absence or deficiency of oxygen; it reduces chromosomal damage during irradiation. ►radiation effects, ►ARE

Anserine (β-alanine-1-methylhistidine): A dipeptide occurring in birds and some mammals but not in humans. ►carnosinemia

Ant (*Formica sanguinea*): 2n = 48. The family of ants includes about 11,000 species ~2% of the total insect fauna. Ants generally follow the pattern of reproduction of other Hymenoptera. The females are the

products of sexual reproduction and are diploid whereas the males hatch from unfertilized eggs and are haploid. The workers are also diploid, like the queen, but due to developmental control they do not develop into functional female queens. In five species of ants, unmated workers may reproduce by thelytokous parthenogenesis and produce females from unfertilized eggs. *Cataglyphis cursor* females (queens) without mating may have parthenogenetic offspring by the fusion of four products of meiosis; such offspring develops into a queen. ►parthenogenesis, ►thelytoky, ►honeybee, ►social insects; Pearcy M et al 2004 Science 306:1780; phylogeny: Wilson EO, Hölldobler B 2005 Proc Natl Acad Sci USA 102:7411.

Antagomirs: Short RNAs, which antagonize microRNAs. Their silencing effect—after injecting them into mice—is very specific and long lasting. They appear promising for therapeutic silencing (Krützfeldt J et al 2005 Nature [Lond] 438:685). Antagomirs harbor optimized phosphorothioate modifications and require > 19-nt length for highest efficiency and can discriminate between single nucleotide mismatches of the targeted miRNA. Degradation is independent of the RNA interference (RNAi) pathway (Krützfeldt J et al 2007 Nucleic Acids Res 35:2885). ►microRNA

Antagonist: An antagonist blocks biological receptor activation. ►agonist

Antecedent: precursor, forerunner

Anteater (*Tamandua tetradactyla*): 2n = 54.

Antelope: (*Antilocapra americana*): 2n = 58.

Antenatal Diagnosis: The determination of a particular condition before birth by amniocentesis or blood samplings or by other means. amniocentesis, ►prenatal diagnosis, ►fetoscopy

Antenna: Feeler organ on the head of insects. ►*Drosophila* (see Fig. A84).

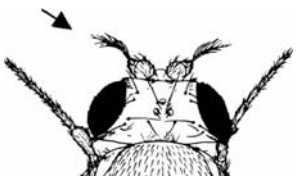

Figure A84. Antenna

Antenna Pigments: Present in chloroplasts, they collect light energy that is transmitted to the reaction centers for photochemical use. ►chloroplasts, ►chlorophyll, ►photosynthesis

Antennapedia: *Drosophila* gene (*Antp*; map location 3–47.5, salivary bands 84B1-2) with numerous alleles. The null alleles result in embryonic lethality. Initially the locus was recognized by mutations that transform the antennae into mesothoracic legs. Numerous other homeotic changes may accompany the mutations. The different alleles may involve various types at the locus. The gene occupies about 100 kb, containing eight exons. These exons are transcribed from promoters P1 or P2 or from both. The transcripts may undergo alternate splicing. The homeobox motif is in exon 8. Actually *Ant* promotes leg differentiation by suppressing antenna-determining genes *extradenticle* (*exd*, 1–54) and *homothorax* (*hth*, 3–48). ►homeotic genes, ►morphogenesis, ►*Polycomb*

Anterior: Indicates a direction in front of something or towards the head.

Anterior-Posterior Polarity: Head to tail anatomical direction.

Anterograde: Ahead or forward moving. ►retrograde

Anther: The pollen-containing parts of the male flowers (see Fig. A85). ►gametogenesis

Figure A85. Anther

Anther Culture: Used for the isolation of haploid plants. The culture may start with microspores that are directly regenerated into plantlets (without an intermediate callus stage) or from anthers. Haploid tissues are isolated and first a callus is formed, then the calli are regenerated into plants. Both procedures use tissue culture methods under aseptic conditions. The haploid cells may diploidize spontaneously or by induction and that results in perfect homozygosis of the plants. ►androgenesis, ►*Asparagus*, ►gametogenesis, ►embryo culture, ►YY plants; Jahne-Gartner A, Lörz H 1999 Methods Mol Biol 111:269.

Antheridium: The male sex organ (gametangium) of lower plants and fungi.

Anthesis: The time of pollen-shedding or receptivity of a flowering plant.

Anthocyanin: Plant flower pigments (delphinidin, cyanidin, pelargonidin, peonidin, petunidin, malvidin, etc.) are synthesized from phenylalanine via

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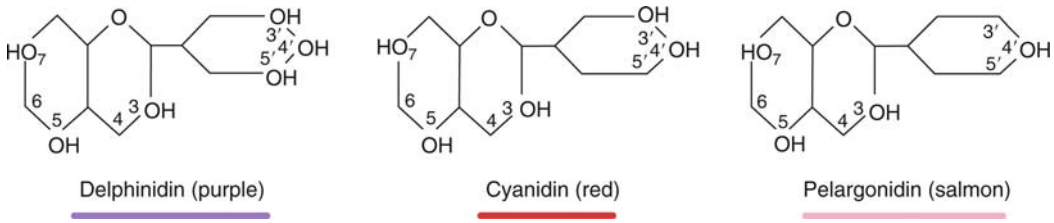

Figure A86. Pelargonidin displays an OH group at position 4′, cyanidin has two OH groups at 3′ and 4′, delphinidin has three OH groups (3′, 4′ and 5′). Peonidin (not shown) has 3′ OCH_3 and 4′ OH. Petunidin: 3′ OCH_3, and 5′ OH. Malvidin: 3′ and 5′ OCH_3 and 4′OH. Further color variations may be brought about by glycosylation and acetylations of the A ring(s) [at left]

trans-cinnamic acid and cinnamoyl-CoA, chalcones and flavonones (see Fig. A86). CH_3 and OH groups on the B ring determine the color produced; glycosylation (hexose or pentose) at the 3 and 5 positions (or at both) on the A ring increases stability of the pigments, and these glycosides are called anthocyanidins. In the petals of roses, a single glucosyltransferase adds a glycosyl group to both the 5 and 3 positions of the A ring of anthocyanidin (Ogata J et al 2005 Nature [Lond] 435:757). Each enzymatic step is controlled by different genes and these original discoveries, beginning in the early twentieth century, prepared the way for biochemical genetics. The color is affected also by the pH of the vacuoles and those too are under genetic control. By the use of antisense constructs of the gene chalcone synthase (CHS), the activity of this enzyme and chalcone flavonone isomerase (CHI) could be reduced indicating that CHS regulates also the expression of CHI. ►chalcone, ►grape; Markham KR et al 2000 Phytochemistry 55:327; Rasusher MD et al 1999 Mol Biol Evol 16:266; van Houwelingen A et al 1998 Plant J 13:39.

Anthranilic Acid: Synthesis begins with the condensation of erythrose-4-phosphate + phosphoenolpyruvate, and from this shikimate and then chorismate are formed. Chorismate through prephenate contributes to phenylalanine and tyrosine and through another path is a precursor of the amino acid tryptophan (actually indole-3-glycerol phosphate ® indole and serine are converted to this amino acid). ►tyrosine, ►phenylalanine

Anthrax: A toxin produced by *Bacillus anthracis*, an endospore-forming bacterium of ~5.23 × 10^6 bp sequenced genome with two plasmids, pXO1 (181 bp) and pXO2 (94,829 bp), that carry virulence genes; but the large chromosome also has virulence factors (Read TD et al 2003 Nature [Lond] 423:81). The toxin affects, primarily, herbivorous animals but it may spread to carnivorous predators and also to humans through the skin, by ingestion or inhalation of dust contaminated by the bacterial spores (see Fig. A87). Inhaling the spore of the most virulent strains may be lethal in 80–90% of the cases. The toxin consists of three proteins: (i) protective antigen (PA) facilitates the formation of a membrane channel for the (ii) edema factor (EF, an adenylate cyclase) and (iii) lethal factor (LF, a zinc-dependent metalloprotease and selective inhibitor of MAPK and MAPKK). For the manifestation of the toxic effects of anthrax the presence of low-density lipoprotein receptor LRP6 must be present. LRP6 enables internalization of the toxin by interacting with PA receptors TEM8/ATR (tumor endothelial marker) and/or CMG2 (capillary morphogenesis gene 2), which is a transmembrane cellular receptor. LRP6 appears to be a good candidate target for anti-anthrax therapy (Wei W et al 2006 Cell 124:1141).

The LF and the EF have a similar effect on *Drosophila* as in mammals and can be used to test the toxic functions in vivo in a much simpler system (Guichards A et al 2006 Proc Natl Acad Sci USA 103:3244). Although LF targets mainly MAPKK, apparently it hydrolyzes also a number of peptide hormones: granuloliberin R, dynorphin A (a 17-amino acid neuropeptide), kinetensin and angiotension-1 (brain peptides). The toxin represses the glucocorticoid receptor. The chemical PD09859 is also a MAPKK inhibitor but it acts differently from LF. Mutation in PA may prevent the uptake of EF and LF and thus in a dominant negative manner may become a potential tool in preventing the toxic effects. Another preventive approach is to block the formation of the heptameric cell-binding subunit of the toxin by a synthetic polyvalent inhibitor (Mourez M et al 2001 Nature Biotechnol 19:958). The bacteriolysin PlyG produced by the γ phage of *B. anthracis*, a monomeric protein of M_r of ~27K, detects and kills the anthrax bacterial spores. The antimicrobial peptide defensin and human neutrophil protein HNP-1 protects against the lethal toxin of this bacterium (Kim C et al 2005 Proc Natl Acad Sci. USA 102:4830). Ciprofloxacin antibiotic provides effective protection. A complex molecule of

a hydroxymate (2R)-[4(fluoro-3-methylphenyl)sulfonylamino]-*N*-hydroxy-2-[-2H-pyran-4-yl) acetamide interacts with LF and may provide up to 100% protection against the bacterium, especially in combination with ciprofloxacin (Shoop WL et al 2005 Proc Natl Acad Sci USA 102:7958). In case of inhalational exposure, vaccination and ciprofloxacin have synergistic protection (Vietri NJ et al 2006 Proc Natl Acad Sci. USA 103:7813).

The virulence genes are borne by the pXO1 plasmid and are regulated by temperature and carbon dioxide as well as by bacterial chromosomal genes encoding surface proteins of the semi-crystalline S-layer. A wide range of cancer cells exhibit increased surface urokinase activity. An engineered anthrax toxin equipped with urokinase plasminogen activator within the furin protease selectively increases the toxicity for cancer cells but not for normal cells. Furin and other proteases destroy the protective antigen of the toxin. The modified toxin thus can destroy cancer cells (Liu S et al 2003 Proc Natl Acad Sci 100:657). ►adenylate cyclase, ►metalloproteases, ►toxins, ►furin, ►urokinase, ►MAPKK, ►bioterrorism, ►microfluidics, ►ciprofloxacin, ►*Bacillus cereus*; Sellman BR et al 2001 Science 292:695; Mock M, Fouet A 2001 Annu Rev Microbiol 55:647; Bhatnagar R, Batra S 2001 Crit Rev Microbiol 27(3):167; Schuch R et al 2002 Nature [Lond] 418:884; danger as a weapon: Webb GF 2003 Proc Natl Acad Sci USA 100:4355; synthetic inhibitors of LF; Forino M et al 2005 Proc Natl Acad Sci USA 102:9499; anthrax inhalation risks based on the Sverdlovsk/Yekaterinburg, Russia accident: Wilkening DA 2006 Proc Natl Acad Sci USA 103:7589; toxin receptor binding: Young JAT, Collier RJ 2007 Annu Rev Biochem 76:243; *B. anthracis* database: http://cmr.tigr.org/tigr-scripts/CMR/GenomePage.cgi?database=gba; http://www.fda.gov/cder/drug/infopage/cipro/.

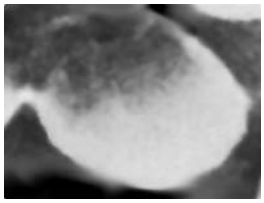

Figure A87. *Bacillus anthracis* spore

Anthropology: The science of human evolution, diversity, development and distribution, including the various human races. The database ALFRED (allele frequency database, http://alfred.med.yale.edu/alfred/) provides comprehensive information on human variation.

Anthropometric Traits: Those physical or physiological characters of humans (such as weight, head circumference, hair color, protein differences, behavior, etc.) that may be used for the characterization of human populations. ►anthropology

Anthropomorphism: The study of behavior assuming that animals share many traits resembling the conscience, cognition and feelings of human beings.

Anti: A conformation of nucleotides, the CO and NH groups in the 2 and 3 positions of the pyrimidine ring (1, 2, 6 positions in the purine ring) are away from the glycosidic ring, while in the SYN conformation they lie over the ring. The anti conformation is most common in nucleic acids and free nucleotides. Kornberg A 1982 DNA replication, Freeman, San Francisco, California.

Antiauxin: Interferes with the action of auxins, e.g., 2,3,5-triiodobenzoic acid inhibits the growth promoting action of 2,4-D (dichlorophenoxyacetic acid) or the indoleacetic acid (IAA) analog 5′-azido-indole-3-acetic acid interferes with enzymes involved with IAA. ►plant hormones

Anti-4-1BB Monoclonal Antibody: A co-stimulatory receptor expressed on activated T cells; it may be effective in amplifying T-cell-mediated immunity in cancer therapy. When used for intra-tumoral adenoviral gene transfer, it improved survival rate and reduced metastasis substantially. ►cancer gene therapy; Martinet O et al 2002 Gene Ther 9:786.

Antibiotic Resistance: Resistance to antibiotics is brought about either by enzymatic inactivation of the antibiotic, or modification of the target, or active efflux of the substance or sequestration by binding to special proteins. Today, antibiotic resistance in the major infectious agents may be up to 98%, depending on the agent and the antibiotic used. Genes in bacterial plasmids and transposons generally determine it. The antibiotic producing organisms have some special means (proteins) to protect themselves against their products. The mechanisms of resistance vary: penicillins and cephalosporins (β-lactamase hydrolysis); chloramphenicol (detoxification by chloramphenicol transacetylase that acetylates the hydroxyl groups or interferes with uptake); tetracyclines (interference with uptake or maintenance of the molecules); aminoglycosides (streptomycin, kanamycin, etc. enzymatic modification of the drug [phosphorylation] interferes with uptake or action); erythromycin, lincomycin (methylation of the small ribosomal subunit). Tetracycline pactamycin and hygromycin B modify, in special ways, the 30S ribosomal subunit and affect the decoding of mRNAs. In the 16S rRNA subunit, 53 sites were

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identified that are, potentially, sites for inhibition of protein synthesis. The majority of these sites affect either protein synthesis or the assembly of the small subunit of the ribosome (Yassin A et al 2005 Proc Natl Acad Sci USA 102:16620). The SOS response (error-prone repair) facilitates the horizontal spread of antibiotic resistance genes (Beaber JW et al 2004 Nature [Lond] 427:72).

Mutations in DNA topoisomerase and genes affecting cell permeability may result in resistance to ciprofloxacin. Ciprofloxacin-caused DNA damage can be corrected by nucleotide excision repair or by homologous recombination. Upon autoproteolysis, the SOS repair repressor lexA gene is sufficiently weakened so it no longer suppresses prokaryotic DNA polymerases Pol II, Pol IV, Pol V, which are accessory or conditional repair genes. Blocking autoproteolysis may be one way to interfere with the development of resistance to ciprofloxacin and rifamycin type antibiotics (Cirz RT et al 2005 PLoS Biol 3(6):e176). The use of antibiotics can contribute to bacterial competence and antibiotic stress can facilitate the acquisition of resistance to different antibiotics. In *Streptococcus pneumoniae*, kanamycin, streptomycin and mitomycin C triggered competence, but erythromycin, tetracycline, novobiocin, rifampicin, vancomycin, and cefotaxime did not. Mitomycin C and fluoroquinolones also induced SOS repair and competence in *E. coli*, but streptomycin and kanamycin did not. This indicates that stress responses are processed differently in these two bacteria (Prudhomme M et al 2006 Science 313:89).

Switching to another antibiotic if failure of effectiveness is encountered may minimize antibiotic resistance. Never switching to a new drug always minimizes the occurrence of a resistant strain but maximizes the failure in the treatment. Immediate switching usually maximizes resistance and minimizes failure. Thus, in most circumstances, the early use of a new drug enhances the effectiveness of the treatment while promoting the rise of high-level resistance in later generations of the bacteria (Wang YC, Lipsitch M 2006 Proc Natl Acad Sci USA 103:9655).

Antibiotic resistance acquired through conjugative transfer of the resistance factors or mutation pose serious problems to medicine, e.g., the recent resistance of *Mycobacterium tuberculosis* to all known antibiotics. Antibiotic resistance genes are used generally to assure the removal (by carbenicillin or claphoran [cefotaxime]) of the carrier *Agrobacteria* after infection with plant transformation vectors. Also, the transformed bacterial, fungal, animal and plant cells are selectively isolated on the basis of antibiotic resistance. Insertional mutagenesis in bacteria is monitored by the inactivation of the resistance genes upon integration. Various antibiotics are used all over the world in animal feed to increase animal productivity by 4–5%. Unfortunately, some of the antibiotic resistance genes may become incorporated into (facultative) human pathogens through animal products and waste and may pose a threat to human health. The soil seems to be an inexhaustible source of antibiotic resistance (D'Costa VM et al 2006 Science 311:374). The advantages gained by antibiotics in the feed may be partially compensated for by improved animal hygiene. ►antibiotics, ►pBR322, ►lactamase, ►aminoglycoside phosphotransferases, ►clavulanate, ►amoxicillin, ►vancomycin, ►tetracycline, ►decoding on ribosomes, ►LexA, ►DNA polymerases, ►biofilm, ►fratricide, ►SOS repair; Witte W 1998 Science 279:996 Walsh C 2000 Nature [Lond]: 407:775; Walker ES, Levy F 2001 Evolution 55:1110; Schlünzen F et al 2001 Nature [Lond] 413:814; Hughes D 2003 Nature Rev Genet 4:432; Miesel L et al 2003 Nature Rev Genet 4:442; Heymann DL 2006 Cell 124:671.

Antibiotics: A wide variety of chemicals produced by microorganisms and plants (also now by organic laboratory synthesis) that are toxic to other organisms. The major types of antibiotics are penicillins, ampicillin and cephalosporins (interfere with bacterial cell wall biosynthesis). Chloramphenicol binds to the 50S ribosomal subunit and blocks the peptidyl transferase ribozyme function during protein synthesis of prokaryotes. Tetracyclines inhibit the entry of the charged tRNA to the A site of the ribosome in prokaryotes. Streptomycin blocks the process of prokaryotic peptide chain elongation, and this as well as paromomycin, can also cause reading errors during translation. Spectinomycin inhibits the function of the 30S ribosomal subunit and reduces ribosomal translocation along with hygromycin B, edeine and pactamycin. Edeine has wide effectiveness but because of its toxicity is not useful as an antibiotic. Kanamycin, geneticin (G418), neomycin, gentamycin, and hygromycin bind to 30S and 50S ribosomal subunits and prevent protein synthesis or cause misreading. Erythromycin inhibits the translocation of the nascent peptide chain on the prokaryotic ribosomes. Lincomycin inhibits chain elongation on the prokaryotic ribosome by its effect on peptidyl transferase but not in eukaryotes. Rifampycin interacts with the β subunits of the prokaryotic RNA polymerase. Fusidic acid interferes with the binding of aminoacylated tRNAs to the ribosomal A site by inhibiting the release of prokaryotic elongation factor EF-G and also eukaryotic elongation factor eEF-2. Kasugamycin blocks the attachment of $tRNA^{fMet}$ to the P site of the prokaryotic ribosome. Kirromycin actually promotes the binding

of elongation factor EF-TU-GTP complex to the prokaryotic ribosome but then inhibits the release of the elongation factor. Thiostrepton, from *Streptomyces azureus*, blocks prokaryotic peptide elongation from both prokaryotic and eukaryotic ribosomes. Cycloheximide interferes with peptide translocation on the eukaryotic ribosome. Anisomycin blocks the peptidyl transferase on the eukaryotic ribosomes and is comparable in effect to that of chloramphenicol in prokaryotes. Streptolydodigins do not block RNA initiation but interfere with the elongation of the RNA chain in prokaryotes. Ciprofloxacin interacts with DNA gyrase. Actinomycin D inhibits, primarily, RNA polymerase II and to a lesser extent the other RNA polymerases but not DNA polymerase in either prokaryotes or eukaryotes; α–amanitin also inhibits eukaryotic RNA polymerase II and in very high concentration Pol III but not Pol I. Pactamycin blocks the eukaryotic initiator $tRNA^{Met}$ to attach to the P site of the ribosome. Showdowmycin interferes with the formation of the eukaryotic eEF-$tRNA^{Met}$ complex. Sparsomycin is a eukaryotic peptide chain translocation blocker; it is not very effective against microbes but works as an anticarcinogen. Cefotaxime (synonym claforan), carbenicillin, and vancomycin are more effective as antibacterial agents than their toxicity to eukaryotic cells and are frequently used in plant tissue culture to prevent bacterial growth. Macrolide antibiotics block the exit tunnel of the peptides on the ribosome. Antibiotics, which interfere with protein synthesis on prokaryotic ribosomes, cause similar damage to the ribosomes of eukaryotic organelles (mitochondria, plastids). The availability of antibiotics in the 1940s opened a new era in medicine and they became, in the 1970s, the most important selectable markers for the construction of vectors for genetic engineering. Antibiotics are used for selective isolation of various genetic constructs in microbial, plant and animal cell genetics. The number of antibiotics is continuously increasing because of the need for effective new drugs since microorganisms develop resistance to the old antibiotics. *Staphylococcus aureus* bacteria are resistant to all antibiotics except vancomycin and it will only be a matter of time when resistance mutations will develop to this too. Actually, fosphomycin (see Fig. A88) is effective against methicillin and vancomycin resistant *S. aureus* (Higgins LJ et al 2005 Nature [Lond] 437:838). There are already

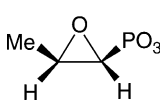

Figure A88. Fosphomycin

Enterococcus faecium strains that are resistant to vancomycin. The development of new antibiotics is becoming increasingly more difficult. A large fraction of the bacterial enzymes are not essential for infection because the metabolites they produce are available in the host cells. The existing antibiotics mostly target the enzymes that are essential for the pathogens and even a most comprehensive survey of the proteome of bacteria will probably reveal only few new targets (Becker D et al 2006 Nature [Lond] 440:303). Recently, a new class of antibiotics (platensimycin: see Fig. A89) was discovered that targets lipid biosynthesis and blocks the membrane system of a wide range of Gram-positive bacteria (Wang J et al 2006 Nature [Lond] 441:358). ►antibiotic resistance, ►protein synthesis, ►selectable marker, ►cell genetics, ►vectors, ►bleomycin, ►antimicrobial peptides, ►ciprofloxacin, ►GE81112; Walsh C 2000 Nature [Lond]:407:775; Palumbi SR 2001 Science 293:1786; Bêhal V 2002 Biotechnol Annu Rev 8:227; ribosomal antibiotics: Auerbach T et al 2004 Trends Biotechnol 22:570; structural bases of selectivity synergism, resistance: Yonath A 2005 Annu Rev Biochem74:649, http://www.hopkins-abxguide.org/.

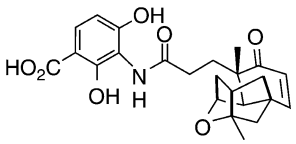

Figure A89. Platensimycin

Antibodies: Specific immunoglobulins that react—as a cellular defense—with foreign antigens. Antibodies contain two light chains, either κ or λ and one of the five heavy-chains (μ, δ, γ, ε, α) and their variants. Both light and heavy-chains contain variable and constant regions. The specificity resides in the variable regions. Antibodies have specificities to about a million different antigens. This specificity is achieved with the aid of a much smaller number of antibody genes by differential processing of the transcripts, mutation, recombination, gene conversion, and transposition within the families of immunoglobulin genes (see Fig. A90). Antibodies are made by the lymphocytes and may be attached to their membrane or may become humoral antibodies (secreted into the blood stream by the B lymphocytes). One particular B cell synthesizes only one type of antibody molecules. Each B cell deposits the first 100,000 antibodies it makes in its plasma membrane and serves there for antigen receptors.

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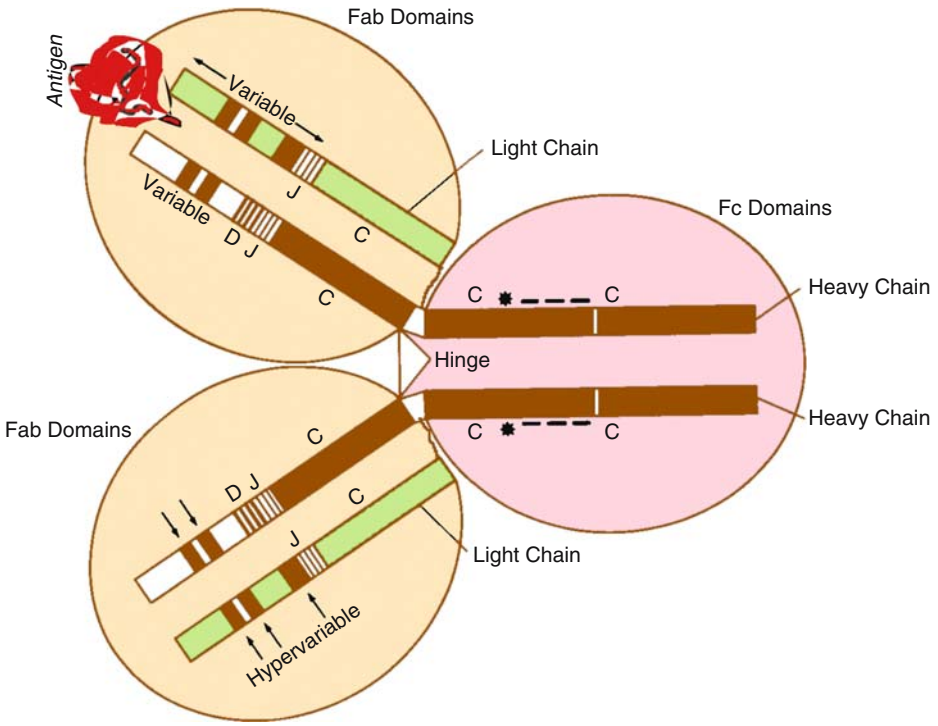

Figure A90. Antibodies have three main domains, the two Fab domains (Fragment antigen binding), including the light chains and parts of the heavy-chains and one Fc (Fragment crystalline) domain. The light chains have a size of about 23 kDA, the heavy-chains vary from 53 to 70 kDa. X-ray crystallography revealed the domains as 2 × 4 nm, oval or cylindrical in shape, and the polypetide chain in each domain is folded in pleated β-sheets. Disulfide bonds hold the dimeric structure of the light and heavy-chains together in variable numbers, depending on the particular molecules. The inter- and intra-chain disulfide bonds are not shown, except at the proline-rich hinge area that provides the molecules with some flexibility. The IgM and the IgE antibody monomers lack hinges but have an additional C-terminal heavy-chain domain. At the amino end of the light and heavy-chains are the variable and hyper variable regions that determine the specificity of the antibody. This region includes approximately 100 to 115 amino acids. The specificity is determined by complementarity between antibody and antigen in the antigen-binding "pocket" arms of the antigen around the area. Induced mutagenesis of the complementarity region may substantially increase the effectiveness of the antibody (Thom G et al 2006 Proc Natl Acad Sci USA 103:7619). The various specificities are determined by combinations of the variable (V), diversity (D) and junction (J) genes that account for about 25% of the amino acid residues, and the remaining 75% are considered the framework. CDR1, CDR2 and CDR3 (shown by the dark bands) generally identify the complementarity determining regions. The variable regions in the light and heavy-chains are homologous. The constant regions (C) show very little variability within a species. There is a glycosylation site in the constant heavy-chain region within the Fc domain (*). Also, in the constant heavy-chains there are sites for binding the activator of the complement (- - -). The complement consists of about 30 different proteins of catabolic functions that are activated in a cascading manner after the binding of the antigen to the antibody and carry out the destruction of the foreign antigen

When a particular antigen binds to the B cell, it stimulates its clonal division and the production of more antibodies. These series of the antibody are then made at the amazing rate of about 2,000 molecules/second and then secreted into the blood plasma. An individual can make about 10,000 different heavy-chain variants and about 1,000 different light chain variants. Since these chains can combine freely, the total number of different antibodies can be $10^4 \times 10^3 = 10^7$. IgM type antibodies (containing gamma immunoglobulin chains) occur at the largest concentration in the blood serum and their half-life is the longest. The general structure of the antibody molecules is diagramed here. Each antibody molecule has two identical antigen-binding sites (see diagram). The majority of the antigens have, however, several

to many antigenic determinants (epitopes). Some of these antigens may be built of repeating units and in these cases they are *multivalent* because they have multiple copies of the epitope. The binding between epitopes (e) and antibody (a) is a concentration-dependent, reversible process: (a + e) ⇔ (ae). When the concentration of the epitope increases, the binding to the antibody is increasing and the intensity of the reaction is expressed by the *affinity constant*: (k) = (ae)/(a)(e). When half of the (a) sites are filled k = 1/e, the values of (k) range from 5×10^4 to 10^{12} moles. Conformational diversity of the same antibody may result in affinity for multiple, distinct antigens (James LC et al 2003 Science 299:1362).

The *avidity* of an antibody for an antigenic determinant depends also on how many binding sites are available. The affinity is increasing with time after immunization (affinity maturation). Antibodies are involved in the destruction of invaders, either through stimulating the macrophage cells to phagocytosis, or by ions, using the complement enzymes or activating the killer cells. It was recently discovered that antibodies could generate H^2O^2 by oxidation of water with the aid of singlet oxygen ($^1O_2$*). This ability adds a chemical to their repertory of defense (Wentworth P et al 2001 Science 293:1806). Usually their turnover is rapid; the half-life of antibodies is days to a few weeks. By chemical modifications antibody/ligand complexes can be generated that do not dissociate and do not cross-react appreciably with other ligands (Chmura AJ et al 2001 Proc Natl Acad USA 98:8480). About 20% of the total plasma proteins represent a diverse set of antibodies. After the B lymphocytes respond to an antigen and differentiate into plasma cells, their rate of antibody production may reach 1,000 molecules/second after immunization (affinity maturation). Receptors (FcRn) of the Fc domain (see diagram) contribute toward the phagocytotic functions, cytotoxicity and to neonate immunity. In the maternal uterus, FcRn/IgG has been detected. The FcRn receptors transfer maternal humoral immunoglobulins to the newborn before the immune system of the progeny is activated. During nursing, the FcRn class receptors mediate the transfer of the IgG/FcRn complex through the milk. Antibody genes can be expressed not just in lymphoid cells but also ectopically, e.g., in bacterial cells when introduced by transformation. In such a system they may form inclusion bodies either in the cytoplasm or in the periplasmic space or may be present as soluble proteins secreted into the cytoplasm. In the periplasmic space disulphide isomerase-like and proline cis-trans isomerase (rotamase) proteins may exist that mediate folding of the antibodies or fragments. The prokaryotic chaperones may also participate in the folding. In the *Camelidae* (camels and llamas), the antibodies contain only heavy-chain (Hamers-Casterman C et al 1993 Nature [Lond] 363:446) and the first domain of the constant region is absent although it is present in the genome (see Fig. A91); but it is not retained during mRNA processing (Nguyen VK et al 1999 Mol Immunol 36:515; Nguyen VK et al 2002 Immunogenet 54:39). The antibody-based immune system is restricted to vertebrates and is present in all gnathostomes (jawed vertebrates); but it is apparently absent from agnathans (jawless vertebrates), such as lamprey and hagfish (Klein J, Nikolaidis N 2005 Proc Natl Acad Sci USA 102:169). ►immunoglobulins, ►immune system, ►complement, ►monoclonal antibodies, ►single-chain Fv fragment, ►hybridoma, ►antibody polyclonal, ►recombinant antibody, ►HLA, ►lymphocytes, ►T cell, ►TCR, ►B lymphocyte receptor, ►killer cell, ►antigen, ►antigen presenting cell, ►MHC, ►neutralizing antibody, ►immunization alloantibody, ►natural antibody, ►periplasm, ►rotamase, ►chaperone, ►antibody engineering, ►anti-idiotype antibody, ►anti-DNA antibody, ►internal image antibody, ►catalytic antibody, ►plantibody, ►antibody gene switching; Heyman B 2000 Annu Rev Immunol 18:709; Ravetch JV, Bolland S 2001 Annu Rev Immunol 19:275; antibody evolution by conformation selection and mutation: Zimmermann J et al 2006 Proc Natl Acad Sci USA 103:13722, http://www.antibodyresource.com/onlinedata.html.

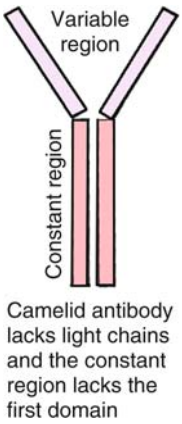

Figure A91. Camelid Antibody

Antibody Antigenization: The modification of the hypervariable region of an antibody by protein engineering in order to enhance the recognition of the new antibody to foreign epitopes by the B and T lymphocytes. ►antibody, ►antigen, ►epitope, ►B lymphocyte, ►T cells

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Antibody, Bispecific: A bispecific antibody has affinity to two different antigens. Such an antibody may not exist.

Antibody, Bivalent: A bivalent antibody has two antigen-binding sites.

Antibody, Chemically Programmed (cpAB): A small molecule is covalently added to an antibody and providing an extension for its effective range (Guo F et al 2006 Proc Natl Acad Sci USA 103:11009)

Antibody, Chimeric: Can be produced with the aid of genetic engineering by fusing the variable regions of one type to the constant region of another antibody. It can also be produced in vivo by homologous recombination in hybridoma cells or by using the *Cre-loxP* system. hybridoma, ►*Cre/loxP*, ►HAMA, ►primatized antibody; Presta LG 2006 Adv Drug Deliv Rev 58:640.

Antibody Detection: Antibody detection is possible through several procedures: antibodies bound to proteins expressed in *E. coli* are detected by I^{125} (isotope)-labeled antibodies that react to the species-specific determinants of the primary antibodies. Protein A labeled with I^{125} second antibody, conjugated to horseradish peroxidase (HRP) or HRP coupled to avidin, may be used to detect a second antibody coupled to biotin or by a second antibody conjugated to alkaline phosphatase, using radio-labeled ligands. Antibodies can also be detected by agglutination and complement fixation. In agglutination, a precipitate is formed upon the reaction. One of the procedures is the *Ouchterlony assay* where the antibody and the antigen are placed in the neighboring wells of agar plates; upon diffusion a visible precipitate is formed about midway between the two wells if the antigen (e) and antibody (a) recognize each other (see Fig. A92).

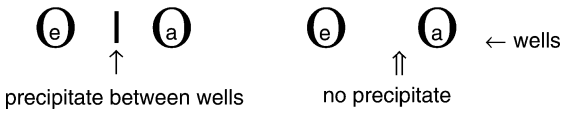

Figure A92. Ouchterlony test

The complement fixing procedure has a unique feature inasmuch as the complement binds only to the antibody that is complexed with the antigen. If the complement is fixed, adding red blood cells and a cognate antibody to the reaction mix, resulting in no hemolysis, it is proof of fixation of the complement and the procedure can be quantitated by employing a series of dilutions. ►antibodies, ►complement, ►immunostaining, ►antibody microarray

Antibody Effector Functions: These functions are carried out by activation of the complement system and by interactions of the antigen through the Fc domain receptors (e.g., FcγR) leading to ADCC. ►antibody, ►complement, ►FcγR, ►ADCC

Antibody Engineering: Antibody Engineering involves genetic modification of the immunoglobulin genes, particularly the complementarity determining regions of the antibody. ►antibody, ►humanized antibody, ►plantibody, ►phage display, ►immunotoxin, ►monoclonal ►antibody, ►transgenic, ►bispecific monoclonal antibody, ►Fv, ►gene fusion, ►antibody polymers, CDR; Maynard J, Georgiou G 2000 Annu Rev Biomed Eng 2:339.

Antibody Fusion: Antibody fusion constitutes gene fusions, which most commonly involve the antibody heavy-chain and enzyme-coding sequences (nuclease, glucuronidase, etc.) or toxins (e.g., angiogenin toxin, neurotoxin), cytokinins (interleukin 2, TNF, IGF), and labeling proteins (aequorin, avidin).

Antibody Gene Switching: is preceded by the pairing between members of the antibody constant heavy-chain gene families and the formation of loops that are then cut off at the stem. This cutting off/deletion produces different heavy-chain elements in the vicinity of the J (junction) genes. The site-specific switch then permits the expression of the genes that are moved to the vicinity of the J genes after the stem of the loop is cut off and the DNA strands are religated. The transcript is further processed by the removal of the introns. This is one of the mechanisms to generate greater diversity in the heavy-chain antibody proteins. The switching is stimulated by cytokines secreted by the T_H lymphocytes. In mouse cells, the IL-4 induces the switch from IgM to IgG1 or IgE. Interferon-γ causes switching from IgM to IgG2a and TGF-β mediates the switch from IgM to IgG2b or IgA or IgE. A defect in switching may result in Hyper-IgM syndrome and the patients thus become susceptible to infections because of low concentrations of IgG and IgA. The murine heavy-chain constant region has eight different genes. A switch region flanks each constant gene, except Cγ. The mammalian switch regions vary substantially yet they are highly repetitive, especially in Gs in the non-template strand. The switch repeats include AGCT and GGGGT subrepeats.

Upon transcription, the RNA:DNA hybrid forms in the switch region, in vitro, and the non-template strand remains single-stranded. At the switch regions, Sγ3 and Sγ2b loops form in the lipopolysaccharide (LPS)-stimulated B cells (see Fig. A93). Most of the recombination (>90–95%) occurs in these two switch

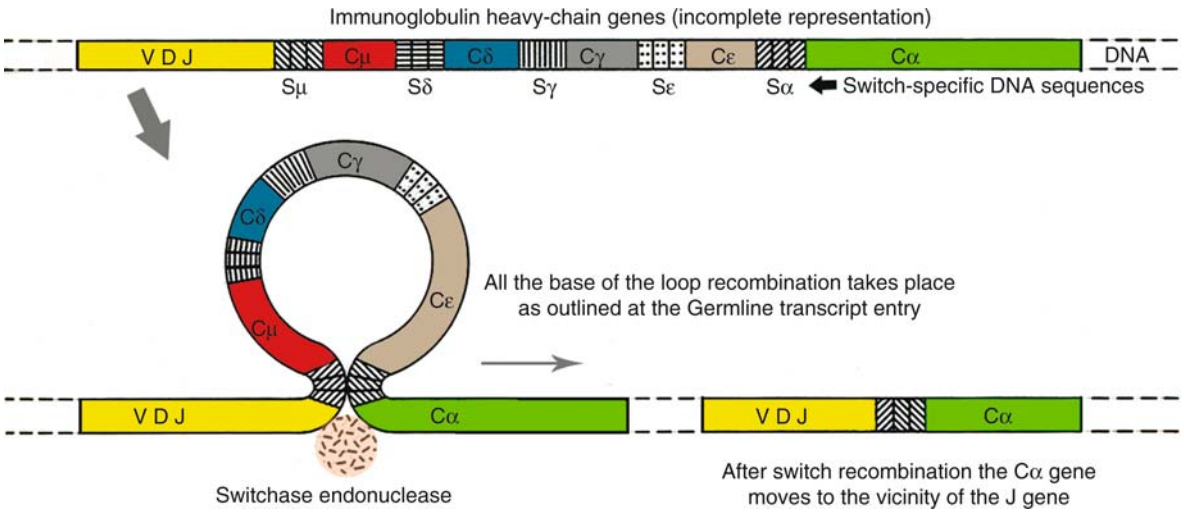

Figure A93. Antibody gene switching

regions respectively (Huang F-T et al. 2006 Proc Natl Acad Sci USA 103:5030).

The basic leucine zipper proteins of the Maf family and Bach transcription factors (Bach2, 6q15; Bach1 21q22.1) regulate the switching from IgM to other immunoglobulins in B cells and are critical for somatic hypermutation (Muto A et al 2004 Nature [Lond] 429:566). Activation-induced cytidine deaminase (AID) seems to be involved in the mediation of switching (Rush JS et al 2005 Proc Natl Acad Sci USA 102:13242). The deamination contributes to the formation of dU:dG lesions, and their resolution leads to class-switch recombination and somatic hypermutation (Rada C et al 2004 Mol Cell 16:163). Switching is different from the V(D)J recombination process. In the jawless (agnathan) fish, the lamprey variable lymphocyte receptors, composed of highly diverse leucine-rich repeats, are sandwiched between the amino- and carboxy-terminal of the receptors. This arrangement can generate large diversity when recombined for the anticipatory (adaptive/acquired) immune reaction (Pancer Z et al 2004 Nature [Lond] 430:174). Translocation between c-myc and IgH is also regulated by AID and uracil glycosylase (Ramiro AR et al 2006 Nature 440:105), a frequent cause of B lymphocyte malignancies. ►immunoglobulins, ►antibodies, ►V(D)J, ►RAG, ►T_H, ►immune system, ►germline transcript, ►somatic hypermutation, ►hypermutation, ►ectodermal dysplasia, ►class switching, ►MSH5, ►acquired immunity, ►AID (activation induced deaminase), ►myc, ►glycosylases; Kataoka T et al 1981 Cell 23:357; Revy P et al 2000 Cell 102:565; Stavnezer J 2000 Science 288:984; Honjo T et al 2002 Annu Rev Immunol 20:165; AID mechanisms: Honjo T et al 2004 Immunity 20:659.

Antibody, Intracellular: By introducing specific antibody genes into a cell and if the transgene is expressed, various processes, interactions between macromolecules, fixing enzymes in active or inactive states, modifying (binding) ligands, targeting intracellular signals, etc., can be explored. Tissue targeting vectors can be constructed for the introduction of genes to specific locations. In these systems, antibodies are coupled to viral vectors, liposomes, or directly to the passenger DNA. Antibodies can be targeted to T cell receptors (TCRs). Bispecific antibodies can be used to re-target effector cells to tumors. ►KDEL, ►monoclonal antibody therapies, ►immune system, ►viral vectors, ►liposome, ►T cell receptor, ►monoclonal antibody therapies; Brekke OH & Sandlie I 2003 Nature Rev Drug Discov 2:52.

Antibody, Isomeric: Isomeric antibodies may exist in two conformational state and thus can bind two structurally distinct antigens. antibody, ►antigen, ►isomers

Antibody Lattice: An antibody lattice or alternating antigen-antibody complex is formed when the cognate antibody is in excess of the antigen, between the Fc domain of the IgG and the antigen. ►antibody, ►antigen

Antibody Microarray: An antibody microarray is the high-throughput profiling of a relatively smaller number of proteins (compared to mass spectrometry). Antibodies are spotted on solid surface and a complex mixture of cell lysates or serum labeled by a fluorescence tag are allowed to recognize the antibodies. Similarly, antigens can be spotted on glass and reacted with cognate antibodies. Allergens, glycans

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and other molecules can be studies in an analogous manner. This procedure is well suited to various biological purposes. ►protein profiling; Huang RP et al 2001 Anal Biochem 294:55; Sreekumar A et al 2001 Cancer Res 61:7585.

Antibody Mimic: An antibody mimic is a small synthetic polypeptide with specificity for a particular natural or synthetic epitope. ►epitope, ►antibody

Antibody, Monoclonal: ►monoclonal antibody

Antibody, Monovalent: A monovalent antibody has only a single binding site for an antigen. Normally the antibody is divalent, i.e., it has antigen-binding sites at both of the light and heavy-chain variability regions. By linking together multiple binding sites the avidity of the antibody increases. ►antibody, ►antibody bispecific

Antibody, Neutralizing: It results in the loss of infectivity, which ensues when antibody molecule(s) bind to a virus particle, and usually occurs without the involvement of any other agency. As such this is unusual of an antibody and is paralleled only by the inhibition of toxins and enzymes (Dimmock NJ 1995 Rev Med Virol 5:165; Finke D et al 2003 Proc Natl Acad Sci. USA 100:199). HIV-1 may escape from the neutralizing antibody by N-linked glycosylation of the viral *env* gene (Wei X et al 2003 Nature [Lond] 422:307). ►acquired immunodeficiency

Antibody, Polyclonal: A polyclonal antibody is a collection of antibodies secreted by different B lymphocytes in response to the epitopes of the same antigen and are therefore not entirely identical. Human polyclonal antibodies can be obtained by transferring them into bovine embryonic cells and thus into calves both the heavy and the lambda-chains of immunoglobulin gamma genes on a human artificial chromosome vector. ►epitope, ►antigen, ►monoclonal antibody, ►recombinant antibody, ►human artificial chromosome, ►nuclear transplantation; Kuroiwa Y et al 2002 Nature Biotechnol 20:889.

Antibody Polymers: Antibody polymers are formed by fusion of immunoglobulin chains. In this process, the immunoglobulin μ chain tailpiece fuses to the C-end of the γ chain which may increase, by two orders of magnitude, the activity of the complement system. Also, simple IgM, IgG tetramers are more effective than dimers. ►antibody, ►immunoglobulins, ►tailpiece, ►complement, ►pIgR

Antibody Preparation: Antibody preparation involves injecting an animal with a pure antigenic molecule. After 2 to3 weeks the animal develops antibodies against the epitope. The animal is then bled and the antibody removed from the serum by precipitation

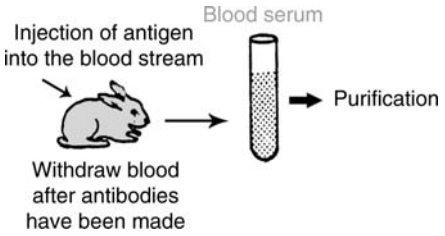

Figure A94. Antibody preparation

with the cognate antigen and further purified. Hundreds of different antibody preparations are commercially available from biochemical supply companies.

Antibody Purification: There are different methods of purifying antibodies. The protein antigen may be coupled to a cyanogen-bromide-activated Sepharose. The epitope then retains the cognate antibodies while all other antibodies flow through. Breaking the complex (with potassium thiocyanate, low-pH buffers, etc.) can then retrieve the antibody. The methods must be adapted to the different proteins. Another procedure is to adsorb antibodies to protein antigens immobilized on diazotized paper or nitrocellulose filters following electrophoresis by SDS-polyacrylamide gels. The antibodies are then eluted with a suitable buffer. Antibodies can be used for qualitative and quantitative assays of antigens, including immunoprecipitation, western blotting and solid-phase radioimmunoassays (RIA). ►Sepharose, ►epitope, ►cyanogen bromide, ►diazotized paper, ►nitrocellulose filter, electrophoresis, ►SDS-polyacrylamide gels, ►immunoprecipitation, ►radioimmunoassay

Antibody, Secondary: A molecule, cell, or tissue may be labeled with the cognate antibody (primary antibody). In order to boost the level of recognition, the primary antibody is reacted with another antibody (secondary antibody), labeled with an isotope (e.g., I^{125}) or a fluorochrome to obtain a stronger signal. ►antibody, ►fluorochromes

Antibody, Single Chain: ►single-chain fragment Fv, ►scFv

Antibody Valency: Specifies the number of antigen-binding sites. ►antibody monovalent

Anticancer Agents: Include alkylating agents, cytotoxic and cytostatic agents, antibiotics (bleomycin, chlorambucil), topoisomerase inhibitors (etoposide, podophyllotoxin), ionizing radiation, etc. ►chemotherapy, ►cancer therapy, ►cancer gene therapy, ►ionizing radiation

Anticarcinogen: ►antimutagens

Antichaperone: Antichaperone is a protein factor promoting aggregation of other proteins. ►chaperone

Antichromatin: Antichromatin is a state of the chromatin not conducive for active transcription. ►chromatin, ►pro-chromatin

Anticipation: In successive generations it may appear as if the genetic trait (disease) would have occurred with an earlier onset in the more recent generations. Frequently this is, however, an artifact because when the investigator knows what is expected, the recognition becomes easier. There is also the possibility that individuals with early onset of the disease died early or failed to leave offspring. In the cases of diseases based on expansion of trinucleotide repeats there is a possibility of increased severity and earlier onset if the patients leave offspring. ►ascertainment test, ►trinucleotide repeats; Kovach MJ et al 2002 Amer J Med Genet 108:295.

Anticlinical Selection: An anticlinical selection is the selection that takes different directions in different environments compared to the *synclinal selection* when the direction is the same. ►cline

Anticoagulation: Blood coagulation is positively regulated by antihemophilic factors. Negative regulation (shutting down the coagulation pathway) is mediated by thrombomodulin, which binds thrombin and activates protein C, which in turn binds protein S and causes factors V*a* and VIII*a* to be degraded. Thrombomodulin (an epidermal growth-factor like molecule) works by binding to thrombin at an exosite where otherwise thrombin would bind fibrinogen. Coumarin impairs the pro-coagulants thrombin, antihemophilic factors X*a*, IX*a* and VII*a* and the anticoagulant proteins C and S. Heparin enhances the inhibition of thrombin and factor X*a* by antithrombin III. ►blood clotting pathways, ►antihemophilic factors, ►thrombin, ►exosite, ►protein C, ►protein S, ►antithrombin, ►vitamin K

Anticoding Strand: An anticoding strand is the transcribed strand of DNA. ►antisense RNA, ►coding strand, ►template strand, ►sense strand, ►plus strand

Anticodon: An anticodon is part of the tRNA, which recognizes an mRNA code word by complementarity. It is one of the means of tRNA identity (see Fig. A95).

In the mitochondria the "universal" genetic code does not entirely prevail but different eukaryotic mitochondria (except higher plants) use a somewhat different codon dictionary. In these systems the anticodons are also different inasmuch as there are no separate tRNAs for each of the synonymous codons.

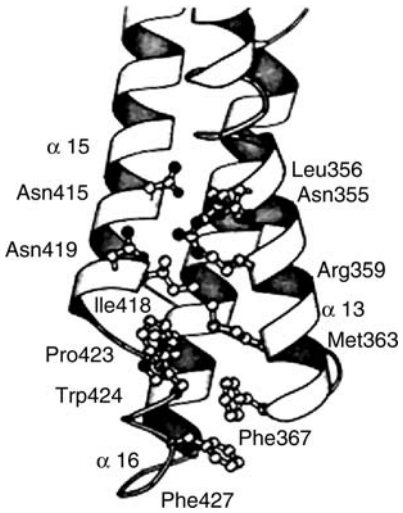

Figure A95. The Anticodon–Binding α–Helix Bundle of Bacterium $tRNA^{Met}$ Synthetase. The Stick–and–Ball Structure shows the exposed side chains of the Amino acids (Courtesy of professor M. Konno. See also Sugiura I et al 2000 Structure 8: 197)

Rather, the mtDNA codons are recognized in pairs or in four-member sets of codons, and the anticodon–codon interaction is by G●U pairing or the 5′-terminal U of the anticodon of the four-member set can pair with any of the four bases in the mRNA codon. Although there are 61 different sense codons in eukaryotes, there are only 54 anticodons in the universal code and 46 species of tRNAs and anticodons are sufficient for protein synthesis on the ribosomes. ►tRNA, ►genetic code, ►wobble; Jukes TH 1984 Adv Space Res 4 (12):177.

Anticorrelation Genes: Have similar (analogous) function and can complement each other without substantial structural homology. Morett E et al 2003 Nature Biotechn 21:790.

Antideterminant: Ribonuclease III, which processes about 20-bp double-stranded RNAs may not cut at any position because some Watson-Crick pairs interfere with scission and serve as an antideterminant. Such an antideterminant is, e.g., a 3-bp sequence from the selenocysteine-accepting tRNA ($tRNA^{Sec}$) and is an antideterminant for EF-Tu binding to this tRNA. ►ribonuclease III, ►selenocysteine, ►EF-TU-GTP; Evguenieva-Hackenberg E, Klug G 2000 J Bacteriol 182:4719; Mohan A et al 1999 RNA 5:245.

Antidiuretic Hormone (vasopressin): Vasopressin is a small peptide hormone (ADH, M_r 1040) which increases water reabsorption in the kidneys and also blood pressure; it affects a variety of functions, including learning and behavior (aggression).

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Nephrogenic diabetes insipidus an X-chromosomal human disease, with problems of maintaining water balance, fails to respond to ADH and is very similar to oxytocin; only two amino acid difference exists between the two. The structure of vasopressin is (see Fig. A96):

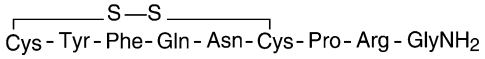

Figure A96. Antidiuretic hormone

It binds to receptor molecules in the plasma membrane in the kidneys and blood vessels and activates a specific membrane, phospholipase. The phospholipase then breaks the bond between glycerol and phosphate in phosphatidylinositol-4,5-bisphosphate and releases inositol-1,4,5-triphosphate and diaglycerol. Vasopressin is encoded in the short arm of the human chromosome 20 along with oxytocin. ►oxytocin, ►diabetes insipidus, ►phospholipase, ►diaglycerol, ►inositol, ►phosphoinositids, ►nocturnal enuresis

Anti-DNA Antibody: DNA is a poor antigen although in the autoimmune disease lupus erythematosus antibodies bind to DNA. Most DNA antibodies are not entirely specific because they bind to repetitive sequences. DNA tracts with stably bound proteins can, however, be used as antigens to specific sequences. ►autoimmune disease, ►antibody, ►antigen; Stollar BD1986 CRC Crit Rev Biochem 20:1; Cerutti ML et al 2001 J Biol Chem 276:12769.

Antidote: Antidotes may be specific for reversing the toxic effect of a compound or nonspecific, e.g., an emetic, which induces vomiting.

Antiestrogen: Antiestrogens bind to the estrogen receptors and antagonize the effects of the hormones. Some, however, may have various levels of agonist activity. ►tamoxifen, ►raloxifene

Antifreeze Protein: Antifreeze protein is present in several species of fishes living in the northern regions. The glycoprotein binds, through free OH groups of amino acids, to the first ice crystals and thus prevents the expansion of the ice and thus the fish is protected. In fishes there are more than eight forms of antifreeze protein, encoded as different proteins, yet they all contain tripeptide (Thr-Ala-Ala/Pro-Ala-) repeats. Mainly, Leu/Phe-Ile/Asn-Phe spacers link the monomers into a large polyprotein. The antifreeze glycoprotein (AFGP) genes usually contain two exons (the small for a signal peptide and the large for the antifreeze) separated by a single intron. Somewhat similar proteins may play a role in other organisms too. A very efficient antifreeze protein was isolated from the insect *Tenebrio monitor*. A 36-kDa glycoprotein isolated from cold-acclimated carrot taproots is similar in sequence to polygalacturonase inhibitor proteins. The antifreeze protein in perennial ryegrass (*Lolium perenne*) appears to control more ice crystal growth than preventing freezing *per se*. ►hysteresis, ►cold hypersensitivity, ►thermo-tolerance, ►mealworm; Miao M et al 2000 Eur J Biochem 267:7237; Tomczak MM et al 2001 Biochim Biophys Acta 1511:255; Haymet AD et al 2001 FEBS Lett 491:285; Fairly K et al 2002 J Biol Chem 277:24073.

Antifungal Response: Insects defend themselves against fungi and microorganisms by the production of proteolytic enzymes, phagocytosis and by the production of antimicrobial peptides. In *Drosophila,* antifungal drosomycin and several antimicrobial/antibacterial peptides, cecropins, diptericin, drosocin, attacin and defensin are produced. The *spätzle, Toll, cactus*, and *dorsal* dorsoventral regulatory genes (corresponding to the mammalian NF-κB cascade) and the immunodeficiency gene, *imd*, mediate these responses. Several species of yeasts also exert antifungal action. ►antimicrobial peptides, ►morphogenesis in *Drosophila,* ►host–pathogen relationship, ►NF-κB

Antigen: An antigen is a substance (usually a protein) which, either alone or in combination with a protein, elicits antibody formation. The protein antigen may be a large molecule with more than a single specificity due to its different subunits. A particular specificity of the antigen is determined by the epitope or a hapten conjugated with the protein molecule to form an antigen that reacts with the paratope of the antibody. The antigen is usually chopped into small fragments to be effectively presented to the lymphocytes. In some cases, internal sequences of the peptides are deleted by a proteasome system and, e.g., the originally 16 residues are spliced into a 9-residue antigen (Vigneron N et al 2004 Science 304:587). ►antibody, ►antigen presenting cell, ►epitope, ►paratope, ►superantigen, ►TI antigens, ►lipid antigen; Kurosaki T 1999 Annu Rev Immunol 17:555; Zinkernagel RM, Hengartner H 2001 Science 293:251.

Antigen, Male Specific: ►grafting in medicine, ►H-Y antigen

Antigen mimic: An antigen mimic is a short polypeptide used for screening specific paratope sites. ►paratope, ►antibody mimic

Antigen Presenting Cell (APC): APC binds antigens, internalizes, processes and expresses them on their surface in conjunction with class II type molecules (one of the two type of molecules coded for by the

MHC genes). T cells recognize the presented antigen through their receptors. Helper T cells can be activated only in the presence of APC cells. Macrophages, dendritic (branched) cells and B lymphocyte cells express class II antigens and can thus serve as APC in vitro and in vivo macrophages and dendritic cells are apparently most important as APC (see Fig. A97).

The activation of helper T cells requires that the T cells and the APC be derived from animals (mice) syngeneic in region *I* of the MHC, and the production of the lymphokine, interleukin-1 (IL-1) and also family member, CD80. Macrophages are rich in lysosomes and can therefore rapidly break up antigens, whereas dendritic cells are poor in lysosome activity and have a more limited capacity for degradation. ►antigen, ►immune system, ►T cell, ►T cell receptor, ►cytotoxic T cell, ►clonal selection, ►CD40, ►HLA, ►syngeneic, ►lymphokines, ►interleukins, ►affinity maturation, ►CD80, ►CD1, ►proteasomes, ►MHC, ►cross presentation; Jenkins MK et al 2001 Annu Rev Immunol 19:23; Guermonprez P et al 2002 Annu Rev Immunol 20:621.

Antigen Processing and Presentation: Antigen-presenting cells mediate the association of the native antigen with an MHC molecule and thereby the antigen is recognized by the T lymphocytes. The antigenic protein must be degraded to some extent by immunoproteasomes and processed for presentation to the MHC molecules. The processing takes place either within endosomal compartments of the cell or by the proteases secreted onto the surface of the immature dendritic cells. The final step in sizing the antigen is mediated by the enzyme ERAAP (endoplasmic reticulum aminopeptidase), which is upregulated by interferon γ (Serwold T et al 2002 Nature [Lond] 419:480). The MHC I associated peptides are generally shorter (9±1 amino acids) than those associated with MHC II molecules that are derived from excreted proteins or other external proteins. Protein disulfide isomerase play a critical role in selecting MHC I molecules (Park B et al 2006 Cell 127:369). Usually the peptides enter the endoplasmic reticulum before their epitope is presented to the MHC molecules. If the proteins lack the signal peptide to be transferred to the endoplasmic reticulum, their epitope may still be presented to the MHC molecules. The MHC Class II molecules are associated with the invariant I_i polypeptide that mediates the folding of the MHC II molecules in the endoplasmic reticulum and compartmentalizing the MHC II molecules for special peptide binding in the endosomes. The processing is mediated by cathepsins but an asparagine-specific cysteine endopeptidase may also be involved in degrading microbial antigens. ►antigen presenting cell, ►HLA, ►lymphocytes, ►immunoproteasomes, ►endosome, ►CLIP, ►major histocompatibility complex, ►TAP, ►T cell, ►cathepsins; York IA, Rock KL 1996 Annu Rev Immunol 14:369; Watts C 1997 Annu Rev Immunol 15:821.

Antigen Receptors: Antigen receptors are molecules on lymphocytes, responsible for the recognition and binding of antigens and antigen-MHC. ►lymphocytes, ►HLA, ►receptor editing, ►LFA, ►CD2, ►CD4, ►CD8, ►CD28, ►CD45, ►CTLA-4, ►ICAM; Davis MM et al 2003 Annu Rev Biochem 72:717.

Antigene Technology: Antigene technology is used for triple helix formation. ►triple helix formation

Antigenic Determinant: ►epitope, ►antibody

Antigenic Distance: The antigenic distance indicates the degree of similarity between/among antigens.

Antigenic Drift: Antigenic drift is the process by which the surface antigens of a pathogen may change by mutation. ►antigenic variation, ►phase variation, ►*Borrelia*, ►*Trypanosoma*

Antigenic Shift: Antigenic shift is a rearrangement in the genetic material of a virus resulting in an escape of the normal immune reaction. ►antigenic drift, ►antigenic variation

Antigenic Sin: Propensity of individuals who had been previously exposed to one virus and later encountered another virus variant of the same subtype, can make antibodies against the original viral hemagglutinin (HA) and also to the new one. This happens because

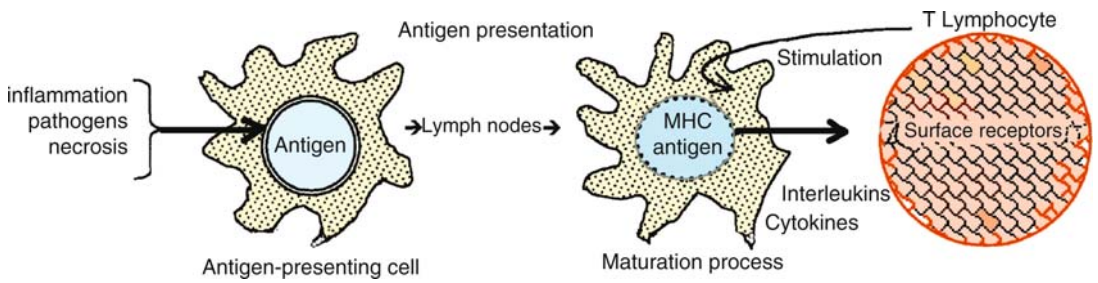

Figure A97. Antigen presenting cell

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the memory B cells or the T cells were activated in a way specific for the progenitor virus. In some instances the variant virus may escape the immune defense of the host because the lymphocyte receptor is altered by mutation although the histocompatibility class I molecules may bind normally. ►hemagglutinin, ►immune system, ►antigen, ►HLA; Good MF et al 1993 Parasite Immunol 15:187.

Antigenic Variation: Antigenic variation is the property of prokaryotic and eukaryotic microorganisms to switch on the synthesis of different surface proteins to escape the immunological defense system of the host organisms. This goal is reached generally by transposition of genes relative to the promoter. In *Plasmodium falciparum*—the malaria parasite—the PfEMP1 (erythrocyte membrane protein family), encoded by ~60 *var* genes determine virulence by immune evasion and intravascular sequestration of the parasite in the host. The PfEMP1 molecules adhere to the surface of the red blood cells and evade detection by the immune system at this place of hiding. By multiplying in the capillaries, clogging and malaria develops. Evasion of the host immune system takes place by switching on one or another member of the PfEMP1 family members while the other alleles are excluded from function. The expression of the *var* genes is controlled by one or another of the upstream promoters (*upsA, upsB, upsC*). The telomeric *var* gene promoters have expression sites near the periphery of the nucleus where they move by an unknown epigenetic mechanism of chromatin remodeling. The A and B promoters are subtelomeric and interact with DNA-binding proteins whereas the C interacts with a *var* intron and controls silencing by using a silent information regulator, PfSIR2 (Voss TS et al 2006 Nature [Lond] 439:1004).

In *Borrelia hermsii*, a bacterium responsible for tick-borne relapsing fever, unexpressed loci of variant antigens copy into a single expression site at rates determined by extragenic features of silent loci rather than similarity between coding sequences of variants at silent sites and the single expression site. Two elements, in particular, determine switch rates. One set of elements overlaps the 5′ ends of the expressed gene and the silent loci; greater sequence identity between elements was associated with a higher switch rate. The second set of elements flanks the expression site on the 3′ side and occurs at variable distances downstream from the silent loci; the nearer an element is to a silent locus, the greater the switch rate of that locus into the expression site (Barbour AG et al 2006 Proc Natl Acad Sci USA 103:18290).

The bacterium *Neisseria gonorrhoeae* (responsible for a venereal disease—manifested primarily in males but transmitted through both sexes—and for the various complications affecting both genders) relies on gene conversion for the purpose. ►phase variation, ►*Borrelia*, ►*Trypanosoma brucei*, ►cassette model of ►yeast, ►gene conversion, ►serotype, ►epigenetic memory; Barry JD, McCulloch R 2001 Adv Parasitol 40:1; Brayton KA et al 2001 Proc Natl Acad Sci USA 98:4130.

Antigenome: An antigenome in the replicative form of the viral genetic material it serves as a template for the synthesis of the genome. The term "Antigenome of a pathogen" is used to denote the array of antibody-binding epitope array. ►RF, ►epitope

Antihemophilic Factors: Blood coagulation requires the formation of complexes between serine protease coagulation factors and membrane-bound cofactors. Tissue thromboplastin, an integral membrane glycoprotein (Factor III, encoded at 1p22-p21) and proconvertin (VII, encoded at 13q34) are required to activate Factors IX and X. Mouse embryonic stem cells stimulated by fibroblast growth factor gave some evidence for correction of Factor IX deficiency (Fair JH et al 2005 Proc Natl Acad Sci USA 102:2958). Factor VIIa is a trypsin-like serine protease that also plays a key role in blood coagulation after binding γ-carboxyglutamic acid-containing domain. A plasma thromboplastin antecedent (XI, 4q35) activates Factor IX. Blood coagulation factor (VIII, Xq28), a 293-kDa plasma glycoprotein, acts in concert with Factor IXa, a proteolytic enzyme, to activate Factor X (Stuart Factor, 13q34). The latter, in turn, activates prothrombin (II, 11p11-q12) to thrombin that acts on fibrinogen (I, 4q28) to convert it to fibrin (responsible for loose clot). The fibrin-stabilizing factors (XIII, α-chain 6p25-p24; β-chain 1q31-q32.1) then generate the firm clots required for blood clotting. The Hageman factor (XII, 5q33-qter) activates thromboplastin antecedent (XI, 4q35). Accelerin (V, 1q23) stimulates the activation of prothrombin (II, 11p11-q12). In classic recessive X-chromosomal hemophilia, Factor VIII is defective. Factor IX (454 amino acid, Xq27.1-q27.2) deficiency, a partially dominant disorder of hemostasis (arrest of blood flow), is involved in Christmas disease. Blood clotting requires, in addition, calcium and thromboplastin (lipoprotein released into blood from injured tissues). A thromboplastin antecedent (XI, 4q35) deficiency is responsible for hemophilia C. The level of Factor IX increases as a normal condition with the advancing age and may be responsible for the increase in cardiovascular and thrombotic disorders among the aged. Bleeding disorders may be the consequence of mutations at the LMAN1/ERGIC-53 (18q21.3-q22) gene, encoding the lectin, mannose-binding protein, or the simultaneous defects of Factors V and VIII

(2p21-p16.3 and 18q21.3-q22). In the latter case the two proteins may not be folded properly and cannot be moved by the endocytotic vesicles (Zhang B et al 2003 Nature Genet 34:220). A similar condition arises by mutation in MCFD2 (multiple coagulation factor deficiency-2, 2p21p16.3). ►hemophilia, ►Hageman trait, ►PTA deficiency, ►prothrombin deficiency, ►Stuart disease, ►vitamin K-dependent clotting factors, blood clotting pathways, ►coumarin-like drug resistance, ►parahemophilia, ►afibrinogenemia, ►dysfibrinogenemia, ►fibrin-stabilizing factor, ►hypoproconvertinemia, ►von Willebrand's disease, ►platelet abnormalities, ►hemostasis, ►APC, ►LINE, ►tissue factor, ►anticoagulation, ►thrombopoietin, ►warfarin; Bajaj SP et al 2001 J Biol Chem 276:16302; Hockin MF et al 2002 J Biol Chem 277:18322; Tuddenham E 2002 Nature [Lond] 419:23, http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a694027.html.

Antihormones: Antihormones are antagonists of hormones which alter the conformation of the hormones or bind to the hormone receptor sites and thus prevent the attachment of hormones to the hormone responsive elements (HRE) in the DNA and thus block the transcription of the hormone-responsive genes. ►hormone responsive element, ►conformation

Anti-Idiotype Antibody: An anti-idiotype antibody is a specific antibody that recognizes a particular paratope (idiotype) of an antibody and binds to it rather than to the epitope of the antigen. Homologous anti-idiotypic antibodies are produced within the species, whereas in different species heterologous anti-idiotypic antibodies are produced. The anti-idiotypic antibody may be generated in the laboratory by first exposing the cell to the epitope, an antigen. This specific antibody so obtained may give rise to another antibody, a mimic of the original. Also, other antibodies may arise in a similar manner, which may respond to the original and also to a mutant antigen. These antibodies may be capable of stimulation of B lymphocytes and T cells and thus both humoral and cellular immunity can be generated. Thus, anti-idiotype vaccine production may become feasible for particular cases, e.g., against the poorly antigenic bacterial polysaccharides or mutant p53 proteins that do not suppress tumor formation. ►antibody, ►idiotype, ►paratope, ►internal image immunoglobulin, ►epitope, ►p53; Birebent B et al 2001 Crit Rev Oncol Hematol 39:117; Bhattacharya-Chatterjee M et al 2001 Curr Opin Mol Ther 3:63.

Antilog: An antilog is the inverse logarithm and it is obtained if the base is raised to the power of the logarithm. The antilogarithm for log_{10} x is 10^x and for *ln*(x) the antilogarithm is e^x. ►logarithm

Antilope (blackbuck, *Antilope cervicapra*): the male is 2n = 31−33, the female 2n = 30−32. ►antelope

Antimetabolite: Antimetabolite is a compound that binds to an enzyme but is not generally utilized as a substrate, and thus interferes with normal metabolism. ►metabolism, ►metabolite

Antimicrobial Peptides (AMP, RAMP): Antimicrobial peptides occur on, or in, animals and plants as a defense system. They can be linear molecules such as *cecropin* (moths, pig, *Drosophila*), making pores by lysis, *magainin* (frog skin) forming pores, or *bactenein* (bovine neutrophiles) affecting membrane permeability. They include disulphides: *defensins* (in several organisms, Hoover DM et al 2001 J Biol Chem 276:39021) making pores, *tachyplesins* (in horseshoe crab), affecting potassium efflux, *protegrins* (pig leukocytes). Many of these peptide genes contain attachment sites for transcriptional activators related to NF-κB, *Rel/Dorsal* oncogene. *Serprocidins* that are high molecular weight protease-like molecules: *protease 3* and *azurocidin* in mammals and *cathepsin G* in human neutrophils that inhibit metabolism. Lipopolysaccharide-binding proteins and bactericidal/permeability-increasing proteins, collectins are components of the mammalian defense system. A defensin-like peptide is expressed exclusively in the epididymis of rats. Plectasin, a defensin family peptide, was discovered in saprophytic ascomycete fungus *Pseudoplectania nigrella* and is highly effective against *Streptococcus pneumoniae* (Mygind PH et al 2005 Nature [Lond] 437:975). Most cells respond to invaders by the mediation of Toll receptors, which initiate and activate the production of antimicrobial peptides against Gram-positive bacterial infection through the peptidoglycan recognition protein (Gobert V et al 2003 Science 302:2126). *Mycobacterium tuberculosis* susceptibility in humans depends on the Toll-like receptor that triggers the upregulation of the vitamin D receptor leading to the induction of the cathélicidine antibacterial peptide (Liu. PT et al 2006 Science 311:1770). A synthetic library of linear peptide-like sequences consisting of alternating acyl chains and cationic amino acids prevents the formation of a stable secondary structure and appears promising as antibiotics (Radzishevsky IS et al 2007 Nature Biotechnol 25:657). ►antifungal response, ►antibiotics, ►opsonins, ►nisin, ►Toll, ►*Mycobacterium*; Hoffmann JA et al 1999 Science 284:1313; Khush RS, Lemaitre B 2000 Trends Genet 16:442; Zasloff M 2002 Nature [Lond] 415:389; molecular pathways of *Drosophila* immunity: Hoffmann JA 2003 Nature [Lond] 426:33; degradation resistance by folding: Raimondo D et al 2005 Proc Natl Acad Sci USA 102:6309; insect antimicrobial systems: Uvell H, Engström Y 2007

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Trends Genet 23:342; defensins database: http://defensins.bii.a-star.edu.sg/; http://nar.oxfordjournals.org/cgi/content/full/32/suppl_1/D590.

Antimitotic Agents: Antimitotic agents block or inhibit mitosis through ionizing radiation, radiomimetic chemicals and inhibitors of the cell cycle. ►radiation effects, ►cancer therapy, ►cytostatic

Antimongolism Chromosome: A chromosome 21 deletion in humans that compensates in some respects for the syndrome accompanied by the trisomy of complete chromosomes 21 (Down's syndrome; by old name mongoloid idiocy). This deletion, G I, causes the formation of large ears, prominent nasal bridges, an antimongoloid slant of the eyelids, long fingers and toes, micro- or dolicephaly and hypo-γ-globulinemia (rather than an excess as in Down's syndrome). ►Down's syndrome, ►dolicephaly, ►microcephaly, ►agammaglobulinemia

Antimorph: A (dominant) mutation, which antagonizes the function of the wild type allele (by competing for the substrate). dominant negative, ►killer genes

Anti-Müllerian Hormone (AMH/AMS): The anti-Müllerian hormone is produced by the Sertoli cells. It masculinizes XX rodents whereas males deficient in AMH become pseudohermaphrodites. SF-1, SOX9 and WT1 regulate AMH. ►Sertoli cells, ►gonads, ►pseudohermaphrodite, SF-1, ►SOX, ►Wilms tumor

Antimutagen: An antimutagen protects against the mutagenic effect(s) of other agents. Generally, hypoxia-reducing agents (such as dithiothreitol) lower the damaging effects of ionizing radiation. Inhibitors of microsomal mutagen activating enzymes (such as 9-hydroxyellipticine, gallic and tannic acids, carbon monoxide, selenium, etc.) may reduce the mutagenic effectiveness of chemicals. ►antimutator, ►mutagen, ►caffeic acid, ►polyphenols, ►methylguanine-O^6-methyltransferase; Novick A 1955 Brookhaven Symp Biol 8:201.

Antimutator: An antimutator lowers mutation rate. An increased level of nuclease activity (editing function) and all other genetic repair mechanisms may act this way. Compounds that inactivate microsomal enzymes involved in conversion of promutagens into mutagens are also antimutagens, or mutations, which reduce oxidative stress. ►AP nucleases, ►ABC excinucleases, ►DNA repair, ►mismatch repair, ►mutator, ►proofreading; Reha-Kranz LJ 1998 Genetics 148:1551.

Antioncogenes: Antioncogenes are the normal alleles of some genes that, in the mutant state, incite tumors. For example, the cloned normal allele of the human retinoblastoma gene codes for a DNA-binding protein and the cancer cells transformed by this gene are suppressed in proliferation. ►tumor suppressor genes

Antipain: Antipain is a protease inhibitor (1–2 μg/mL) and is effective against cathepsin A and B, papain and trypsin protease enzymes.

Antiparallel Pairing: Antiparallel pairing of polynucleotide chains means that at the same end of the double helix one has 5′ and the other has 3′ ends of the paired nucleotides (see Fig. A98).

Figure A98. Antiparallel

Antiphospholipid Syndrome: Antiphospholipid syndrome is the endocytosis defect which involves greater risk of thrombosis, thrombocytopenia, and recurrent and spontaneous abortions. The antibodies may attack phospholipids, or the protein-phospholipid complex or proteins like β2qglycoprotein. ►endocytosis

Antipodal: Refers to haploid cells (nuclei) located in the plant embryosac at the end opposite to the place of the egg and the micropyle. ►embryosac

Antipyretic: An antipyretic is a fever reducing drug.

Antiport: Antiport is the membrane transport of substances in opposite directions. A substance could also be sequestered through the antiport within another compartment. The Na^+/H^+ antiporters in different organisms (bacteria/plants/humans) determine the sodium/proton balance in the cells and are keys to adaptation to high salinity or extreme pH. It is supposed that the ion exchange is regulated by a conformational change elicited by pH at the entry site (Hunte C et al 2005 Nature [Lond] 435:1197)

Antirecombination: Antirecombination prevents recombination between not entirely homologous DNA strands, i.e., between homeologous DNA.

Antidepression: Refers to the situation when transcription factors bound to the DNA upstream of the promoters interfere with the binding of unspecific DNA binding proteins, which normally exert repression. ►insulator

Antirestriction Mechanisms: Antirestriction mechanisms are those which prevent the cleavage of the DNA by different mechanisms, e.g., methylation of critical bases (e.g., phages T2, T4, SPβ), inhibition of the endonuclease (e.g., T3, T7 phages), enhancing host-encoded methylase (phage λ), carrying hydroxymethyl cytosine in place of cytosine (T-even phages), 5-hydroxymethyluracil substitution for thymine (SPO1, SP8, φ25), reducing certain vulnerable

restriction sites in their DNA (f29), etc. ►restriction endonucleases, ►restriction-methylation; King G, Murray NE 1995 Mol Microbiol 16:769.

Antiridge: ►ridge

Antirrhinum majus (snapdragon): Is a higher plant of the *Scrophulariaceae* family (2n = 16). It is an attractive autogamous flowering plant and a favorite in genetic and cytogenetic studies. A large collection of mutants and transposable elements are available (see Fig. A99). ►TAM, ►snapdragon, ►peloric; http://www.antirrhinum.net/; http://www.mpiz-koeln.mpg.de/english/research/saedlerGroup/schwarzSommer/index.html.

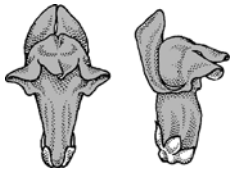

Figure A99. Antirrhinum

Antisense DNA: library can be used for transformation and isolation of mutations or for other purposes of preventing gene expression. The 25-base oligodeoxyribonucleotide phosphorothioate (TCTTCCTCTC TCTACCCACGCTCTC, Hybridon. Inc., trade name GEM 91) binds to the translation initiation site of the *gag* gene of the HIV-1 pathogen of acquired immunodeficiency and may inhibit the production of new infectious particles because of the defect in packaging. The human L1 (LINE) retrotransposon has two promoters, a sense promoter that directs the transcription of the full-length L1 tract and an antisense promoter that drives in the opposite direction and into adjacent sequences and thus generates chimeric transcripts. Both promoters are situated within the 5′ non-translated region of L1 (Nigumann P et al 2002 Genomics 79:628). Antisense transcripts occur not only in tumors but also in normal cells. In the mouse, 72% of the transcriptional units (TU) overlap with some transcripts of the opposite strand. From all Tus, (4520) are full-length sense/antisense pair transcripts. Antisense transcription is different in different chromosomes; it is lower in the X chromosome than in the autosomes (RIKEN 2005 Science 2005 309:1564). Antisense transcripts have a regulatory and evolutionarily role to play and do not appear to be due to accidental leakage (Dahary D et al 2005 Genome Res 15:364). ►OL(1)p53, ►*Bcl*, ►antisense RNA, ►aptamer, ►peptide nucleic acid, ►antisense technologies, ►cancer gene therapy, ►G3139, ►acquired immunodeficiency, ►HIV, ►phosphorothioate, ►antisense technologies, ►L1; Zhang YM et al 2001 J Nucl Med 42:1660; Lehner B et al 2002 Trends Genet 18:63.

Antisense Oligodeoxynucleotide (AS ODN): ►antisense DNA, ►antisense RNA, ►selection and design: http://www.bioit.org.cn/ao/aobase/.

Antisense RNA: Is a transcript of a gene or transposon that may inhibit translation by pairing with the 5′ end of the correct (sense) mRNA and thus prevent its ribosome binding and expression. In several bacterial plasmids, by inhibiting the synthesis of the replication initiator protein, the antisense RNA limits copy number. Some synthetic oligonucleotide analogs may block replication and transcription, interfere with splicing of exons, disrupt RNA structure, destabilize mRNA by interfering with 5′ capping of mRNA, inhibit polyadenylation, activate ribonuclease H. When coupled to alkylating agents they can cross-link nucleic acids at the recognized sequences, can be used as vehicles for targeted DNA cleavage, may inhibit receptors, etc. The various functions require a large variety of specific antisense constructs. Usually, the antisense oligonucleotides are 12–50-nucleotide long. According to calculations in the human genome, any 17-base sequence occurs only once, and in the mRNA populations, 13mer residues are unique. Shorter sequences do not have sufficient specificity. Long antisense sequences may have self-binding tracts that may cause lowered affinity for their target. Natural antisense RNA transcripts (NATs) occur in all types of biological systems, from viruses to higher eukaryotes. This fact indicates that in eukaryotes both strands of the DNA may be transcribed. In the human genome, 2,667 loci were reported as showing transcripts of the complementary strands (Yelin R et al 2003 Nature Biotechnol 21:379). In *Arabidopsis* ~30% of the annotated genes displayed significant antisense RNA expression (Yamada K et al 2003 Science 302:842). The cis-NATs are transcribed at the same locus but from the opposite strand of the DNA. The trans-NATs are transcribed at sites different from that where encoding of the sense transcript takes place. The trans-NATs can regulate the expression of several genes like the microRNAs (Wang, X.-J. et al. 2005 Genome Biol 6: R30). Among five species of fungi, the number of genes involved with antisense transcripts is variable (Steigele S, Nieselt K 2005 Nucleic Acids Res 33:5034)

Antisense RNA (or DNA) was expected to become an important therapeutic tool for fighting infections and cancer. This technology is still under development for finding cures against cytomegaloviruses, HIV1, Papilloma virus, autoimmune diseases (arthritis, etc.), leukemia (CMV) and blocking the immune

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system in case of organ transplants. Surprisingly, the antisense RNA may trigger an immune reaction because the CpG blocks are unmethylated and the animal immune system responds to them as to bacterial molecules. In bacteria these bases are largely unmethylated in contrast to eukaryotes where a substantial fraction of the DNA is methylated. The phosphorothioate oligodeoxynucleotides or oligoribonucleotides are taken up by a variety of cell types, including some prokaryotes (*Vibrio*), and bind either to DNA, RNA or protein. Phosphorothioate LD_{50} is about 750 mg/kg. Antisense RNAs may block embryonic development and can be used to inhibit gene expression at defined stages. Although antisense RNA is supposed to be very specifically for the intended target, it may affect several genes that have short or long sequences homologous to the target. A deletion in the hemoglobin gene cluster juxtaposes another gene (LUC7L, an U1Snrp component) to the HBA2 gene, which normally is situated 335–337 bp downstream from the polyA addition site of HBA2 and transcribed in the opposite direction of the hemoglobin gene. The LUC7L is also truncated by the deletion and thus lacks the termination signals and consequently its transcript fuses with the CpG island of HBA2. This condition generates an antisense RNA, which causes complete methylation of the island and silencing of the intact HBA2 and thereby α-thalassemia (Tufarelli C et al 2003 Nature Genet 34:157). In addition, the antisense RNA may bind and affect different proteins as an aptamer. Furthermore, the nucleic acid degradation products concomitant or following the administration of the antisense RNA may also result in unspecific inhibition in the cells. ►host-pathogen relations, ►triplex, ►aptamer, ►pseudoknot, ►peptide nucleic acid, ►phosphorothioates, ►methylphosphonates, ►cap, ►fruit ripening, ►anthocyanin, ►co-suppression, ►RIP, ►Cytomegalovirus, ►Papilloma virus, ►autoimmune disease, ►leukemia, ►transplantation antigens, ►antisense technologies, ►sense strand, ►AS ODN, ►anticoding strand, ►coding strand, ►triple strand formation, ►RNA double-stranded, ►hybrid arrested translation, ►RNAi, ►G quartet, ►U1 RNA, ►thalassemia, ►Xist, ►microRNA, ►TUF; Helene C, Toulme JJ 1990 Biochim Biophys Acta 1049:99; Matveeva OV et al 2000 Nucleic Acids Res 28:2862; Sohail M et al 2001 Nucleic Acids Res 29:2041; http://www.prl.msu.edu/PLANTncRNAs/database.html, natural antisense RNA: http://natsdb.cbi.pku.edu.cn/.

Antisense Strand of DNA: An antisense DNA strand is the template strand of DNA from which the mRNA or other functional, natural RNAs, are replicated as complementary copies. ►antisense RNA

Antisense Technologies: Use RNA and DNA targets for the suppression or modification of gene expression. The antisense molecule then blocks the synthesis of RNA and protein (see Fig. A100). Various forms of antisense molecules have been used (see antisense RNA); for antisense DNA technology, the nucleotides are ligated, for example, e.g., by phosphorothioate linkage and not by the normal phosphodiesterase linkage in order to protect the antisense strand from nuclease attack. For the production of antisense nucleic acids, the oligonucleotides are modified either in the base of the sugar or through changes in the sugar phosphate background. The good antisense molecules are expected to allow for RNase H activity to remove the natural target (preventing its translation) and then bind stably to DNA, blocking protein synthesis. The modification usually prevents enzymatic disposal of the antisense constructs. The antisense sequences may have side effects. Guanine-rich antisense sequences may have an undesirable affect on the telomerase enzyme, may form quadruplex structures, interfere with replication of the chromosomes, and may bind to proteins and may modify their function. In order to minimize these deleterious consequences various alterations have been attempted. The number of phosphorothioates is reduced or in a five base sequence the terminals ("wings") are modified whereas, in-between, an RNase H-competent 2′-deoxy-oligodeoxynucleotide "window" is preserved. This approach basically is the generation of an "artificial restriction endonuclease" site. Another possibility involves targeting a mutant, activated oncogene by a single mismatch antisense RNA. The mismatch is expected to reduce the chance of cleavage at the heteroduplex site, but increase the chance of cleavage by RNase H at the oncogenic mutation and the perfectly matched mutant mRNA,

Figure A100. Antisense technologies

thus achieving suppression of malignancy. Antisense oligonucleotides also have therapeutic applications by correcting for defects in mRNA splicing, to induce exon skipping and restoring normal reading frames in cases when deletion or nonsense mutation cause the disease (Aartsma-Rus A et al 2004 Am J Hum Genet 74:74). A two exon skipping may change the more serious symptoms of Duchenne muscular dystrophy to the milder Becker type. Besides these changes, good uptake should be secured, e.g., by the use of cationic lipids and by assuring membrane permeabilization with the stability of the internalized oligonucleotides. The nerve cells apparently take up oligonucleotides more readily than other type of tissues if introduced by injection. There however is a blood/neuron barrier after intravenous or intraperitoneal applications. Antisense constructs readily target the liver and kidneys, but the degradation and excretion are most rapid in and from these tissues. Endocytosis and pinocytosis can take up antisense oligonucleotides but then they are usually locked up in the vesicles within the cells. When injection or electroporation introduces the antisense molecules, they may reach the nucleus. The half-life may be less than 5 min and within 10 h half the antisense oligonucleotides are lost. The antisense construct may have a variety of effects on the cells and the observed consequences may be the result of non-antisense type of action. The antisense DNA oligonucleotides usually target the AUG initiator codon, the 5′ cap, the first splice acceptor, the polyadenylation, or the translocation breakage point site in cancer. The actively transcribed RNA is a superior target. At the proper dosage the AO have minimal or no effect on normal cells but may be quite effective. (►antisense RNA, ►fruit ripening, ►peptide nucleic acid, ►triple helix formation, ►methylphosphonates, ►phosphoramidate, ►phosphorothioates, ►cancer gene therapy, ►ribonuclease H, ►TFD, ►PKA, ►mixed backbone oligonucleotides, ►aptamer, ►G3139, ►BCL, ►fomivirsen, ►cationic lipid, ►tricyclo-DNA, ►muscular dystrophy; Galderisi U et al 1999 J Cell Physiol 181:251; Cotter FE et al 1999 Biochim Biophys Acta 1489:97; Kushner DM, Silverman RH 2000 Curr Oncol Rep 21:23; Astriab Fisher A et al 2002 J Biol Chem 277:22980; Fu C et al 2002 Anal Biochem 306:135; Sazani P et al 2002 Nature Biotechnol 20:1228.

Antisense Transcript: ►antisense RNA

Antiserum: An antiserum is a blood serum that contains specific antibodies obtained from an animal after natural or artificial exposure to an antigen. Antisera are collected from the blood of fasted animals by centrifugation and allowed to clot at room temperature. The clot is then discarded and the straw-colored serum may be preserved either by lyophilization and stored at room temperature or at 4° with 0.02% sodium azide or deep frozen at −20° to −70°C. The antisera generally contain polyclonal antibodies. ►antibody polyclonal, ►monoclonal antibody

Antiserum Purification: Of polyclonal antibodies by affinity chromatography on protein A-Sepharose columns. Protein A binds the Fc domain of IgG of various sources but not with equal intensity. Further purification may be obtained by affinity chromatography with an immobilized antigen of high purity. ►antibody purification, ►antibody, ►immunoglobulins

Anti-Shine–Dalgarno Sequence: CCUCC is complementary to the GGAGG Shine-Dalgarno consensus near the 3′-end of the 16S rRNA molecule. ►Shine-Dalgarno

Antisuppression: Inactivates suppressor genes. ►suppressor gene, ►suppressor tRNA

Antitermination: Antitermination permits the RNA polymerase to ignore transcription termination instructions such as bacterial rho and thus proceed through the termination signal. In phage l, after the transcription of two *immediate early genes*, the RNA polymerase should stop. The switch to transcribe the next set of genes is controlled by gene N, transcribed from the left promoter (PL) and terminated by the rho-dependent tL1 terminator and cro, transcribed from the right promoter (PR) and terminated by the rho-dependent tR1 terminator. The product of the N gene is protein N (pN), an antiterminator that permits readthrough to the delayed early genes in both tL1 and tR1. Although pN has a half-life of about 5 min, transcription is maintained because N is part of the delayed early transcripton. Gene Q is also part of the delayed early transcripton and its product pQ is also an antitermination protein that allows, by readthrough, the transcription at the late promoter PR. The recognition site for pN is upstream at the N utilization sites, NutL and NutR; the former is near the promoter but the latter is near the terminator. pN can act on both rho-dependent and rho-independent systems. Different phages have different nut sites, yet all these work in a similar manner. The nut elements include boxA and boxB; the former is required for binding the bacterial antitermination proteins, used by phages as well as by bacteria. The boxB is a phage-specific element.

Mutations in bacteria (rpoB) interact with pN. The nus loci (A, B, G) are involved with transcription termination; nus E codes for a protein in the 30S ribosomal subunit (p10). The product of nusA is a general transcription factor interacting with p10 and it affects termination by binding to boxA. Gene nusG organizes the various Nus proteins that together

A

control rho-dependent termination, whereas the nusA product combined with pN may interfere with termination where it normally is supposed to take place. In *E. coli* antitermination involves also the ribosomal rrn genes. This operon has in its leader sequence a boxA where the NusB-S10 protein dimer binds to the RNA polymerase as it passes through. This binding enables pol to continue transcription through the rho-dependent terminators of the transcripton. Protein NusA does not bind to the bacterial RNA polymerase when it is associated with the s factor but after pol attaches to the promoter, σ may be released and that provides an opportunity for transcription and for the formation of the core polymerase-Nus complex. After termination of transcription the pol complex is released from the DNA and the separation of Nus from pol takes place. Thus, the polymerase core enzyme may be in two alternative states, one with σ for transcription and another with Nus with the potential for termination of transcription. Antitermination may then be mediated through pN after the polymerase binds Nus. Gene Q of phage λ also has a role to play in antitermination by permitting, through its product, the passage over the terminator signals. Transcription is modulated by preventing termination of transcription at T-rich sequences that occur at random within the gene, but they dissociate the RNA polymerase from the DNA when it arrives at the T-rich region at the end of the gene and where termination of transcription is expected. Other antitermination (attenuation) proteins act in the amino acid operons of bacteria, and allow the expression of the operon only after the protein that mediates attenuation of transcription is made. Thus, attenuation is not always dependent on the presence of an excess of charged specific tRNAs that slow down transcription when the supply of this particular amino acid is sufficient. In eukaryotes the Pol II-transcribed U1-RNA is involved in proper processing of the 3′-ends of the RNA used for reinitiation of transcript elongation. ►attenuation, ►RNA polymerases, ►rho, ►lambda phage, ►half-life, ►rrn, ►transcription, ►σ transcription termination in prokaryotes, ►T box, ►terminator, ►transcription termination in eukaryotes, ►rho factors, ►tryptophan operon, ►*hut* ►operon; Mason SW, Greenblatt 1992 J Biol Chem 267:19418; Yarnell WS, Roberts JW 1999 Science 284:611, Grundy FJ et al 2002 Proc Natl Acad Sci USA 99:11121.

Antithrombin (AT-III, 1q23-q25): Is an α-globulin, neutralizing the blood clotting contribution of thrombin. Antithrombin—especially when cleaved at the COOH-terminal loop—blocks angiogenesis and tumor development. ►thrombin, ►blood clotting pathways, ►antihemophilic factors, ►protein C, ►protein S, ►dysfibrinogenemia, ►angiogenesis, ►anticoagulation

Antitoxin: ►immunization

Antitrypsin Gene (AAT or PI): In the human chromosome 14q32.1 prevents the activity of the protease trypsin and elastase. The α-antitrypsin gene is supposed to be involved in pulmonary emphysema (increase of lung size because dilatation of the alveoli [the small sacs] of the lung) and liver disease. Different mutations may lead to one or the other, or to both of these diseases. The so-called Z mutant group prevents the exit of the AAT protein from the liver, where it is synthesized, and as a consequence the liver disease (cirrhosis) appears. Smoking may increase the chances of the development of cirrhosis in the individuals of ZZ genotype by 3 orders of magnitude. The incidence of AAT deficiency is about 8×10^{-4} in the white population of the USA. The total length of the α-antitrypsin gene is 10.2 kb with coding sequences of 1,434 bp. Oral administration of 4-phenylbutyric acid facilitates the release of AAT from the endoplasmic reticulum and as a "chemical chaperone," may prevent the injuries resulting from AAT deficiency. The 14q32 chromosomal site includes the serpin gene encoding the corticosteroid-binding globulin (CBG) and a DNase-1 hypersensitive site. The AAT gene can be inserted into sheep eggs and under favorable conditions the milk may contain the protein it encodes. ►emphysema, ►cirrhosis of the liver, ►liver cancer, ►endoplasmic reticulum, ►serpin, ►corticosteroid, ►DNase hypersensitive site, ►acquired immunodeficiency; Crystal RG 1989 Trends Genet 5:411; Brigham KL et al 2000 Hum Gene Ther 11:1023.

Antivector Cellular Immunity: Antivector cellular immunity in a vaccination may cause a serious problem if the vector, e.g., adenovirus, occurs in the population and if the animal/human cells have already developed antibodies against a particular serotype, thereby diminishing the effectiveness of such a vector. Antivector immunity can be circumvented by the use of a chimeric vector. In a novel vector the hypervariable region of the rare adenovirus serotype Ad48 replaced, in a rAd5 adenovirus-derived vector, the seven short hypervariable regions of the Ad5 hexon protein. The engineered vector expressed well the simian HIV Gag protein in naïve mice and rhesus monkeys and it did not show neutralizing suppression. Such a construct may open a new approach to vaccination and gene therapy (Roberts DM et al 2006 Nature [Lond] 441:239). ►human gene transfer, ►gene therapy, ►HIV, ►acquired immunodeficiency, ►hexon

Antiviral Antibodies: Result when immunization against some viral diseases is not fully successful. Monoclonal (or enriched polyclonal) antibody therapies have been considered against human respiratory syncytial virus (RSV), rabies, hepatitis B and C, herpes simplex viruses, cytomegalovirus and acquired human immunodeficiency (HIV). These preparations may be administered intramuscularly. ►monoclonal antibody therapies

Antiviral Protein: Zinc-finger anti-viral protein (ZAP) is a host antiviral factor that specifically inhibits the infection of cells by Moloney murine leukemia and multiple members of the alphavirus family, including Sindbis virus (SIN). An overexpression of ZAP prevents the accumulation of the viral RNA in the cytoplasm. The N terminus of ZAP contains four CCCH-type zinc-finger motifs. ZAP binds directly to specific viral RNA sequences through these zinc-finger motifs. The target sequence of ZAP in MLV was mapped to the 3′-LTR, and the target sequences in SIN were mapped to multiple fragments, but no obvious common motifs have been found in these sequences yet. Particularly, ZAP does not target ARE-containing mRNAs. Despite the lack of primary sequence homology, ZAP shares considerable similarities with tristetraproline (TTP). Both ZAP and TTP directly bind to their cognate target RNAs, and the zinc-finger motifs are required for the binding. ZAP directly interacts with the exosome, and it seems that ZAP destabilizes RNA by directly binding to the target RNA and recruiting the exosome to degrade the target RNA. Type I interferons (IFNs) play an essential role in the host response to viral infection through the induction of numerous IFN-stimulated genes. IFN-stimulated gene 15 (ISG15) is an ubiquitin homolog that is rapidly up-regulated after viral infection, and it conjugates to a wide array of host proteins. It appears to be a novel antiviral molecule with activity against both RNA and DNA viruses and can provide a target for the development of therapies against important human pathogens (Lenschow DJ et al 2007 Proc Natl Acad Sci USA 104:1371). ARE, ►exosome, ►tristetraproline, ►zinc finger; (Guo X et al 2007 Proc Natl Acad Sci USA 104:151.

Antiviral siRNA Design Tool: ►RNAi; http://sivirus.rnai.jp/.

Antizymes: Antizymes are proteins that bind to enzymes and direct their degradation by proteasomes without ubiquitin (see Fig. A101). The proximal or distal products of the enzymes they inhibit induce their synthesis. Antizymes regulate polyamine enzymes such as ornithine decarboxylase. Antizyme (AZ) ornithine decarboxylase (ODC) fusion proteins provide the means of targeted protein destruction by proteasomes without prior ubiquitination (Matsuzawa S-i et al 2005 Proc Natl Acad Sci USA 102:14982; see diagram redrawn). ►proteasome, ►polyamines, ►ubiquitin; Coffino P 2000 Proc Natl Acad Sci USA 97:4421; Chattopadhyay MK et al 2001 J Biol Chem 276:21235.

Antley-Bixler Syndrome (trapezoidocephaly-synostosis syndrome): Is a defect in bone formation, abnormality of the face and other developmental anomalies due to mutation in the fibroblast growth factor receptor 2 (FGFR2) gene. ►craniosynostosis syndromes, ►fibroblast growth factor, ►Apert or Apert-Crouzon syndrome

Anucleate: Is a cell after the nucleus has been removed. ►cytochalasins, ►cytoplast, ►nuclear transplantation

Anus: Is the end opening of the intestinal tract.

Anxiety: In mice, glyoxylase 1 and glutathione reductase 1 seem to regulate this condition (Hovatta I et al 2005 Nature [Lond] 438:662). ►stress, ►phobia, ►panic disorder, ►panic obsessive disorder, ►BDF

Aorta: Is the main arterial vein (carrying blood away from the heart) originating in the left heart ventricle

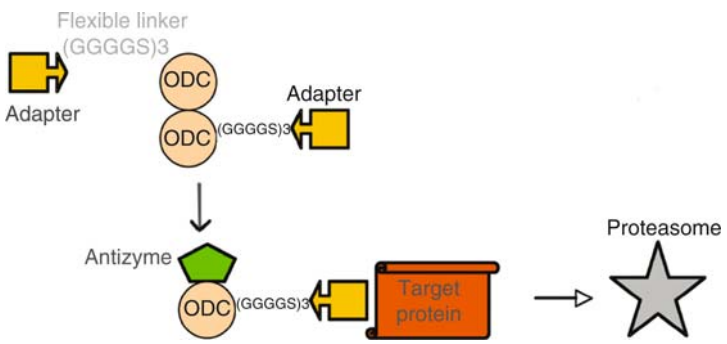

Figure A101. Antizyme

A

and passing through the chest and abdomen. ►coarctation of the aorta

Aortic Stenosis: ►coarctation of the aorta

Aotus: owl monkey ►cebidae

AP: ►amino purine, ►base analog mutagen

AP1, AP2, AP3, AP4, AP5 (activated protein): Is a group of transcription factors. AP1 is similar to the one coded for by the chicken virus, oncogene *v-jun.* The human gene at chromosomal location 1p32-p31 shows 80% homology to the avian viral protein gene; their binding is greatly enhanced by the *fos* oncogen. AP1 generally appears as a heterodimer of Jun and FOS and FraIn yeast AP1 has a homolog, GCN4, and the mammalian homolog is TFIID. The yeast and their mammalian factors can substitute for each other. This family of genes encodes the AP transcription factors where the binding motif is well conserved but other sequences may vary. These proteins bind to 5′-TGANTCA-3′ consensus in DNA. AP2 binds only to TC-II but not to TC-I of the two identical and adjacent TC motifs (5′-TCCCCAG-3′) upstream in the promoter of eukaryotic genes. AP2 binding affects enhancer activity. AP2 is an essential morphogenetic factor; in its deficiency head development is impaired. AP2 seems to have negative control on the cell cycle possibly by activation of p21 protein. AP3 binds to TC-II and to the adjacent GT-I motif (5′-G[C/G] TGTGGA[A/T]TGT-3′) and also to the so-called core enhancer sequence (5′ -GTGG[A/T][A/T][A/T]G-3′) that is similar to parts of viral and prokaryotic enhancers but does not function by itself alone. AP4 binds to the 5′-CAGCTGTGG sequence that partially overlaps the GT-II motif (that is identical to GT-I, except two bases). AP5 binds to GT-II and adjacent sequences (5′-CTGTGGAATGT-3′) and it is present in some cell types but not in others. The mouse Jun genes (chromosomes 4 and 8) are inducible by serum and the phorbol ester, 12-o-tetradecanoyl phorbol 13-acetate (TPA). The AP loci of *Arabidopsis* are completely different and mean apetala, a defective flower type. ►oncogenes, ►transcription factors, ►adaptin, ►epsin, ►endocytosis, ►Jun, ►Fos, ►Fra, ►PC4; Shaulian E, Karin M 2002 Nature Cell Biol 4:E131.

AP180 (assembly protein): Mediates the assembly of clathrin for endocytosis. It is built of four adaptin proteins (100, 100, 50, 25 kDa, respectively). ►endocytosis

AP Endonucleases (APE): APE are basically repair enzymes, in both prokaryotes (2 enzymes) and eukaryotes (encoded in humans by HAPIm BAP1, APE/APEX) that cut DNA 5′ or 3′ to modified (alkylated or otherwise mutated) DNA bases or at apurinic and apyrimidinic sites from where glycosylases have already removed damaged purines or pyrimidines. Usually the first step is the recognition of the altered bases and the DNA sequence is cut in the vicinity. Then the exonuclease activity removes the damaged section and creates a gap. After that a repair synthesis adds the correct bases to the 3′-OH ends, using the undamaged strand of the double helix as a template. Ligation by covalent bonds restores the integrity of the DNA. The glycosylases have some specificity for deaminated cytosine residues; the uracil-*N*-glycosylase removes uracil residues and the hypoxanthine-*N*-glycosylase removes hypoxanthines formed by deamination of adenine. These endonucleases have thus antimutator activities. The eukaryotic DNA uses pol β or pol δ and pol ε for filling the gap. ►antimutator, ►DNA repair, ►glycosylases, ►DNA polymerases, ►AP site; Sobol RW, Wilson SH 2001 Progr Nucleic Acid Res Mol Biol 68:57.

AP lyase: Releases apurinic and apyrimidinic sites from the DNA. ►apurinic site, ►apyrimidinic site, ►DNA repair

AP Site: ►apurinic site, ►apyrimidinic site

Apaf-1 (apoptotic protease activating factor/CED4): Interacts with caspase-9 after being activated by a cytochrome c and dATP. Then caspase-3 triggers the process of apoptosis. Somehow, the caspase-3 is linked to an endonuclease that cuts up chromosomal DNA in the cells destined for apoptosis. The Apaf gene (and some others) may be disabled by methylation and then apoptosis is interfered with and the road opens up to carcinogenesis, as it happens in chemotherapy-resistant metastatic melanoma. ►caspase, ►apoptosis, ►AIF, ►melanoma, ►Crohn disease, ►Huntington's disease; Bratton SB et al 2001 EMBO J 20:998; Soengas MS et al 2001 Nature [Lond] 409:207; molecular structure; Riedl SJ et al 2005 Nature [Lond] 434:926.

Apandry: Is the development of a diploid fruiting body of fungi by the fusion of two female nuclei, without the involvement of any male gamete.

APC: ►antigen presenting cell, ►Gardner syndrome, ASE1

APC: (anaphase-promoting complex; also called cyclosome): It is a ∼13-subunit, ∼1700-kDa ubiquitin ligase protein complex containing CDC27, CDC16, CDC23, CDC26, Apc1p, Apc2p, Apc4p, Apc5p, APC9, APC10/DOC, Apc11p, Apc13 and bimE. APC is required for the progression from metaphase to anaphase. It is regulated by CDC20 and CDH1 in humans, *fzy* and *fzr* in *Drosophila* and the APC complex mediates ubiquitination of the superfluous cyclins and anaphase-inhibitory proteins such as

securin. Securin is required for the prevention of the separation of sister-chromatids until there is a firm association with the mitotic spindle fibers. Premature separation may result in aneuploidy. Protein Rae1–Nup98 complex regulates securing degradation (Jeganathan KB et al 2005 Nature [Lond] 438:1036). This degradation is a requisite for exiting from each phase of the cell cycle and for entry into the next one. APC recognizes a 9 amino acid destruction box at the N-terminus of cyclins and some other proteins such as Pds1p/Cut2p anaphase inhibitors of yeasts or the spindle protein Ase1. ►cell cycle, ►CDCs, ►bimE, ►CDC20, ►CDH1, ►PDS, ►ubiquitin, ►E2, ►Rbx1, ►mitotic exit, ►SCF, ►tetratrico sequences, ►cullin, ►SIC1, ►PDS, ►CDH, ►D box, ►sister chromatid cohesion, ►securin, ►separin, ►nucleoporin, ►Mnd2, ►MPF, ►substrate ordering, ►Evi oncogene; Page AM, Hieter P 1999 Annu Rev Biochem 68:583; Schwab M et al 2001 EMBO J 20:5165; Peters J-M 2002 Mol Cell 9:931; Burton JL et al 2005 Mol Cell 18:533.

APC (activated protein C): Mediates cleavage and inactivation of antihemophilic factors Va and VIIIa with the cooperation of protein S. Its mutation which conveys resistance to blood coagulation may increase the risk of thrombosis by 5–10 fold and is the most common genetic cause of thrombosis. ►protein C, ►protein S, ►antihemophilic factors, ►thrombosis

APC: ►adenomatous polyposis coli

APE: A apurinic/apyrimidinic endonuclease which recognizes these sites and cleaves the nucleic acid backbone as part of the repair function. APE activity is essential for cellular viability (Fung H, Demple B 2005 Mol Cell 17:463). ►excision repair; Gros L et al 2004 Nucleic Acids Res 32:73.

APECED (autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy): Is a human autoimmunity syndrome involving a Zn-finger-like protein (a transcription factor) encoded in chromosome 21q22.3 by the gene called AIRE (autoimmune regulator). It also affects diabetes. ►autoimmune disease, ►Zinc fingers

Aperiodic Crystal: Is the term used for the chromosome by the physicist Erwin Schrödinger in 1944. (See Stent GS 1995 Ann NY Acad Sci 758:25)

Apert or Apert-Crouzon Syndrome: Involves acrocephaly (top of the head pointed), syndactyly (fingers fused) and mental retardation, although some individuals have near normal intelligence (see Fig.-A102). The symptoms vary. Many of the cases are sporadic, in others, autosomal dominant inheritance is most likely; chromosomal rearrangement may also

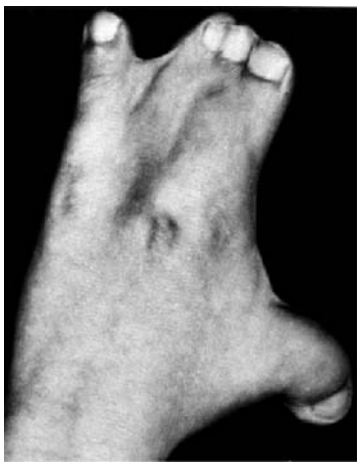

Figure A102. Syndactyly. (From Bergsma, D. 1973 Birth Defects. By peremission of the March of Dimes Foundation)

be present in some cases. This condition may also be caused by a defect in FGFR2 (fibroblast growth factor receptor), a protein tyrosine kinase, encoded at 10q25-q26. An insertion of an Alu element in the gene results in an alternately spliced keratinocyte growth factor receptor (KGFR). It is allelic to the Crouzon and Pfeiffer syndromes. ►syndactyly, ►mental retardation, ►craniosynostosis syndromes, ►Crouzon syndrome, ►Pfeiffer syndrome, ►Jackson-Weiss syndrome, ►tyrosine kinase receptor

Apes: Closest to humans among animals. The human non-repetitive DNA sequences appear 98.7% identical to that of chimpanzees and 98.38% to that of gorillas. ►primates, ►chimpanzee; Hacia JG 2001 Trends Genet 17:637.

Apex: Refers to the top part of a cell, organ or any structure. The shoot apex of plants gives rise to the leaves, stem and inflorescence. The topless (*tpl-1*) dominant negative mutation of *Arabidopsis* transforms the apex into a root pole by suppressing transcription (Long JA et al 2006 Science 312:1520). ►apical, ►meristem

Apex: ►arrayed primer extension

APH: Aminoglycoside phosphotransferases are enzymes phosphorylating aminoglycoside antibiotics, resulting in resistance to the antibiotics when the enzyme is present (introduced by transformation). ►APH[3′]II, ►antibiotics, ►aminoglycosides

APH(3′)II: The aminoglycoside phosphotransferase enzyme inactivates kanamycin, neomycin and geneticin, commonly used antibiotic resistance markers for

A

transformation in tissue culture; synonymous with NPTII. ►aminoglycoside, ►antibiotics

Aphakia: A rare abnormality of the development of the embryonal lens caused by homozygosity of the human gene (1p32) FOXE3 (Valleix S et al 2006 Amer J Hum Genet 79:358). ►eye diseases

Aphasia: Aphasia is a form of brain injury resulting in the partial or complete inability to speak/understand language. About two-dozen human gene loci in several chromosomes may be responsible for aphasia. ►MASA syndrome

Apheresis: The separation of certain component(s) of a patient's blood and reinfusion of the remainder.

Aphidicolin: A tetracyclic diterpene of fungal (*Cephalosporium*) origin capable of blocking cell division and of antiviral activity; it is an inhibitor of DNA polymerase α, δ and ε (see Fig. A103) (Wright GE et al 1994 FEBS Lett 341:128). ►pol, ►terpenes

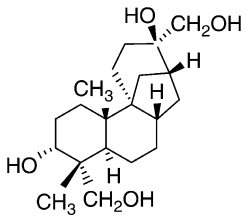

Figure A103. Aphidicolin

Aphids (*Aphididae,* homoptera): Aphids are small sucking insects and parasites of almost all plant species (see Fig. A104). At the site of the infestation the plants secrete honeydew that may attract other types of insects. They reproduce sexually at the end of the growing season after the males have differentiated. During the rest of the year only the females are found. The females reproduce parthenogenetically and their ca. 20 generations produce daily three to seven nymphs. Thus, the progeny of a single individual may run into billions during the year. Besides the direct damage by sucking, they spread viral diseases of plants. They can be controlled by contact or systemic insecticides. Aphids harbor 60–80 large cells (bacteriocytes), which contain the symbiotic *Buchnera* bacteria with ~100 copies of a genome of 640,681 bp. The bacteria supply essential amino acids to the aphids and rely on the host for cell-surface molecules, regulator genes and defense. The genotype of the symbiotic bacterium *Hamiltonella defensa* determines the degree of resistance of pea aphids (*Acyrtosiophon pisum*) to parasitoid wasp *Aphidius ervi* (Oliver KM et al 2005 Proc Natl Acad Sci USA 102:12795). In addition to the most common *Buchnera*, several other bacterial species may cohabit with aphids and some are transmitted to the female by copulation and subsequently transmitted by the females during parthenogenic reproduction (Moran NA, Dunbar HE 2006 Proc Natl Acad Sci USA 103:12803). ►parthenogenesis, ►parasitoid, ►biological control; Abbot P et al 2001 Proc Natl Acad Sci USA 98:12068.

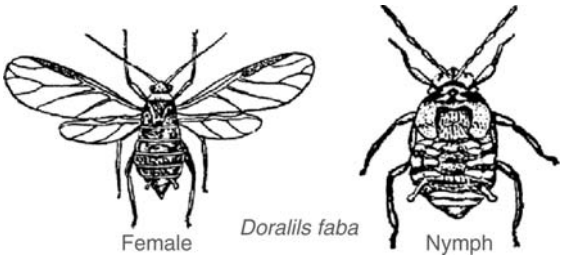

Figure A104. Aphids

Aphrodisiac: Aphrodisiacs are compounds that stimulate sexual interest. ►yohimbine

Apical: Indicates top position. ►apex

Apical Dominance: Apical dominance is the phenomenon whereby the main central stem of the plant is dominant over (i.e., grows more strongly than) other side stems, and on a branch, the main stem of the branch is further dominant over its own side branchlets. The terminal bud of the main stem of a plant prevents or suppresses the formation of lateral buds or branches by auxin although auxin does not enter the lateral bud. In *Arabidopsis* the flavonoid pathway represses lateral outgrowth by diminishing the expression of auxin transporters in the stem and bud (Lazar G, Goodman HM 2006 Proc Natl Acad Sci USA 103:472).

Apical Ectodermal Ridge (AER): AER refers to the group of cells at the tip of the limb bud, involved in the differentiation of the limbs of animals. ►ZPA, ►morphogenesis, ►organizer

Apicomplexan Plastid: ►apicoplast

Apicoplast (apicomplexan plastid): An apicoplast is an acquired ~35 kb DNA-containing plastid type body (from endosymbiosis by green algae) in several parasites (e.g., *Toxoplasma, Plasmodium*). The *Plasmodium falciparum* apicoplast contains about 466 proteins, which are mainly nuclear encoded and imported with the aid of signal peptides and transit peptides. The apicoplast has an as yet undefined essential role in the survival of the parasite and can be targeted by antibiotics as a measure of defense. The 9.1 Mbp *Cryptosporidium parvum* genome (3,807 genes) has been sequenced. This intestinal parasite

has no apicoplast and its degenerate mitochondria has lost its genome (Abrahamsen MS et al 2004 Science 304:441). ►signal peptide, ►transit peptide, ►toxoplasmosis, ►microneme, ►rhoptry; Wilson RJM 2002 J Mol Biol 319:257; Foth BJ et al 2003 Science 299:705; Ross DS 2005 Science 309:72. *Cryptosporidium, Plasmodium* and *Toxoplasma* database: http://ApiDB.org.

Apigenin: A flavone plant pigment.

Apis mellifera (honeybee): The *Apis mellifera* refers to social insects with three types of individuals: diploid egg-laying queen (2n = 32), haploid drones, and sexually undifferentiated diploid workers. The drones hatch from unfertilized eggs. The difference between the queen and the workers is due to different nutrition of the larvae. ►arrhenotoky, ►honey bee; Robinson GE et al 1997 Bioessays 19:1099; mapping: Solignac M et al 2007 Genome Biol 8(4):R66; HGS 2006 Nature [Lond] 443:931.

Aplasia: Failure of the development of an organ or a type of tissue.

Aplastic Anemia: Aplastic anemia is a condition of several blood diseases where the bone marrow may not produce the cellular elements of the blood. ►anemia, ►Duncan syndrome

Aplysia: Refers to a sea mollusc, an invertebrate small animal, frequently used for behavioral and memory studies. Hawkins RD et al 2006 Biol Bull 210:174.

APM: Affected—pedigree-member or APM is used in determining identity by descent and as a non-parametric method to detect linkage. ►IBD

Apnea (familial obstructive sleep, snoring): Apnea is a breathing disorder of any age; it is also responsible for sudden infant death. The genetic basis for apnea is unclear. The composer Johannes Brahms might have been afflicted by it. ►narcolepsy; Palmer LJ et al 2003 Am J Hum Genet 72:340.

APO1: ►Fas

Apo-2: ►TRAIL

Apoaequorin: ►aequorin

Apobec1: Developmentally active, tissue-specifically distributed deaminase of 5-methyl-cytosine into uracil. ►AID

APOBEC (apolipoprotein B mRNA-editing complex, CEM15): A cellular protein in defense against infection by single-strand RNA viruses (HIV, MLV, etc.). The eight genes are in human chromosome 22q12-q13. The protein packaged into the virion has a deaminase activity and changes the viral code by converting C residues to U during reverse transcription. It also increases mutation of C/G → T/A (Schumacher AJ et al 2005 Proc Natl Acad Sci USA 102:9854). HIV fights this defense by suppressing its synthesis with the help of the Vif viral proteins. APOBEC3G deaminase is encapsulated by the HIV virion and facilitates restriction of HIV-1 infection in T cells (see Fig. A105). It binds at random to single-strand DNA and then jumps and slides processively to deaminate the CCC target motif. Sliding is lost when it encounters double-strand DNA but it continues jumping. Deamination is mainly in 3′→5′ direction (Chelico L et al 2006 Nature Struct Mol Biol 13:392). Apobec also inhibits retrotransposition of endogenous retroviruses, LINE-1 elements and Alu sequences, which would still have the ability to move in the mouse genome (Esnault C et al 2005 Nature [Lond] 433:430; Bogerd HP et al 2006 Proc Natl Acad Sci USA 103:8780). The crystal structure of APOBEC-2 has been determined (Prochnow C et al 2007 Nature [Lond] 445:447). ►HIV, ►MLV, ►reverse transcription, ►retroviruses, ►LINE, ►retroviral restriction factors, ►AID; Gu Y, Sundquist WI 2003 Nature [Lond] 424:21; Zhang H et al 2003 Nature [Lond] 424:94; Harris RS, Liddament MT 2004 Nature Rev Immunol 4:868; Ribeiro AC et al 2005 J Virol 79:823; Turelli P, Trono D 2005 Science 307:1061.

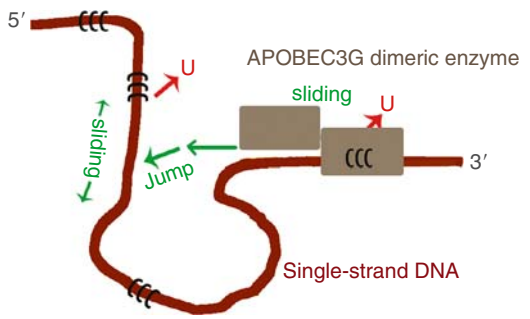

Figure A105. APOBEC3G jumping and sliding during deamination

Apocrine Gland: The tip of the secreting organ is cast off with the secretion.

Apocytochrome B Gene (cob): Located in mitochondrial DNA of yeast; cytochromes are heme-containing proteins involved in electron transport. ►mitochondrial genetics, ►mtDNA

ApoE: ►apolipoprotein

Apoenzyme: The enzyme protein without the co-factors required for activity.

A

Apoferritin: The protein part (M_r 460,000) of ferritin, it contains ferric hydroxide clusters. About 20–24% of it is iron. Ferritin is the most readily available iron storage facility in the body. ►ferritin

Apogamety (apogamy): Embryo formation without fertilization from a cell of the embryo sac, other than the egg cell. ►apomixis

Apoinducer: DNA binding protein that stimulates transcription. ►transcription

Apolar: Molecules are generally insoluble in water because they do not have symmetrical positive and negative charges.

Apolipoproteins: Lipid-binding proteins in the blood that transport triglycerols, phospholipids, cholesterol and cholesteryl esters within the body. Apolipoproteins are not only the most important parts of the high-density lipoprotein (HDL), but are also preferred in order to lower the risk of coronary heart disease. Different classes are distinguished (APOA1, human chromosome 11q23.2-qter and mouse chromosome 9), APOA2 (1q21-q23), APOC2 (19q13.2), APOC3 and APOA4 are in the same region. APOA1 protects against cardiovascular disease by combination with high-density lipoproteins. Its crystal structure is known (Ajees AA et al 2006 Proc Natl Acad Sci USA 103:2126). Apolipoprotein B (human chromosome 2p24) exists in two lengths due to different editing of the transcript. APOC cluster is in human chromosome 19q13.2 and APOE appears to be linked to it. APOE deficiency causes hyperlipidemia and atherosclerosis. APOE isoform E4 is involved in dementia associated with HIV infection and Alzheimer's disease. ApoE ε4 allele increases the risk of Alzheimer's disease whereas allele ε2 lowers the risk (Dodart J-C et al 2005 Proc Natl Acad Sci USA 102:1211). Some other apolipoproteins are genetically less well defined. Apolipoprotein A-IV may protect against atherosclerosis without an increase of HDL levels. Apolipoprotein B deficiency lowers male fertility in knockout mice. Apolipoprotein L-1 is a high-density apolipoprotein bound particle that kills *Trypanosoma brucei brucei*, except subspecies *T. b. rhodesiense* and *T. b. gambiense*. Its killing effect is based on M60-W265 region, which is homologous to bacterial colicins and it lyses holes in lysosomal membranes (Pérez-Morgan D et al 2005 Science 309:469). ►cholesterols, ►fatty acids, ►atherosclerosis, ►arteriosclerosis, ►HDL, ►hyperlipidemia, ►hypobetalipoproteinemia, ►hyperlipoproteinemia, ►abetalipoproteinemia, ►lipoprotein lipase, ►cholesterol, ►megalin, ►Alzheimer's disease, ►AIDS, ►Tangier disease, ►hypo-α-lipoproteinemia, ►*Trypanosomatids*; Mahley RW, Rall SC Jr 2000 Annu Rev Genomics Hum Genet 1:507; Pennachio LA et al 2001 Science 294:169; Davidson WS, Thompson TB 2007 J Biol Chem 282:22249.

Apomeiosis: Gamete development without a meiotic process. ►meiosis, ►apomixis

Apomict: A plant which reproduces by apomixis. ►apomixis, ►*Rosa canina*

Apomixia: Parthenogenesis, common in *Caenorhabditis elegans*, bees, wasps, aphids, in some crustacea, lizards, isopoda, lepidoptera, etc.; it does not occur in humans. ►parthenogenesis, ►apomixis

Apomixis: Embryo (zygote) development without fertilization in plants and fungi. It occurs regularly in certain species, e.g., in the polyploid *Festuca*, hawkweeds (*Hieracium*), etc. Some apomicts reproduce sexually after doubling the chromosome number. Apomicts may make possible the fixation of heterozygous condition. Apomixis may be genetically very different from somatic embryogenesis. If apomixis is preceded by meiosis, and the egg parent was heterozygous, segregation may occur among the apomictic progeny. In aposporous apomixes, the megagametophyte develops from a somatic cell of the ovule. ►parthenogenesis, ►apomixia, ►apogamety, ►agamospermy, ►androgenesis, ►*Hieracium*; Koltunov AM 1993 Plant Cell 5:1425; van Dijk O, van Damme J 2000 Trends Plant Sci 5:81; Grimanelli D et al 2001 Trends Genet 17:597.

Apomorphic: A species trait evolved from a more primitive state of the same. ►plesiomorphic, ►symplesiomorphic, ►synapomorphic, ►autapomorphy

Apopain (caspase 3, human chromosome 4q35): ►apoptosis

Apoplast: Intercellular material of plants. (Sattelmacher B, Horst W (eds) 2007 Springer Berlin, D.)

Apoptosis (programmed cell death, PCD): The cells and the nuclei shrink and are generally absorbed after fragmentation. Apoptosis is an indispensable process for the majority of organisms. Unneeded cells are disposed of, room is made for differentiated cells and it is a safeguard against cancerous growth. A generalized outline of the apoptotic cell death pathway is presented here. Ceramide is one of the regulatory molecules of the process. Tumor necrosis factor (TNF) is an inducer of apoptosis. The metabolites of ceramides, sphingosine and sphingosine-1-phosphate prevent the symptoms of apoptosis. These two molecules are supposedly second messengers for cell proliferation mediated by platelet-derived growth factor. The activation of protein kinase C brought about by sphingosine kinase and the increase of the level of sphingosine-1-phosphate inhibits the ceramide-mediated apoptosis. The latter molecules also stimulate the ERK-controlled

reactions and inhibit the stress-activated kinases SAPK/JNK. In *Caenorhabditis* more than a dozen *ced* (cell death) genes have been identified. Ced3 protein is an interleukin-1 converting (ICE) cysteine protease enzyme, involved in ceramide production. Ced9 is a suppressor of cell death and EGL-1 releases the suppression and CED-tetramer facilitates the conversion of the CED-3 zymogen (enzyme precursor) to an active CED-3, which brings about cell death. The apoptotic pathway mediated by CED-3 is illustrated after Yan N et al 2005 Nature [Lond] 437:831. CED-9 has 23% identity to the human oncogene BCL-2, controlling follicular lymphoma. If this human gene is transfected to the nematode it suppresses apoptosis, indicating that the same function is controlled over a wide evolutionary range (see Fig. A106).

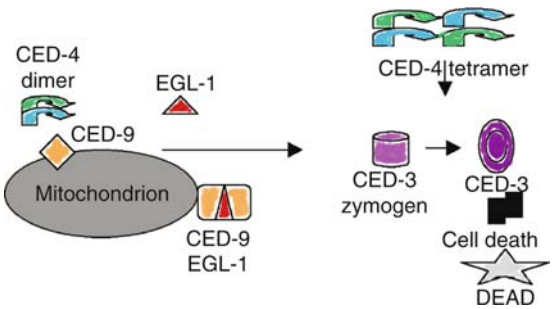

Figure A106. Death pathway CED-3

The *reaper* gene (*rpr*) of *Drosophila* is an activator of apoptosis and it is homologous to *ced-3* of *Caenorhabditis*. Another *Drosophila* gene, *hid* (*head-involution defective*), is linked to *reaper*. The 65-amino acid RPR protein has similarity to the "death domain" of the tumor necrosis factor receptor (TNFR) family. TNFR1 and Fas induce cell death when activated by ligand binding or when over-expressed. Other death receptors are DR3 (Ws1, Apo3, TRAMP, Lard) and Dr4. They may directly connect to the Fas-associated death domain (FADD/MORT1) or to the tumor necrosis factor-associated death domain receptor (TRADD). FADD recruits procaspase 8. TRAIL is another killer protein for which DR3 and Dr4 serve as receptors. Curiously, the latter receptors are present in non-apoptotic cells. The lack of killing effect in these cells is explained by other TRAIL receptors TRID (TRAIL receptor without an intracellular domain) or DcR1 (decoy receptor 1). These receptors have glycophospholipid anchored cell surface portions that trap TRAIL but do not allow the transfer of the death signal to FADD and actually function as a decoy preventing the death signal transduction even for Dra3 and Dra4. The dead cells are disposed of generally by the macrophages without producing inflammation in the tissue. The apoptotic cells are recognized generally by the altered sugar groups or phosphatidylserine on their surface. The phagocytes recognize apoptotic cells by their phosphatidylserine receptors (PSR). The absence of PSR during early mammalian organogenesis results in respiratory and brain anomalies (Li MO et al 2003 Science 302:1569; Wang X et al 2003 Science 302:1563). The macrophage secretes an extracellular protein, thrombospondin, which recognizes apoptotic cells. The *Alg-2* (apoptosis-linked gene) encodes a Ca^{2+}-binding protein that is required for T cell receptor-, Fas- and glucocorticoid-induced apoptosis. *Alg-3* is a homolog of Alzheimer's disease gene, which is basically a senescence gene. Apoptosis may be a very natural response of the cells to be disposed when no longer needed. In some cancers the proliferation is not under control because regulators of the process go awry. The baculovirus apoptosis inhibitor proteins (Cp-IAp and Op-IAP) as well as neuronal apoptosis inhibitor proteins (NAIP), located in human chromosome 5q13.1, are defective or deleted in spinal muscular atrophy. BAX is a hetero-dimeric protein that works in the opposite direction as BCL2 (chronic lymphocytic leukemia, B cell). The gain of function BAX mutations, knockouts were viable but in the lymphocyte cell lineages apoptosis was induced. In other cell lineages hyperplasia was observed. Thus, the BAX expression depends on the cellular context. The wild type BCL2 gene functions similarly to *Ced-9* of *Caenorhabditis*, i.e., it suppresses apoptosis. The enzyme apopain, cleaving poly(ADP-ribose) polymerase (PAR) is also necessary for apoptosis to proceed. Apopain is generated from the proenzyme called CPP32, a protein related to ICE and CED-3. Lymphocyte apoptosis may be mediated by Type 3 inositol 1,4,5-trisphosphate receptor in the plasma membrane by promoting the influx of calcium. Apoptosis of neurons is mediated by the activation of JNK (JUN [oncogene] NH2-terminal kinase) in a process opposing the effect ERK (extracellular signal-activated kinase) in the absence of the nerve growth factor (NGF). The p35 protein of the baculovirus *Autographa californica* has similar antiapoptotic property for insects as well as for mammals as the Ced-9 gene product of *Caenorhabditis*. Ced-9/Bcl-2 gene product inhibits both the apoptosis promoting and protecting effects of the Ced-4/Apaf-1 products. CED-4 interacts with CED-3 and they oligomerize. Their oligomers may associate with BCL and this results in processing (in the presence of ATP) of CED-3 leading to cell death. In order to activate the death pathway the EGL-1 protein stops the interaction of CED4-CED3 with BCL. CED-10/RAC1 mediates the removal of apoptosed cells through actin reorganization (see Fig. A107). (Kinchen JM et al 2005 Nature [Lond] 434:93).

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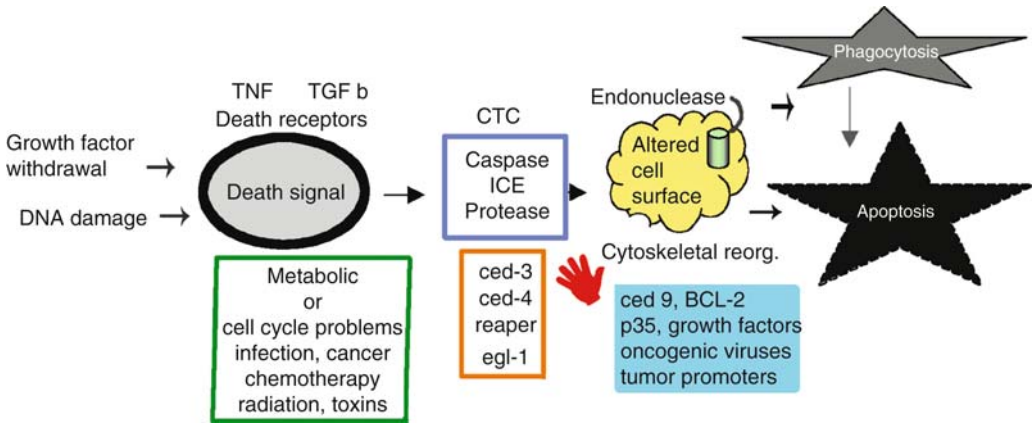

Figure A107. Pathway to apoptosis and its inhibition

Ced-9 is homologous to the mammalian BCL-2. *Ced-3* and *Ced-4* are considered to be promoters of apoptosis. Actually, *Ced-4* has two transcripts; the short transcript promotes apoptosis whereas the long transcript is somewhat protective. Excessive manifestation of *ced-4L* can actually prevent programmed cell death. It is interesting to note that the structurally unrelated *BCL-x* and *Ich-1* genes are also involved in apoptosis, similarly to *Ced-4*, all have two alternative transcripts. This indicates that RNA splicing may have an important role in programmed cell death.

Before caspase could be fully functional ced-4 moves from the mitochondrion to a perinuclear location. The basic leucine zipper proteins (bZIP) PAR (proline and acid rich) and other members of the protein family can also control apoptosis. PAR mediates cytochrome c release during apoptosis by remodeling mitochondrial cristae with the aid of the dynamin-related protein OPA1 (Cipolat S et al 2006 Cell 126:163; Frezza C et al 2006 Cell 126:177).

Inappropriate activation of apoptosis may be involved in diseases such as AIDS, degeneration of the nervous system (Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, retinitis pigmentosa), constriction or obstruction of the blood vessels (ischemic stroke), anemias, liver diseases, autoimmune diseases, etc. The diagram given here is modified after Thompson CB 1995 Science 267:1456.

Recently, the generic name CASPASE has been suggested (c for cysteine protease, aspase for cleaving at aspartate) for the ICE-ced protease enzyme system. The individual enzymes would also be designated by numbers. After the initiation of the apoptotic pathway cytochrome c is released from the mitochondria by the action of the BAX protein and this in turn leads to the activation of the caspases by Apaf-1. The mitochondrial route of apoptosis is initiated by the facilitation of the permeability of the outer membrane of the mitochondria. The permeability enables the leakage of mitochondrial proteins involved in the activation of caspases (Green DR, Kroemer G 2004 Science 305:626). According to some, there are two pathways of apoptosis, one through the Fas and another through the Apaf/mitochondrial route. Protein BAR (member of the BCL family) may coordinate these two pathways. BCL-2/CED-9 protein blocks caspase activation. "BH-Only" proteins of the Bc*l* family (Bad, Bil Blk, Hrk/Dp5, Bid, Bim, Noxa, EGL-1) share 9–6 amino acids and are initiators of apoptosis. The X-chromosome-linked IAP (inhibitor of apoptosis) directly inhibits caspase-3 and 7 proteases. Another protease inhibitor is known by the synonyms FLIP, Casper, Flame, Cash and I-FLICE. The CED-3 enzymes are cysteine proteases, accompanied by nucleases that cut the DNA to approximately 180–200 bp fragments, the size of a nucleosomal unit (hence the name caspase-activated DNase [CAD]). There is a closely associated other protein inhibitor of CAD (ICAD or DFF45 in humans). ICAD releases CAD after caspase-3 cut and its role is that of a chaperone. CAD is produced as a complex with ICAD and the action of caspase-3 permits CAD to move into the nucleus from the cytoplasm. The site of cutting is between two nucleosomes by the 343 amino acid nuclease, a basic protein. Actually the whole complex process involves a number of other proteins that interact and affect the outcome of cell death or proliferation (see Fig. A108).

Apoptosis is used for multiple purposes besides aging. Differentiation, homeostasis, cellular defense mandate this process of suicide for damaged or unnecessary cells. The purpose of the apoptotic process is to free the system from unwanted cells and stop proliferation (e.g., prevent cancer and autoimmune disease) and maintain healthy conditions. Glucocorticoids are effective stimulators of apoptosis. After a stroke or Alzheimer's disease overactive

Figure A108. Apoptosis can be imaged by introducing into the cell the firefly luciferase gene *(Luc)* attached to the regulatory domain of a silencer estrogen receptor (ER) domain. In between Luc and ER there is A DEVD cleavage site for caspase-3. When caspase is activated at apoptosis the DEVD link is severed and the silencing effect of ER is removed and luciferase is expressed. This is a non-invasive real-time monitoring procedure. (Modified after Laxman B et al 2002 Proc Natl Acad Sci USA 99:16551)

apoptosis may, however, damage the brain. Low level of apoptosis may be the cause of follicular B cell lymphoma. Tumor formation may be caused by the overexpression of Bc*l*-2 suppressor of apoptosis. The suppression of Bc*l*-2 may, however, promote apoptotic death of cancer cells. The suppression of survivin, an apoptosis inhibitor may also cause death of cancer cells. TRAIL, caspases and caspase inhibitors, respectively have also been considered for cancer therapy. p53 tumor suppressor may channel damaged cells to an apoptotic path.

It has been estimated that in the human body 10 billion cells suffer apoptosis daily and about the same number of cells arise again by mitosis. Humans have more than 200 genes that are involved with apoptosis and their manipulation has therapeutic significance (Schwerk C, Schultze-Osthoff K 2005 Mol Cell 19:1).

Programmed cell death also occurs in plants during the differentiation of the vascular system (xyleme), fruit ripening and senescence, the hypersensitive defense reaction against pathogens. Although plants do not have caspases, the vacuolar processing enzyme, a protease has a similar function in controlling virus infection by hypersensitive reaction (Htsugai N et al 2004 Science 305:855).

►aging, ►Hayflick's limit, ►necrosis, ►ceramides, ►sphingosine, ►ERK, ►SAPK, ►T ►cell, ►signal transduction, ►TNF, ►TNFR, ►Fas, ►DISC, ►TGF, ►p53, ►TRF2, ►interleukins, ►leukemia, ►lymphoma, ►cysteine proteases, ►fragmentin-►2, ►perforin, ►ICE, ►FADD/►MORT-►1, ►FLICE, ►granzymes, ►Down's syndrome, ►acquired immunodeficiency, ►Alzheimer's disease, ►amyotrophic lateral sclerosis, ►retinitis pigmentosa, ►aplastic anemia, ►CTC, ►apopain, ►addiction module, ►altruism, ►DAP kinase, ►Myc, ►TRAIL, ►DR, ►chaperone, ►p35, ►phagocytosis, ►macrophage, ►Apaf, ►Smac, ►ARF, ►PAK, ►BCL, ►BID, ►BAK, ►RAC, ►IEX, ►nur77, ►transmission, ►IAP, ►survival factor, ►survivin, ►necrosis, ►APAF, ►AIF, ►L-DNase IImtPTP, ►dynamin, ►mitochondrial ►diseases in humans, ►porin, ►acinus, ►glucocorticoid, ►T cell receptors, ►anoikis, ►death ►signaling, ►hypersensitive reaction, ►addiction ►module, ►Endonuclease G, ►paraptosis, ►phenoptosis, ►*Caenorhabditis*; Nature [Lond] 407:769 ff; Huang DCS, Strasser A 2000 Cell 103:839; Vousden KH 2000 Cell 103:691; Fesik SW 2000 Cell 103:273; Strasser A et al 2000 Annu Rev Biochem 69:217; Engelberg-Kulka H, Glaser G 1999 Annu Rev Microbiol 53:43; Aravind L et al 2001 Science 291:1279; Joza N et al 2001 Nature [Lond] 410:549; Wei MC et al 2001 Science 292:727; Hunot S, Flavell RA 2001 Science 292:865; Nature Cell Biol 2002 June issue for several papers, Igney FH, Krammer PH 2002 Nature Rev Cancer 2:277, http://www.apoptosis-db.org/welcome.html.

Apoptosis Inhibitors: These are viral (baculovirus) proteins aimed at overcoming the host defense against viral infection by cell death. Similar proteins targeting primarily caspase-9 and apoptotic mitochondrial cytochrome c occur in insects, mammals as well as in humans.

Apoptosome: A complex of apoptosis proteins including caspases, Apaf, etc. ►apoptosis, ►caspase, ►Apaf; Acehan D et al 2002 Mol Cell 9:423; review: Schafer ZT, Kornbluth S 2006 Developmental Cell 10:549.

Aporepressor: Repressor proteins that require another molecule, the co-repressor (frequently a late product of the metabolic pathway) to be active in controlling transcription. ►transcription, ►tryptophan operon, ►tryptophan repressor

Aposematic Coloration: Warning display of animals and plants against invaders, e.g., bright color of poisonous snakes or poisonous mushrooms or plants. ►Batesian mimicry, ►Müllerian mimicry; Brodie ED III, Agrawal AF 2001 Proc Natl Acad Sci USA 98:7884.

Apospory: Seed formation without fertilization from diploid cells of the nucellus or integumentum. ►apomixis, ►agamospermy diplospermy, ►adventitious embryo, ►amixia

Apostatic Selection: Predators often prefer the most abundant types of prey and thus maintain the polymorphism of the prey population. Polymorphism in populations is maintained by frequency-dependent selection that seems to be paradoxical to the principle of natural selection but under experimental conditions some rare phenotypes have the unexpected advantage of survival (Olendorf R et al 2006 Nature

A

[Lond] 441:6330; ►selection types, ►frequency-dependent selection; Bond AB, Kamil AC 2002 Nature [Lond] 415:609.

Aposymbiotic: An organism cured from the symbiotic partner. ►symbionts

Apothecium: An open fruiting body of fungi on which the asci develop; it is similar to perithecium but the latter is a closed fruiting body. Among the genetically widely used organisms *Ascobolus* develops apothecia (see Fig. A109). ►perithecium

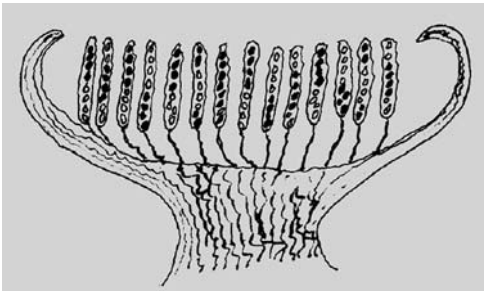

Figure A109. Apothecium. (After Weier TE et al 1973 Botany. Wiley & Sons, New York)

Apotransferrin: A transport protein without its ligand. ►transporters, ►ligand

apo-VLDL: ►apolipoprotein

AP-PCR: Arbitrarily primed PCR. ►polymerase chain reaction, ►methylation-specific PCR

APP (amyloid precursor protein): ►Alzheimer's disease, ►amyloids, ►secretase, ►memory

Apple (*Malus* spp.): About 25 species all with x = 17, most of them are diploid although tetraploid and triploid varieties also occur. Apples are frequently self-incompatible but cross-fertilize with other apples. They do not easily hybridize with pears (*Pyrus*), but they hybridize with *Sorbus* (mountain ash). ►pears

Application Programs (computer): Programs serving special purposes such as word processing, graphics, telecommunication, DNA sequencing, data management, etc.

Appressor: Cylindrical or globular fungal organs at the end of the hyphae with a rigid wall. It serves for infection by rupturing the cell wall of plants and invasion of the tissues with the aid of the penetration peg. The process may rely on cutinase, cellulase and other enzymes but it may utilize high turgor mechanical pressure.

Appressorium: An enlarged fungal structure at the point of invasion of the host tissue (see Fig. A110).

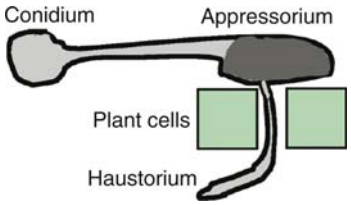

Figure A110. Appressorium

APRF (acute-phase response factor, 17q21): A transcription factor related to the p91 subunit of the interferon-stimulated gene factor-3α (ISGF-3α). It is phosphorylated by the mediation of cytokines, and along with Jak1 kinase, it is associated with gp130. Interleukin-6, leukemia inhibitory factor (LIF), oncostatin M (OSM, 252 amino acids, encoded at human chromosome 22q12.1-q12.2 at the same general location as LIF) and ciliary neurotrophic factor (CNTF, 11q12.2), cytokines, neurokines and neuronal differentiation factors are also involved. LIF and OSM may promote atherosclerosis by inhibiting the replacement of defective endothelial cells. ►gp130, ►signal ►transduction, ►cytokines, ►embryogenesis, ►leukemia inhibitory factor, ►ciliary neurotrophic factor, ►atherosclerosis

Apricot (*Prunus armeniaca*): x = 7; 2x and 3x forms are known.

APRIL (a proliferation-inducing ligand): A member of the TNF ligand family with homology to CD95. The tumor necrosis factor ligand 13B (encoded at 13q32-q34) is also called TNFSF-13B and April. ►TNF, ►CD95, ►BAFF; Stein JV et al 2002 J Clin Invest 109:1587.

Aprotinin: Inhibitor (at concentrations 1–2 mg/mL) of proteases kallikrein, trypsin, chymotrypsin, plasmin but not of papain. ►protease, ►kallikrein, ►trypsin, ►chymotrypsin, ►plasmin, ►papain

APSES (present in **A**SM-1-**P**hd1-**S**tuA-**E**FGTF1-**S**ok2 proteins [among others]): A helix-loop-helix-like structure regulating developmental processes. ►DNA binding protein domains

Aptamer: An oligo-RNA, oligo-DNA or a protein—oligo-RNA complex that can bind specifically a particular protein or other molecule (see Fig. A111). E. G., a thrombin-binding aptamer inhibits the action of thrombin in blood clotting and thus prevents the formation of blood clots. Human neutrophil elastase, fibroblast growth factors, vascular endothelial growth factor, selectin, antibodies have been successfully

isolated by the SELEX procedure. Short RNA aptamers inserted into the 5′ untranslated region of a mRNA may bind various ligands including (fluorescent malachite green) and may facilitate the control of translation behind it. Cancer cell-specific aptamers can distinguish normal cells from cancer cells and may facilitate fast and effective early diagnosis (Shangguan D et al 2006 Proc Natl Acad Sci USA 103:11838). ►antisense ►RNA, ►SELEX, ►elastase, ►FGF, ►riboswitch, ►selectin, ►antibody, ►mRNA ►display; Hermann T, Patel DJ 2000 Science 287:820; Cerchia L et al 2002 FEBS Lett 528:12; Famulok M 2004 Nature [Lond] 430:976.

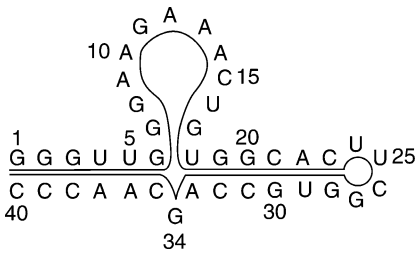

Figure A111. RNA aptamer of ATP

Aptazyme: A ribozyme with an aptamer. ►ribozyme, ►aptamer

Apurinic Endonuclease: ►AP ►endonucleases

Apurinic Site (AP): A site from where a purine has been removed from the nucleic acid. It has been estimated that mammalian cells lose about ten thousand purines daily. The apurinic sites are removed by excision repair and deoxycytidyltransferase can include deoxycytidine across the apurinic site and DNA polymerase ζ makes further repair. ►glycosylases, ►abasic ►sites, ►depurination, ►excision repair; Lindahl T, Nyberg B 1972 Biochemistry 11:3610; Haracska L et al 2001 J Biol Chem 276:6861.

Apyrase: An acid tri- and diphosphatase enzyme that also degrades nucleotides.

Apyrimidinic Endonuclease: ►AP endonucleases

Apyrimidinic Site: A site from where a pyrimidine has been removed from a nucleic acid.

Aquaporin (AQP2, 12q13, APQ4, 18q11.2-q12.1): Six transmembrane domain proteins (M_r 28K) and water channel in fluid absorbing and fluid secreting cells. The AQP1 monomer contains 269 amino acids, forming two tandem repeats of three membrane-spanning domains and amino and carboxy termini located on the cytoplasmic side of the membrane. The AQP family includes proteins with wide distribution in diverse species across the plant, animal and microbial world. The aquaporin channel of plants is closed when two conserved serine residues are dephosphorylated or when a conserved histidine is protonated during anoxia by flooding. In closed conformation a D loop caps the channel from the cytoplasm. In open conformation the D loop is displaced and removes the blockade of the entrance of the channel from the cytoplasm (Törnroth-Horsfield S et al 2006 Nature [Lond] 439:688). cAMP-dependent mechanisms or PKA activate the aquaporin channel. It is important for various types of cells, diabetes, kidney function, *Drosophila* neural development, nematodal infestation of plants, etc. Aquaporin 7 deficiency activates adipose glycerol kinase and may lead to obesity (Hibuse T et al 2005 Proc Natl Acad Sci USA 102:10993). The deletion of aquaporin-4 in mice reduces brain edema. The disruption of the rodent aquaporin-1 gene (*AQP1*) impairs angiogenesis and cell migration and thus reduces tumor growth (Saadoun S et al 2005 Nature [Lond] 4324:786). ►CHIP, ►forskolin, ►cAMP, ►PKA, ►cell ►membranes, ►ion ►channels; Borgnia M et al 1999 Annu Rev Biochem 68:425; Murata K et al 2000 Nature [Lond] 407:599; Sui H et al 2001 Nature [Lond] 414:872; Uehlein N et al 2003 Nature [Lond] 425:734; King LS et al 2004 Nature Rev Mol Cell Biol 5:687.

Aquaretic: Secreting bloody fluids.

Aqueous: Prepared with water (e.g., a solution) or watery in appearance.

Aquifex aeolicus: A chemolithoautotroph bacterium capable of growth at 95 °C. Its completely sequenced DNA genome is 1,551,335 bp. ►chemolithoautotroph

Aquilegia (Columbine): 700 species have a genome size of ~400 Mb; under development for ecological and evolutionary genetic studies (see Fig. A112).

Figure A112. Columbine

***Arabidopsis* Mutagen Assays**: In the mature embryo of plants two diploid cells represent the inflorescence. Therefore, if the seeds are exposed at such a stage to a mutagen, in the progeny of the emerging plants the

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segregation is about 7:1 for recessive mutations. This also indicates that one of the two apical cells became heterozygous for the new mutation induced. For mutagen assays it is sufficient to open up the immature fruits of the plants before the seed coat becomes opaque (about 10–14 days after fertilization) and albina or other color mutations in the cotyledons or embryo defects can be determined. Within a single fruit the segregation for recessives is 3:1 (see above). The fruits on the plants emerging from the treated seed already contain the F_2 generation. Generally, two opposite fruits next to each other are examined because the phyllotaxy index assures that these are sufficient for complete sampling. Such a test permits the identification of about 80% of the spectrum of visible mutations. Since the plants are diploid and the "germline" consists of two cells, the mutation rate on genome basis is calculated by counting all independent mutational events and dividing it by the total number of plants tested x 4. *Arabidopsis* can activate many types of promutagens and therefore provides an efficient and low cost method for assessing the genotoxic effects of a wide variety of agents in a single culture (see Fig. A113). ►bioassays for genetic toxicology, ►*Arabidopsis thaliana*, ►phyllotaxy; Rédei GP, Koncz C 1992 In: Koncz C et al (eds) Methods in Arabidopsis Research, World Scientific, Singapore, p 16; Hays JB 2002 DNA Repair 1:579.

Figure A113. *Arabidopsis.*

Figure A114. Open *Arabidopsis* fruit.

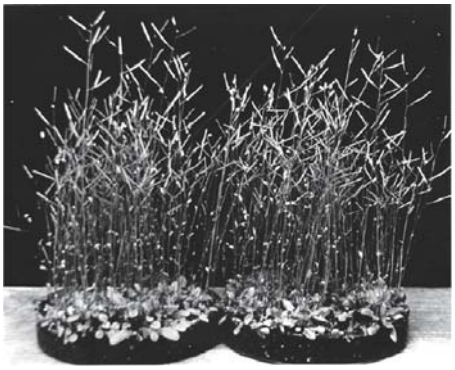
Arabidopsis thaliana: An autogamous plant of the crucifer family, 2n = 10, the genome size has been estimated to be 9×10^7 to 1.5×10^8 bp (the current best estimate is ~121–125 Mbp). Its life cycle may be as short as 5–6 weeks. Its seed output may exceed 50,0000 per plant. Its mitochondrial DNA is 366,924 bp, 10% duplicated, and apparently codes for 58 genes. Because of its small size thousands of individuals may be screened even on a Petri plate or grown for the entire life cycle in test tubes where the plants may produce more than 100 seeds. Its plastid DNA is approximately 154 kbp encoding 79 proteins and 17% is duplicated. It is the first higher plant with the genome completely mapped and sequenced in 2000. Transposons constitute 14% of the nuclear DNA and 4% of the mitochondria; the plastids appear free of moving elements. Chromosome 2 and 4 sequences became available by late (1999) (Nature [Lond] 402:761 and 769).

The initial data indicate higher gene number than in *Drosophila* or *Caenorhabditis*. At present the predicted gene number of *Arabidopsis* is ~30,700 from which ~25,540 have been annotated as protein-coding whereas the remaining are pseudogenes or partial genes (Yamada K et al 2003 Science 302:842). Interestingly, more than two decades ago, on the basis of mutation frequency in *Arabidopsis,* the total number of genes was estimated to be about 28,000 (Rédei GP et al 1984 In: Chu EHY, Generoso WM (eds) Mutation, Cancer, and Malformation. Plenum, p. 306). All chromosomes display on an average ca. 60% duplication. Although many of the genes show homologies to those of other organisms, there is 38.9% identity with the human breast cancer gene (BRC2), Werner syndrome (37.4%) and the Niemann-Pick disease (42.7%). Interestingly, many genes with apparently so far unidentified function and specific for plants were revealed by the sequences.

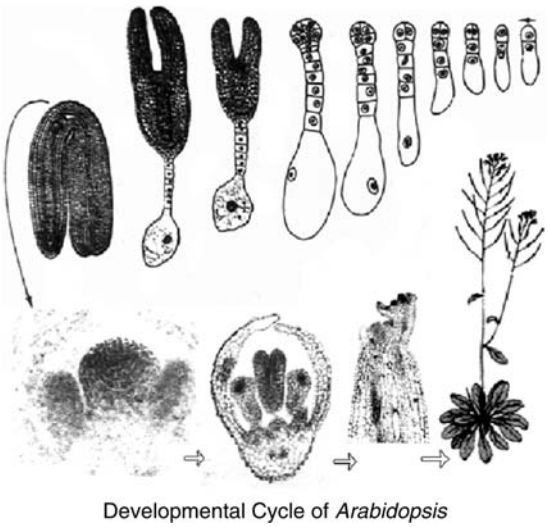
Annotation of the full-length cDNA: Seki M et al 2002 Science 296:141. A global gene expression map is available including from embryogenesis to seed development and senescence. The expression pattern of large gene families indicates that many families are co-opted for specific developmental processes. (Schmid M et al 2005 Nature Genet 37:501).

Information is available through Arabidopsis Biological Resource Center, Ohio State University, (1735) Neil Ave., Columbus, OH 43210, USA. Tel.: 614-292-1982 (Scholl, seeds), 614-292-2988 (Ware, DNA). E-mail: arabidopsis+@osu.edu. Orders: by Fax 614-292-0603. Science 282:6612; Marra M et al 1999 Nature Genet 22:265; Mozo T et al 1999 Nature Genet 22:271; Nature [Lond] 408:796 [2000]; Bennetzen JL 2001 Nature Genet 27:3; Allen KD 2002 Proc Natl Acad Sci USA 99:9568); genome-wide mutant screens: Alonso JM, Ecker JR 2006 Nature Rev Genet 7:524; taxonomic identities: Koch MA, Matchinger M 2007 Proc Natl Acad Sci USA 104: 6272;

E-mail seedstock@arabidopsis.org, dnastock@arabidopsis.org,



Hundreds of Columbia wild type Arabidopsis plants can be raised to maturity in 9 cm diameter Petri plates on commercial Promix soil-substitute medium under long-day illumination in greenhouse (Redei, unpublished).



Developmental Cycle of *Arabidopsis*

Figure A115–118 Features of Arabidopsis

NASC http://nasc.nott.ac.uk; http://arabidopsis.info/,

TAIR: http://arabidopsis.org; http://mips.gsf.de/proj/thal/db,

Arabidopsis Genome Encyclopedia: http://rarge.gsc.riken.jp/,

cis-acting elements, T-DNA, regulation: http://arabidopsis.med.ohio-state.edu/,

interactions: http://www.ptools.ua.ac.be/at_idb,

EMB-EBI bioinformatics protein index; http://www.ebi.ac.uk/IPI/IPIarabidopsis.html,

genetics, genetics, genomics; http://bioresearch.ac.uk/browse/mesh/D017360.html,

nucleolar markers: http://bioinf.scri.sari.ac.uk/cgi-bin/atnopdb/home,

small RNAs: http://asrp.cgrb.oregonstate.edu/ mitochondria; http://www.plantenergy.uwa.edu.au/applications/ampdb/index.html,

gene co-expression data mining tool: http://www.arabidopsis.leeds.ac.uk/act/.

Arabinose Operon: Consists of three juxtapositioned structural genes *araB* (l-ribulokinase), *araA* (L-arabinose isomerase) and *araD* (L-ribulose-4-epimerase) transcribed in this order into a polycistronic araBAD mRNA starting at the O^{BAD} operator and

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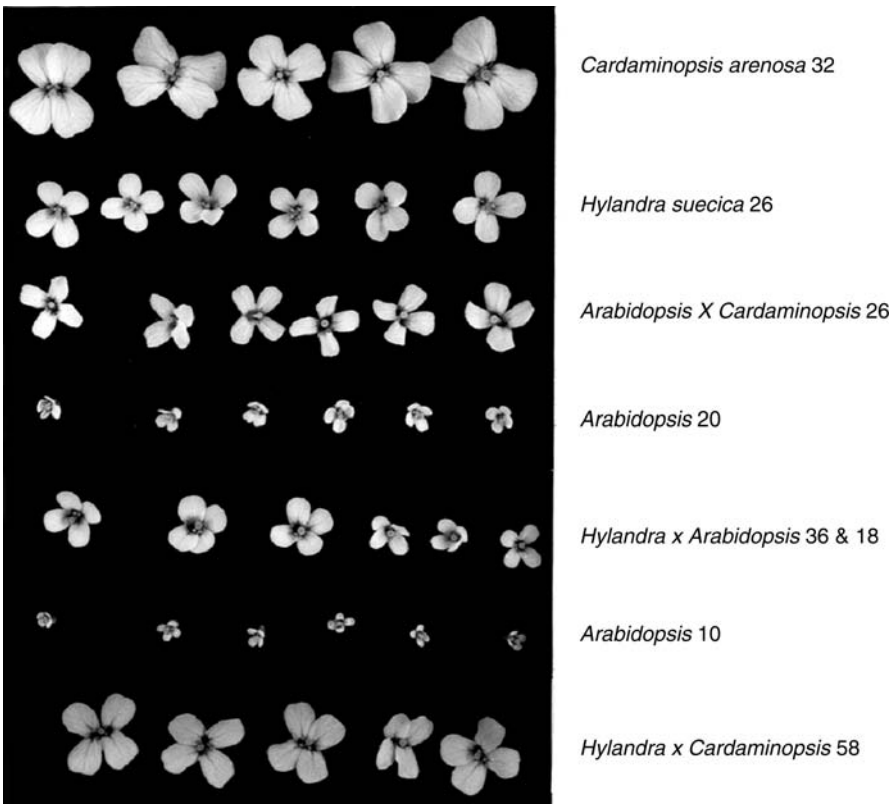

Figure A119 *Arabidopsis*, related species and hybrids with somatic chromosome numbers. (Rédei GP 1960 unpublished)

initiated by the P^{BAD} promoter. The repressor-activator site functions by positive or negative control and it is transcribed in the opposite direction from the O_C operator and uses the P_C promoter. These genes are near the beginning of the *E. coli* map, while another gene *araF* is located near map position 45. They form a common regulatory system: a regulon. The activation of the *ara* operon not only requires the presence of the substrate arabinose, but also that the catabolite activating protein cyclic adenosine monophosphate complex be attached to the promoter. This operon is subject to catabolite suppression and as long as glucose is present in the medium (even when arabinose is also available) its transcription cannot begin. ►operon, ►polycistronic, ►operator, ►catabolite activating protein, ►cAMP, ►negative control; Schleif R 2000 Trends Genet 16:559.

Arabinosuria: An early name of pentosuria but it was subsequently found that L-xylulose was misidentified as arabinose; the current name of the recessive disorder is (essential) pentosuria. ►pentosuria, ►xylulose

Arachidonic Acid (arachidate): An unsaturated fatty acid, which, is known as arachidonate when there are four double bonds in the molecule (it is synonymous with eicosatetraenoate). It occurs in lipids and plays a role in mediating signal transduction. Cyclooxygenase mediates the formation of prostaglandins, prostacyclins and thromboxanes whereas lipoxygenase catalyzes the synthesis of leukotrienes from arachidonic acid. ►fatty acids, ►cyclooxygenase, ►lipoxygenase signal transduction, ►atherosclerosis

Arachnodactyly (5q23-q31): A characteristic of the Marfan syndrome involving unusually long fingers and toes. Unlike the Marfan syndrome (FBN1), here the mutation involves the fibrillin gene FBN2 (see Fig. A120 for a photograph). ►Marfan syndrome, ►fibrillin; Belleh S et al 2000 Am J Med Genet 92:7.

Figure A120. Arachnodactyly

Aracne (algorithm for the reconstruction of accurate cellular networks): From phenotypic and biochemical information scale-free networks of interconnected gene hubs are determined (Basso K et al 2005 Nature Genet 37:382). ►networks, ►genetic networks

ARAF Oncogenes: Have been assigned to the mouse X-chromosome whereas in humans ARAF 1 is in chromosome Xp11-p11-2 and ARAF 2 was localized to either 7p11.4-q21 or 7p12-q11.21. These oncogenes are homologous to the RAF1 oncogene and are supposed to encode a serine/threonine kinase. ►RAF1

Aragorn: A computer program for the detection of tRNA and tmRNA genes. (Laslett D, Canback B 2004 Nucleic Acids Res 32:11)

Arboviruses: Parasites of blood-sucking insects and vertebrates, their genetic material is RNA.

Arbuscular Mycorrhiza: The hyphae of the fungus actually penetrate the roots of the plants and form their branching structures. ►mycorrhiza

ARC: ►DRIP

Archaea: The third major group of living systems besides bacteria and eukarya. *Methanococcus jannaschii* DNA (1.66 megabase) has been sequenced in (1996) and 1,738 predicted protein-coding genes have been identified. The organism has two, 58-kb and 16-kb, extrachromosomal elements. Only 38% of its genes appear similar to genes (by nucleotide sequences) of other fully sequenced bacteria or budding yeast. The metabolic genes bear similarities to bacterial genes whereas its genes involved in transcription, translation and replication bear greater resemblance to eukaryotic genes. Their genome displays nucleosomal structures. For a complete nucleotide sequence see World Wide Web at http://www.tigr.org/tdb. In halobacteria the genes are in linkage equilibrium, which is an indication of frequent genetic recombination (Papke RT et al 2004 Science 306:1928). Archaea in the rhizosphere of rice plants are responsible for an estimated 10 to 25% of the global methane emission. The genome of 3,179,916 bp of the methanogenic strains contains 3,103 coding sequences (Erkel C et al 2006 Science 313:370). ►life form domains, ►evolution of eukaryotes, ►linkage disequilibrium; Whitman WB et al 1999 Genetics 152:1245; Podani J et al 2001 Nature Genet 29:54.

Archaebacteria: Groups of prokaryotes that appear to have some similarities to eukaryotes in as much as displaying nucleosome-like structures in their DNA, introns in their genes, unlinked 5S RNA genes and their transcriptase enzyme are somewhat related antigenically to similar enzymes in lower eukaryotes. ►archaea

Archaeogenetics: Studies the descent of humans mainly on the basis of mitochondrial and Y-chromosomal population information.

Archegonium: Female sexual organ (gametangium) of lower plants where the eggs develop.

Archeogenetics: The application of molecular genetics techniques to ancient populations, their bone remains or otherwise preserved biological samples and their evolving descendants. The studies are based on mitochondrial DNA that can reveal the pattern(s) of human/animal evolution and migration of females and the analysis of Y chromosomal makeup provides comparable information on the male lineages. ►Eve foremother of mtDNA, ►Y chromosome

Archeozoic: Geological period 400 to 100 million years ago when protists (unicellular organisms) evolved.

Archespore: The ancestral, enlarged cell that develops into the megasporocyte (megaspore mother cell) in plants. ►megagametophyte

Archezoa: ►microsporidia

Architectural Editing: Proteins from the endoplasmic reticulum are selectively transported. The new proteins are retained until properly folded and the misfolded chains are degraded. ►endoplasmic reticulum

Architectural Proteins: Modulate DNA structure in such a way that transcription factors gain better access to the promoter area. ►UBF, ►high-mobility group proteins

Archival DNA: Stored in museum, herbarium or other preserved samples of long dead cells; can be amplified with PCR techniques for analysis and for obtaining information on old populations or on extinct species. ►PCR, ►ancient DNA

Archtype: A hypothetical ancestral form in evolution.

Arcsine: The inverse of sine ($\sin^{-1}$), it denotes the angle of whose sine is given. ►sine

Arcsine Transformation: ►angular transformation

ARE (anoxia response element): DNA sequences regulating responses to anaerobiosis. ARE responding genes represent detoxification and antioxidant defense. ►anoxia; Li J et al 2002 Physiol Genomics 9:137.

ARE: AU-rich elements in the 3′-untranslated region of RNA involved in the regulation of translation Cheong C-G, Tanaka-Hall TM 2006 Proc Natl Acad Sci USA 103:13635; Vasudevan S, Steitz JA 2007 Cell 128:1105; ►AMD, ►HuR [human AUY-rich elements], http://rc.kfshrc.edu.sa/ared/.

α-Repeat: A 171 bp abundant (up to 1,000,000) repeat in the human genome, localized primarily in the centromeric regions of the chromosomes. This and

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the Alu repeats constitute 5–10% of the human genome. ►Alu family

ARF (ADP-ribosylation factor, $p14^{ARF}$ [human]/ $p19^{ARF}$[mouse]): A GTP-binding protein of the monomeric Raf family of G proteins involved in the transport between the endoplasmic reticulum and the Golgi apparatus and within the Golgi complex. The ARF alters the membrane lipid composition. It is also required for the physiological effect of cholera and pertussis toxins. p^{ARF} regulates tumor suppressors p53 and RB through the E2F-1 transcription factor. A novel nuclear protein NIAM (nuclear interactor of ARF and MDM2 binds both the ARF and the p53 antagonist MDM2). NIAM protein is normally expressed at low to undetectable levels in cells partly because of, MDM2-mediated ubiquitination and proteasomal degradation. When reintroduced into cells, NIAM activated p53, caused a G1 phase cell cycle arrest, and collaborated with the ARF in an additive fashion to suppress proliferation. Notably, NIAM retains growth inhibitory activity in cells lacking ARF and/or p53, and knockdown experiments revealed that it is not essential for ARF-mediated growth inhibition. Thus, NIAM and ARF act in separate anti-proliferative pathways that intersect mechanistically and suppress growth more effectively when jointly activated. Intriguingly, silencing of *NIAM* accelerated chromosomal instability, and microarray analyses revealed reduced *NIAM* mRNA expression in numerous primary human tumors (Tompkins VS et al 2007 J Biol Chem 282:1322).

When c-Myc oncoprotein level increases, the ARF blocks c-Myc and its ability to induce hyperproliferation. Also, the ARF does not affect the transcription of Myc and enhances apoptosis independently from p53 (Qi Y et al 2004 Nature [Lond] 431:712). The short mitochondrial form of $p19^{ARF}$ induces autophagy and caspase-independent cell death (Reef S et al Mol Cell 22:463). The ARF is turned on by Sec7 guanine nucleotide exchange factor domain proteins, which are inhibited by brefeldin. ►signal transduction, ►cholera toxin, ►pertussis toxin, ►GTPase, ►SecA, ►SecB, ►translocase, ►translocon, ►ARNO, ►Golgi, ►G proteins, ►raf, ►tumor suppressor, ►p53, ►retinoblastoma, ►E2F1, ►$p16^{INK4}$, ►guanine nucleotide exchange factor, ►brefeldin, ►cytohesins, ►MDM2, ►Myc, ►Sirtuin, ►RNAS polymerase III, ►Pokemon, ►MDM2, ►ABA; Sherr CJ 1998 Genes Dev 12:2984; Randle DH et al 2001 Proc Natl Acad Sci USA 98:9654.

ARF1: A GTPase protein activating phospholipase D. It is activated by PtdIns (phosphatidyl inositol), and participates in the recruitment of coatomer and trans-Golgi network (TGN) clathrin. ►coatomer, ►phosphoinositols, ►trans-Golgi network, ►clathrin, ►GEF, ►Sec, ►Ypt, ►COP ►transport ►vehicles

ARF1 (auxin response factor): Modulates the action of auxin response elements (AuxRE, TGTCTC) in combination with transcription factors. auxins, ►plant ►hormones

Arfaptin: An adaptor mediating cross-talk between the ARF and small G-proteins Rac, RHO and RAS in signal transduction. signal ►transduction, ►ARF, ►cross-►talk, ►G-proteins; Peters PJ et al 2002 Nature Cell Biol 4:240.

ARG: An oncogene related to ABL in human chromosome 1q24-q25 and in mouse chromosome 1. It encodes a tyrosine kinase, different from that of the ABL product. ►oncogenes, ►ABL

Arg: Abbreviation for arginine.

Arginase: ►argininemia

Arginine (2-amino-5-guanidinovaleric acid): A positively-charged essential amino acid. Arginine methylation and demethylation play an important role in the regulation of gene expression. ►urea cycle, ►nucleosome, ►nuclear receptors; Lee Y-H et al 2005 Proc Natl Acad Sci USA 102:3611.

Argininemia (hyperargininemia): The accumulation of high levels of arginine in the blood and urine caused by autosomal recessive arginase deficiency (ARG1 and ARG2 genes). ARG1 (6q23) coded enzyme represents 98% of the arginase activity in the liver and its deficiencies the common argininemia. Arginine accumulates in the blood because it is not degraded. It is a relatively rare disease. Treatment with benzoate and restriction of arginine intake may ameliorate the condition. Shope virus infection may restore arginase activity in the cells. ►amino acid metabolism, ►citrullinemia, ►citrullinuria, ►urea cycle

Argininosuccinic Aciduria: A rare hereditary disorder (human chromosome 7cen-q11.2) involving mental retardation, seizures, hepatomegaly (enlargement of the liver that may become cancerous), intermittent ataxia, brittle and tufted hair, and accumulation of large quantities of arginosuccinic acid (an intermediate in the arginine-citrulline [urea] cycle) in the blood, urine, and the cerebrospinal (brain and spinal cord) fluid. Early and late onset types have been distinguished. The basic defect is arginosuccinase or arginosuccinate lyase deficiency. ►urea cycle

Arginyl tRNA Synthetase: The enzyme that charges the appropriate tRNA with arginine. The encoding gene was located to human chromosome 5. ►aminoacyl tRNA synthetase

Argon Dating: Potassium (^{40}K) decays to argon (^{40}Ar) with a half-life of about 1.25 million years. The gaseous Ar is trapped in the volcanic rocks after it is formed but expelled from the molten lava before the eruption because of the intense heat. Thus, the amount of ^{40}Ar indicates the time elapsed since the volcanic deposits were formed. If any relics (e.g., human bones) are found in the layers, their age can be inferred by potassium-argon dating of the rocks in case the time exceeds the limits of carbon dating. ►radio carbon dating

Argonaute (AGO): Exists in different forms. The enzyme agonaute-2 mediates the degradation of mRNA in response to interfering dsRNA (Liu J et al 2004 Science 305:1437). This protein may also function downstream of Dicer or RNA-dependent RNA polymerase in gene silencing in eukaryotes and probably in prokaryotes. AGO mediates through siRNA the dimethylation of histone H3 lysine 9 (H3K9me2) and RNA-dependent RNA polymerase complexes (Irvine DV et al 2006 Science 313:1134). ►RNAi, ►piRNA, ►PAZ, ►RISC, ►Dicer, ►miRNP, ►rasiRNA, ►RNA-directed DNA methylation; Williams RW, Rubin GM 2002 Proc Natl Acad Sci USA 99:6889; Martinez J et al 2002 Cell 110:563; Kidner CA, Martiensen RA 2004 Nature [Lond] 428:81, crystal structure: Song J-J et al 2004 Science 305:1434; minireview: Tanaka Hall TM 2005 Structure 13:1403; mammalian miRNA: http://www.ma.uni-heidelberg.de/apps/zmf/argonaute/interface/.

Argos: A secreted *Drosophila* protein containing a single EGF motif. It is a repressor of eye and wing determination and it acts against *Spitz*. ►*Spitz*, ►DER, ►EGF; Klein DE et al 2004 Nature [Lond] 430:1040.

Argosomes: Epithelial membrane vesicles that are capable of moving cargo between cells. Greco V et al 2001 Cell 106:633.

Argyrophilic Grains: May accumulate in the brain in some dementias; they are stained by bound silver salts, reduced by light or reducing compounds and appear black in post-mortem study.

Arias Syndrome: Probably the same as Gilbert syndrome or Crigler-Najjar syndrome II.

Arithmetic Mean: $\overline{x} = \frac{\Sigma x}{N}$ is the sum of all measurements (x) divided by the number of measurements (N). ►mean

Arithmetic Progression: A series with elements increasing by the same quantity, e.g., 1, 3, 5, 7, 9. ►geometric progression

ARKβ: β-adrenergic receptor, also called GRK2. ►adrenergic receptor, ►GRK1

Arlequin: A software for the analysis of population genetics data (http://anthro.unige.ch/software/arlequin/).

Arm Ratio: The relative length of the two arms of a eukaryotic nuclear chromosome. ►chromosome arm, ►chromosome morphology

Armadillo: *Euphractus sexcinctus* 2n = 58; *Dasypus novemcinctus* 2n = 64; *Cabassous centralis* 2n = 62; *Chaetophractus villosus* 2n = 60.

Armadillo (arm, 1–1.2): *Homozygosity* of the recessive allele is lethal. The normal allele of *Drosophila* is involved in embryonic differentiation in connection with other genes. Its vertebrate homolog encodes β-catenin. It is positively regulated by *Wg* (*wingless*) and down-regulated by axin. ►morphogenesis in *Drosophila*, ►*wnt*, ►axin

Armitage-Doll Model: Interprets carcinogenesis as a multistage process developed by a series of subsequent mutations. ►Knudson's two-mutation theory, ►Moolgavkar-Venzon model

ARMS (amplification refractory mutation system): Along with PCR, it may detect the strand that contains a known mutation or identify polymorphism of a particular DNA stretch. Two sets of primers are used for amplification and one of the primers has a difference at the site of the suspected mutation. The different nucleotide is inserted at the 3′ end of the primers and extension of the strands follows. However, the penultimate base frequently leads to a mismatch in both mutant and wild type primers and may be difficult to find a primer suitable to obtain a sequence-specific amplification. ►PCR, ►primer, ►primer ►extension, ►mutation ►detection; Chiu RW et al 2001 Clin Chem 47:667; Carrera P et al 2001 Methods Mol Biol 163:95.

Arms of Bacteriophage λ: When the stuffer segment is removed a left and a right segment (arms) of the genome remains and these are used for vector construction. ►stuffer DNA, ►lambda phage

aRNA: Ancient RNA. ►ancient organisms, ►ancient DNA

ARNO (ARF nucleotide binding site opener): A 399 amino acid human protein involved in the GDP⇆DGTP exchange of ARF. This and similar proteins contain an amino-terminal coiled coil, a central secretory protein domain (Sec) and a C-terminal pleckstrin domain. It is a homolog of the yeast Gea1, and both are inhibited by brefeldin. ►ARF, ►GTP, ►pleckstrin, ►brefeldin, ►endocytosis

Arnold-Chiari Malformation: Multifactorial recessive brain anomaly. The brain stem is herniated into the foramen magnum (interconnecting the brain and

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the vertebral column) resulting in hydrocephalus and anencephalus as well. ►anencephaly, ►hydrocephalus

ARNT (arylhydrocarbon-receptor nuclear translocator): A helix-loop-helix heterodimeric transcription factor with the AHR and other receptors mediating the metabolism of xenobiotics. ►aryl hydrocarbon receptor, ►xenobiotics, ►helix-loop-helix

Aromatase (ARO): A ~500 amino acid cytochrome 450 (CYP19) protein (estrogen synthetase) converting C19 androgen into C18 estrogen. It is encoded at human chromosome 15q21.1. It is present in the skin, muscle, fat, ovary, placental and nerve tissues. Its deficiency in females causes virility and pseudohermaphroditism and lowered fertility in male mice. An excess of it in human males may cause gynecomastia. ►estradiol, ►steroid hormones, ►gynecomastia, ►pseudohermaphroditism

Aromatic Molecule: A closed ring molecule with C in the ring, linked by alternating single and double bonds; they are frequently conjugated with other compounds.

ARP (autonomously replicating pieces): ►macronucleus

ARP2/3 Complex (actin-related protein complex): An actin assembly complex involved in the movement of cells and mitochondria during cell division and budding of yeast. It appears to be involved in regulating cell shape (Mathur J et al 2003 Development 130:3137). Arp4 is found in large multisubunits of the INO80 and SWR1 chromatin remodeling complexes, in the NuA4 histone acetyltransferase complex and in the assembly of the kinetochore (Ogiwara H et al 2007 Nucleic Acids Res 35:3109). ►actin; Robinson RC et al 2001 Science 294:1679; Cooper JA et al 2001 Cell 107:703.

ARPKD: ►renal-hepatic-pancreatic kidney disease, ►polycystic kidney disease

Array [V80] Hybridization: This is designed to identify single (or a small number) of nucleotide changes in genomic DNA. The procedure requires a large array of oligonucleotide probes, which are obtained by light-directed parallel chemical synthesis. Using in each oligonucleotide set four probes, which differ only in one of the four bases, A, T, G, C, whereas the flanking bases are kept identical. The complementary synthetic probes then query each sequence of the target:

The single-base different hybridization probes are distinguished on the basis of the signals provided by the differences in the fluorescence labels and hybridization intensities of the probes. The procedure also permits the identification of more than one base and deletions. A confocal device can thus scan an entire genome and its great merit lies in its rapidity (see Fig. A121). ►light-directed parallel synthesis, ►DNA chips, ►microarray hybridization; Chee M et al 1996 Science 274:610.

Figure A121. Array hybridization

Arrayed Library: Cloned DNA sequences are arranged on two-dimensional microtiter plates where they can be readily identified by row and column specifications. ►DNA library, ►microarray

Arrayed Primer Extension (APEX): An array of oligonucleotide primers is immobilized by their 5′-end on a glass surface. The DNA is amplified by PCR, digested enzymatically and annealed to the immobilized primers. A template-dependent DNA polymerase extends the sequence using fluorescent-labeled dideoxynucleotides. Mutation is revealed by a change in the color code of the primer sites. The procedure is suited for analysis of DNA polymorphism. ►primer, ►PCR, ►dideoxynucleotide; Kurg A et al 2000 Genet Test 4:1.

Arrest, Transcriptional: Transcription is stopped because the supply of one or more types of nucleotides has run out or even due to protein factors. It can usually be restarted by the missing building block. T-rich sequences in the non-template DNA strand are frequently liable for the arrest. Genes like *LexA*, *lac* repressor, CAAT-box-binding and other binding proteins may block or impede transcription. In some instances the RNA polymerase may either bypass or remove the binding proteins in its way. The nucleosomal structure may not interfere with transcription although in some cases it may retard it. The degree of interference may depend on the dissociation of the protein. Strong positive or negative supercoiling of the DNA may impede RNA elongation. Some RNA polymerases may transcribe through the gaps of a few nucleotides but the transcript will have deletions. ►pause transcriptional, ►*lexA*, ►*lac* operon, ►nucleosome, ►supercoiled DNA, ►RNA polymerase

Arrestin: A 45-kDa phosphoprotein which regulates the phototransduction and β_2 adrenergic pathways (by non-visual arrestins) in animals. It is dephosphorylated when it interacts with the trimeric

G-protein-coupled signal receptor. It may serve as a deactivator of G protein-mediated signaling path by binding to the SH^3 domain of the cellular Src molecules. Arrestin may also recruit clathrin to the receptor complex, resulting in the internalization of the complex into clathrin-coated pits. In such a situation it may stimulate cross-talk with the MAP kinase pathway. β-Arrestin 2 acts as a scaffold and transducers for seven-membrane spanning receptors and can regulate development through the *Hedgehog–Smoothened* pathway (Wilbanks AM et al 2004 Science 306:2264). Sinophilin antagonizes most of the arrestin functions (Wang Q et al 2004 Science 304:1940). ►phototransduction, ►signal transduction, ►desensitization, ►adrenergic receptor, ►PDZ, ►Src, ►cross-talk, ►clathrin, ►cargo receptors, ►*hedgehog*, ►seven-membrane protein, ►endocytosis, ►MAP, ►retinal dystrophy, ►dopamine, ►Oguchi disease, ►adaptin, ►AP180; Krupnick JG, Benovic JL 1998 Annu Rev Pharmacol Toxicol 38:289; Lefkowitz RJ, Shenoy SK 2005 Science 308:512.

Arrhenotoky: A mechanism of sex determination. The males are haploid and the females are diploid for the sex genes (as in bees and wasps). The males develop from unfertilized eggs (a form of parthenogenesis) and display one or the other allele(s) for what the diploid females (queens) are heterozygous for. The homozygous diploid males are either sterile or lethal or destroyed by the workers in the colony. This type of sex determination is seen in nearly 20% of animals (mites, white flies, scale insects, thrips, rotifera, etc.) ►chromosomal sex determination, ►sex determination, ►complementary sex determination, ►wasp; Cowan DP, Stahlhut JK 2004 Proc Natl Acad Sci USA 101:10374.

Arrhythmia, Cardiac: ►LQT

Arrowsmith: A computer tool for identifying the links between MedLine articles. http://arrowsmith.psych.uic.edu/arrowsmith_uic/index.html.

Arrythmogenic Right Ventricular Cardiomyopathy (RVD): Eight different dominant and one recessive (17q21) forms of the disease, involving degeneration of the myocardium (heart muscles), followed by fibrous-fatty replacement have been described. ARVD1 (14q24.3), ARVD22 (1q42), ARVD3 (14q11-q12), ARVD4 (2q32), ARVD5 (3p23), ARVD6 (10p12-p14), ARVD7 (10q22) and ARVD8 (6p24) are the known dominant mutations. In mice, mutation of a laminin receptor gene (*Lamr1*) contained in an intron-free retroposon caused RVD. The transposon may move to different chromosomes. The gene product was bound to the heterochromatin protein HP1. HP1 is a regulator of heterochromatin sites and LAMR1 protein apparently caused the degeneration of cardiomyocytes (Asano Y et al 2004 Nature Genet 36:123). cardiomyopathy, ►heart disease, ►long QT syndrome, ►laminin; Rampazzo A et al 2002 Am J Hum Genet 71:1200.

ARS (autonomously replicating sequences): These are nearly 100 bp long origins of replication of yeast chromosomal DNAs. The different ARS sequences share a consensus of 11 base pairs (5′-[A/T]TTTAT[A/G]TTT[A/G]-3′), and there are some additional elements around it that vary in the different chromosomes from where they were derived. ARS1 contains subdomains A, B1 that are recognized by ORC. Subdomain B2 unwinds DNA, and B3 is where ABF1 binding factor is attached. Artificial yeast plasmids must contain ARS sequences to be maintained and they may remain stable as long as selective pressure exists for their maintenance, i.e., they carry essential genes for the survival of the yeast cell (missing from or inactive in the yeast nucleus). ARS elements occur also in organellar and other DNAs. ►YAC, ►yeast vectors, ►DUE, ►cell cycle, ►ORC, ►MCM, ►Abf; Marilley M 2000 Mol Gen Genet 263:854.

Arsenic (As^{3+} or As^{5+}): Refers to common contaminants produced by burning coal and glass manufacturing which are serious environmental poison (in impure drinking water) and human carcinogen (although not for rodents) (see Fig. A122). It may cause chromosomal deletions in rodents and humans by the generation of oxyradicals. Arsenic trioxide (As_2O_3) is an activator of the MAP kinases. Chronic arsenic poisoning may cause melanotic spots on the palm. Arsenic chaperone, ArsD, is encoded by the *arsRDABC* operon of *Escherichia coli* and it transfers trivalent metalloids to ArsA, the catalytic subunit of an As(III)/Sb(III) efflux pump. Interaction with ArsD increases the affinity of ArsA for arsenite, thus increasing its ATPase activity at lower concentrations of arsenite and enhancing the rate of arsenite efflux. Cells thus become resistant to environmental concentrations of arsenic and toxicity (Lin Y-F et al 2006 Proc Natl Acad Sci USA 103: 15617). Arsenic trioxide is an anticancer agent (Lu J et al 2007 Proc Natl Acad Sci USA 104:12288). ►MAP, ►soil remediation; Basu A et al 2001 Mutation Res 488:171; Oremland RS, Stolz JF 2003 Science 300:939; Croal LR et al 2004 Annu Rev Genet 38:175.

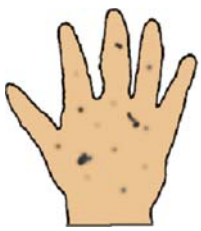

Figure A122. Arsenic spots

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ART (assisted reproductive technology): This may benefit about 15% of infertile couples. Various techniques are available to assist in conception. Although most of these technologies appear safe, some concerns have been raised (Powell K 2003 Nature [Lond] 422:656). More recent evidence, however, indicates that the concerns are unwarranted and the offspring from intracytoplasmic sperm injection does not suffer any detectable harm (see Fig. A123) (Rosenwaks Z, Bendikson K 2007 Proc Natl Acad Sci USA 104:5709). ►artificial insemination, ►intrauterine insemination, ►in vitro fertilization, ►ROSI, ►oocyte donation, ►GIFT, ►intrafallopian transfer of gamete and zygote, ►surrogate mother, ►sperm bank, ►insemination by donor, ►preimplantation, ►genetics [►PGD], ►sex selection, ►micromanipulation of the oocyte, ►ICSI, ►IUGTE, ►counseling genetic; Baritt JA et al 2001 Human Reprod 16:513; Trounson A, Gardner D (eds) 2000 Handbook of In Vitro Fertilization. CRC Press, Boca Raton, Florida.

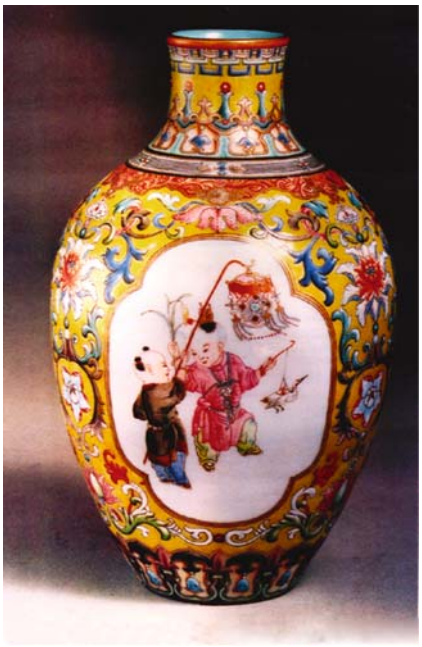

Figure A123. Qing dynasty enameled porcelain

Art in Science: Artworks and ancient relics provide much information about anthropology, evolution of species, diseases and technology. ►Lascaux, ►mammoth, ►body mass index in humans, ►inbreeding depression, ►Toulouse Lautrec, ►depression, ►chimera, ►gynecomastia, ►Native Americans, ►Van Gogh, ►Poliovirus, ►obesity, ►gout, ►musical ►talent, ►Mondrian

Artemis: A single-strand-specific 5′→3′ exonuclease, which upon activation by a protein kinase (DNA-PK_{CS}) gains endonuclease function for 5′ and 3′ overhangs and hairpins. Its mutations render DNA hypersensitive to double-strand breaks and the loss of B and T lymphocytes results in severe combined immune deficiency. This exonuclease is required along with ATM and other proteins for the repair of radiation-induced double-strand breaks (Riballo E et al. 2004 Mol Cell 16:715). ARTEMIS is also required for plant cell and chloroplast division. ►ATM, ►endonuclease, ►exonuclease, ►lymphocyte, ►severe combined immunodeficiency, V(D)J; Ma Y et al 2002 Cell 108:781; Fulgosi H et al 2002 Proc Natl Acad Sci USA 99:11501.

Artemis: DNA sequence viewer and annotation tool. ►ACT; http://www.sanger.ac.uk/Software/Artemis.

Arterial Calcification of Infancy (occlusive infantile calcification, 6q dominant): Calcification of the internal lamina of the arteria due to defective ectonucleotide pyrophosphatase/phosphodiesterase 1. Normally the pyrophosphate generated by the enzyme prevents calcification. Rutsch F et al 2003 Nature Genet 34:379.

Arterial Tortuosity Syndrome (20q13.1): A disease of the arterial wall due to disruption of the elastic fibers which produces twists, elongation and aneurysm (sac formation). In one of the genes (SLC2A10), glucose transporter (GLUT10) deficiency upregulated TGF-β (Coucke PJ et al 2006 Nature Genet 38:452). ►Loeys-Dietz syndrome, ►Marfan syndrome

Arteriosclerosis: This refers to thickening and hardening of the walls of arterial veins, a common form of heart disease. ►atherosclerosis

Arthritis: An inflammation and erosion of the major component (aggrecan) of cartilage in the joints is caused by several factors with incomplete penetrance and expressivity. It is a common occurrence in familial gout, a hyperuricemia (excessive uric acid production). Rheumatoid arthritis is generally described as an autoimmune disease. About one- third of the cases involve the HLA-DRB1 *04 alleles in the presence of this condition. The telomeres in $CD4^+$ T lymphocytes are eroded during the first two decades of life followed by reduced homeostasis in T cell proliferation later (Schönland SO et al 2003 Proc Natl Acad Sci USA 100:13471). It appears to be autosomal dominant but the genetic control is not entirely clear. The erosion is mediated by aggrecanase (a metalloproteinase with thrombospondin, glycoprotein secreted by the endothelium). ADAMTS5 (a disintegrin and metalloprotease with thrombospondin-like repeats) destroys aggrecan, and its knockout is a promising therapeutic measure

for arthritis in mouse (Glasson SS et al. 2005 Nature [Lond] 434:644; Stanton H et al 2005 Nature [Lond] 434:648). IL-6, IL-8, GM-CSF promote inflammation whereas IL-10, IL-1ra, soluble TNF-R reduce inflammation in rheumatoid arthritis. Anti-TNF-α antibody treatment may offer some promise. In some forms the basic problem is that the lymphocytes target the cell's glucose-6-phosphate isomerase. Its prevalence is about 1% in the general population. ►rheumatic arthritis, ►arthropathy, ►arthropathy-►camptodactyly, ►connective tissue disorders, ►cartilage, ►TNF, ►IFN, ►IL, ►NF-κB, ►*Borrelia*, ►metalloproteinase, ►ADAM, ►osteoarthritis, ►IL-6, ►IL-8, ►IL-►10, ►IL-►1, ►IL-17, ►GM-CSF, ►TNF-R, ►ZAP-70, ►telomeres, ►T cell; Ota M et al 2001 Genomics 71:263; Feldmann M, Maini RN 2001 Annu Rev Immunol 19:163; Firestein GS 2003 Nature [Lond] 423:356.

Arthroconidiation: A process of fungal conidiation involving germination of conidia, forming hyphae with coupled septation and nuclear division. ►conidia, ►hypha, ►septate

Arthrogryposis: There is unclear (autosomal) genetic determination of this malformation of low recurrence which causes deformation of limbs, hip dislocation, scoliosis (crooked spine), frequently short stature, amyoplasia (poor muscle formation), etc. Distal arthrogryposis (DA1, 9p13.2-p13.1, 9p21-q21) is responsible for dominant club foot and encodes tropomyosin. The DA2B locus (11p15.5) encodes a mutant isoform of troponin (Sung SS et al 2003 Am J Hum Genet 72:681). A neurogenic type is in chromosome 5q35; it is a non-progressive multiple joint contracture disease that is not lethal. *Arthrogryposis–renal dysfunction–cholestasis syndrome* is caused by *VPS33B* mutations, in chromosome 15q26 is neurogenic, with renal tubular dysfunction and neonatal cholestasis that leads to death during the first year of life. X-linked forms have also been described. Severe forms are the *lethal congenital contractural syndrome* (LCCS) in 9q34, 12q13 and 19p13; it is likely that they involve mutation in PIP5K1C encoding phosphatidylinositol-4-phosphate 5-kinase, type I, gamma (PIPKI), an enzyme that phosphorylates phosphatidylinositol 4-phosphate to generate phosphatidylinositol-4,5-bisphosphate, PIP_2 (Narkis G et al 2007 Am J Hum Genet 81:530). *Lethal congenital contractural syndrome type 2* (LCCS2, 12q13) is an autosomal recessive neurogenic form of arthrogryposis that is associated with atrophy of the anterior horn of the spinal cord (Narkis G et al 2007 Am J Hum Genet 81:589). ►limb defects, ►connective tissue disorders, ►Freeman-Sheldon syndrome, ►clubfoot, ►tropomyosin, ►troponin, ►phosphoinositides

Arthroophtalmopathy: ►Stickler syndrome

Arthropod: An invertebrate animal with a segmented body like insects, spiders, crustaceans, etc.

Arthropathy: Any disease that affects the joints.

Arthropathy-Camptodactyly (synovitis): This is based on autosomal recessive inheritance. It involves inflammation of the joints (synovial membranes) resembling arthritis. It may have an onset in early childhood. ►connective tissue disorders

Arthus Reaction: An inflammatory immunological reaction to antigen introduced into sensitized animals. The lesion causes activation of the complement and the large number of infiltrating neutrophils release lysosomal enzymes that lead to tissue destruction. ►antigen, ►antibody, ►immune response, ►complement, ►neutrophil, ►lysosomes

Artichoke *(Cynara scolymus):* Vegetable crop; 2n = 2x = 34.

Artifact: Refers to something that is man-made or a result of human handling of the object, rather than due to entirely natural causes.

Artificial Chromosome: ►YAC, ►BAC, ►PAC, ►human artificial chromosome

Artificial Insemination: This method may be used to overcome the consequences of male infertility in humans or to obtain a larger number of offspring of male animals with economically desirable characters and high productivity. Generally, the sperm is obtained from sperm banks where the semen is preserved at very low temperatures. The cryopreservation may protect against sexually transmitted disease. ►sperm bank, ►ART, ►intrauterine insemination, ►surrogate mother, ►AID, ►AIH, ►ART, ►bioethics

Artificial Intelligence: A device (computer) with the ability to function similarly to human intelligence, i.e., capability of learning, reasoning and self-improvement. ►robot scientist

Artificial Seed (synthetic seed): This is formed usually from somatic embryos that are enclosed by a Na-alginate (polymer of mixed mannuronic and glucuronic acids) capsule in the presence of a calcium salt ($CaNO_3$ or $CaCl_2$). Within the capsule an "artificial endosperm" of nutrients may be included. Partially dehydrated embryos may also be used as artificial seed. Artificial seeds may be used for studying the physiology of such constructs and also for micropropagation of some plants. ►micropropagation

Artificial Selection: This process may alter the structure of the population in a way similar to natural selection. When the selection is relaxed or reversed due to

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genetic homeostasis the selection may still be effective for various traits (e.g., bristle number in *Drosophila*, oil or protein content in plants, etc.) that are under polygenic control (see Fig. A124). ►selection, ►selection conditions, ►selection index, ►gain, ►homeostasis

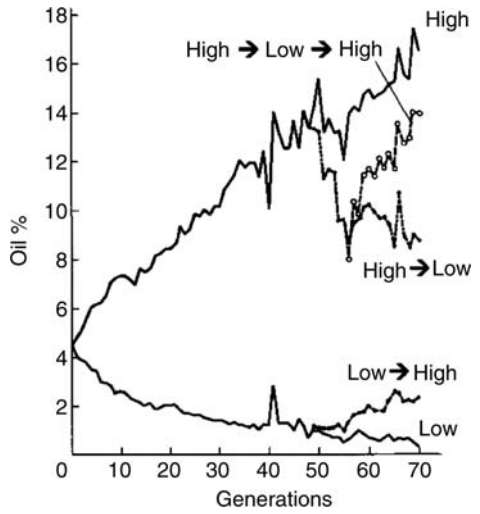

Figure A124. Artificial selection. Selection and reversed selection of oil content in maize. (After Dudley JW (1973) Rep. 28th Annu. Corn Sorghum Res. Conf. Am. Seed Trade Asssoc. Washington, DC, p. 126)

Arts Syndrome: ►ataxia

Arylesterase (ESA, paraoxonase): Encoded in human chromosome 7q22, this enzyme breaks down parathion and related insecticides. ►cholinesterase, ►pseudocholinesterase

Aryl Hydrocarbon Receptor (ARH): Mediates the carcinogenic and teratogenic, immunosuppressive, etc. responses to arylhydrocarbons present in many environmental toxins (dioxin, benzo(a)pyrene, cigarette smoke, polychlorinated and polybrominated biphenyls, etc.). ARH regulated genes include cytochromes P450, uridine diphosphate-glucuronosyl transferase, growth factors and proteins. In yeast 54/4507 genes examined modify the ARH signal transduction in five modules involving receptor folding, nuclear translocation, transcriptional activation, receptor level and the PAS complex. (Yao G et al 2004 PloS Biol 2:355). ►ARNT, ►PAS, ►genetic networks, ►networks, ►items under separate entries

Arylsulfates: These are aromatic molecules with bound sulfate. Arylsulfatases deficiency is observed in the lipidosis group of diseases, collectively designated as metachromatic leukodystrophy. ►lipidoses, ►Krabbe's leukodystrophy, ►metachromatic leukodystrophy

α-Satellite DNA This refers to centromeric repetitive DNA. ►repetitious DNA, ►satellite DNA

AS: ►asparagine synthetase

AS ODN (antisense oligodeoxynucleotide): This may bind oncogene mRNA and may inhibit cancer growth and regulate the formation of megakaryocytes. It may be used in gene therapy. ►antisense technologies, ►cytofectin, ►megakaryocytes, ►gene therapy, ►cancer gene therapy

ASAP: Cell adhesion molecule of the ARF family of proteins. ASAP1 is a regulator of protein sorting though membranes, it activates GTPase and regulates the cytoskeleton. ►ARF, ►protein sorting, ►cytoskeleton, ►polycystic kidney disease

ASAP: Aster associated protein binds microtubules at the COOH end. Over manifestation or under manifestation of ASAP results in aberrant spindle, delays in mitotic progression and causes cell death because of defects in cytokinesis (Saffin J-M et al 2005 Proc Natl Acad Sci USA 102:11302). ►aster, ►spindle, ►cytokinesis

Asbestos: Mineral silicate fibers are carcinogenic supposedly by being phagocytized and then accumulate around the cell nucleus where they may interfere with chromosome segregation. The mechanical irritation may contribute to mesothelial (lung) cancer. The cells with asbestos release TNF-α and other cytokines. In vitro, asbestos is lethal to mesothelial cells. The treatment of human mesothelial cells with TNF-α considerably reduces toxicity by activating the NF-κB signaling pathway thereby constituting a potential therapy for asbestos damage (Yang H et al 2006 Proc Natl Acad Sci USA 103:10397). ►TNS, ►NF-κB; Tweedale G 2002 Nature Rev Cancer 2:311.

Ascaris megalocephala (horse threadworm): It shows very unusual chromosome behavior (see Fig. A125). It has only one pair of large chromosomes in the germline but during somatic cell divisions these large chromosomes are fragmented into numerous small chromosomes. On the basis of this organism Van Beneden discovered in (1883) reductional division in meiosis, a cornerstone of the cytological basis of Mendelian segregation.

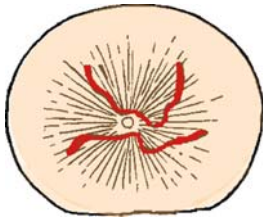

Figure A125. *Ascaris megalocephala univalens*. (Boveri, T.)

A. megalocephala univalens has 2n = 2, *A. megalocephala bivalens* 2n = 4, and *A. lumbricoides* 2n = 43 chromosomes. ►chromosome breakage programmed

Ascertainment Test: This is generally required in larger mammals with few offspring to determine the segregation ratios on the basis of pooled data of several families. The problem involved in biased sampling (because those families where the parents are heterozygous for the recessive gene escape identification if no homozygotes are observed among the progeny) can be corrected for. The solution is mathematical. According to Mendelian expectation, 3/4 of single-child families has no affected children. Among the two-child families $(3/4)^2 = 9/16$ is the probability that neither will be of recessive phenotype. Of the remaining 7/16 of the families, 6/7 will have one recessive and one dominant and 1/7 should have 2 recessives. Thus, the average expectation is (1)×(6/7) + (2)×(1/7) = 8/7 = 1.143. In three-child families 27/64 will have no affected offspring, 9/37 will have 2, and 1/37 are expected to have 3 recessives. Therefore, the average expected is (1)×(27/37) + (2)×(9/37) + (3)×(1/37) = 1.294. In the same manner the average expectation of recessives for various sizes of families can be determined (see Table A5):

Using this information the number of observed and expected data for affected and unaffected families of varying sizes can be analyzed with the chi square procedure and the goodness of fit can be evaluated:

$$\chi^2 = \frac{(25 - 26.9)^2}{26.9} + \frac{(24 - 22.1)^2}{22.1} = 0.298;$$

The degree of freedom = 1, and the probability of fit is >0.5 (for χ^2 only, values below 0.05 would have some ground for doubting the fit). A simpler (and less reliable) procedure for determining the average number of recessives $(\widehat{q})$

$$\widehat{q} = \frac{R - N}{T - N}$$

where R is the number of recessive segregants observed, N is the number of families showing recessives, and T is the total number of children of these families.

The *ascertainment bias* (the correction for truncated/ incomplete selection of families on the basis of probands) can also be estimated by the Bernstein formula: Expected number of affected recessives $E_r = sn_s(p/1 - q^s)$ where s = number of sibs per family, n_s = number of families with s number of sibs, p = segregation ratio, $q = 1 - p$. The results of the ascertainment may not be valid for populations which were not part of the samplings in complex cases. Using DNA sequence information the ascertainment bias may be eliminated because penetrance or expressivity does not affect the correct molecular information. ►chi square, ►sib, ►proband, ►penetrance, ►expressivity, ►segregation ratio; Burton PR et al 2000 Am J Hum Genet 67:1505; Lake SL et al 2000 Am J Hum Genet 67:1515; Haghighi F, Hodge SE 2002 Am J Hum Genet 70:142; Epstein MP et al 2002 Am J Hum Genet 70:886.

Aschheim-Zondek Test (AZT): Uses subcutaneous injection of the urine of human females into immature female mice to test for early pregnancy. Swelling, congestion and hemorrhages of the ovaries and precocious maturation of the follicles in the mice are positive indicators of pregnancy of the tested person. Today, a hemagglutination test or a chorionic gonadotropin test is used. Pregnancy immediately

Table A5. Ascertainment test

Number of Children	1	2	3	4	5	6	7	8
Average Homozygotes	1.000	1.143	1.297	1.463	1.639	1.825	2.020	2.223

Number of Sibs/Family	Families	Number of Affected Sibs		Number of Unaffected Sibs	
		Observed	Expected	Expected	Observed
1	7	7	7×1 = 7.00	0	0
2	10	8	10×1.143 = 11.43	12	8.57
3	4	6	4×1.297 = 5.19	6	6.81
5	2	4	2×1.639 = 3.28	6	6.72
	Total 25		26.90	24	22.10

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raises dramatically the level of this hormone. ►hemagglutinin, ►gonadotropin

Asci: Is the plural of ascus. ►ascus

Ascidians: Invertebrate (chordate) sea animals with sexual and asexual reproduction. ►*Ciona intestinalis*; Davidson B, Christiaen L 2006 Cell 124:247, http://www.ascidians.com/; http://crfb.univ-mrs.fr/aniseed/index.php.

Ascites: In this condition the abdominal fluid (may contain also cells) is excreted in response to cell proliferation in the abdominal cavity because of a neoplasia. The fluid is serum, containing polyclonal antibodies. Cirrhosis or hypoalbuminemia, and experimental injections may also cause ascites. ►cirrhosis of the liver, ►albumin

Ascobolus: This fungal genus is advantageously exploited for tetrad analysis. ►tetrad analysis

Ascobolus immersus: An ascomycete where the dissection of the ascospores is very simple, the spores spring off when touched and can be captured on microscope slides. This fungus has been extensively used in studies of recombination and gene conversion; x = 12, 16, 18.

Ascocarps: Refer to those sites in fungi where the perithecia and apothecia (fruiting bodies) develop.

Ascogenous Hyphae: These diploid or bikaryotic hyphae lead to the formation of fruiting bodies in fungi. ►fruiting body, ►hypha

Ascogonium: This refers to the gametangium (oogonium), the female sexual organ of fungi (also called protoperithecium).

Ascomycete: A large group of different fungi producing either asexual conidiospores and/or ascospores within asci as a consequence of meiosis. ►tetrad analysis

Ascorbic Acid (vitamin C): This anti-scurvy (antiscorbutic) substance is required for proper hydroxylation of collagen and its deficiency causes skin lesions and damages the blood vessels, i.e., symptoms of scurvy. It is also a reducing compound and upon oxidation it is converted into dehydroascorbic acid (see Fig. A126). Together with Fe(II) and O_2 it is a hydroxylating agent for aromatics. In the process H_2O_2 is formed. It has been claimed that high daily doses of ascorbic acid lower the risks of common cold and other ailments. Further, it has been found to be weakly mutagenic, probably because of its ability to generate free radicals. Most primates and guinea pigs cannot synthesize this vitamin because of numerous alterations in the gene (human chromosome 8p21) encoding L-gluconolactone oxidase and depend on dietary supplies (Nishikimi M et al 1994 J Biol Chem 269:13685). There is a need for an ascorbic acid transporter SLC23a1 (Sotiriou S et al 2002 Nature Med 8:514). The biosynthetic pathway in plants differs from that in animals, algae or fungi. Over expression of a NADPH-dependent D-galacturonate reductase may substantially increase ascorbate production in plants (Agius F et al 2003 Nature Biotechnol 21:177). Vitamin C degradation in plant material can take place enzymatically (via hydrolysis of 4-oxalyl-L-threonate) or during cooking (Green MA, Fry SC 2005 Nature [Lond] 433:83). The therapeutic applications of ascorbate against flu or cancer are controversial although high intravenous doses may have anticancer effects because of H_2O_2 effects (Chen Q et al 2005 Proc Natl Acad Sci USA 102:23604). In the presence of ascorbate low 0.2–2 μM doses of chromate caused 10–15 times more chromosomal breakage in primary human bronchial epithelial cells or lung fibroblasts (Reynolds M et al 2007 Nucleic Acids Res 35:465). ►vitamin C, ►Charcot-Marie-Tooth disease; Lee SH et al 2001 Science 292:2083; Smirnoff N et al 2001 Annu Rev Plant Physiol Plant Mol Biol 52:437.

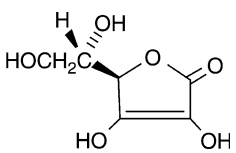

Figure A126. Ascorbic acid

Ascospores: Haploid products of meiosis formed within an ascus (see Fig. A127). ►ascus, ►tetrad analysis

Figure A127. Ascospores

ASCT1: This is a zwitterionic amino acid transporter. ►transporters, ►zwitterion

Ascus: A sac-like structure in the *Ascomycete* fungi, containing the four products of meiosis (spores). In many fungi the number of ascospores may increase to eight due to a mitotic division following meiosis. The spores in the asci may be arranged in the same linear order as in the linear tetrad of meiosis (ordered tetrads such as *Neurospora, Ascobolus, Aspergillus*, etc.) or may be scrambled (unordered tetrad such as in yeast). Asci have been used very effectively to study the mechanics of recombination because the results of single meiotic events could be analyzed separately. ►tetrad analysis

Ascus-Dominant: A mutation or even a deletion affects (prevents) the expression of the dominant allele within an ascospore. It has been attributed to reduced dosage, defects in inter-nuclear communication and transvection. ►transvection

ASE1 (anaphase spindle elongation): This is a gene encoding MAP, required for elongation of the mitotic spindle and separation of the spindle poles. The anaphase-promoting complex (APC) degrades it. ►MAP, ►spindle, ►cell cycle, ►centriole

Aseptic: This means that the culture is free from contaminating microorganisms. ►axenic, ►pasteurization, ►autoclaving, ►filter sterilization

Asexual Reproduction: This does not involve fusion of gametes of opposite sex or mating type. Yet, genetic changes in asexual or mainly asexual crustacean *Daphnia* lines genotyped at 126 microsatellite loci and sequencing 16 nuclear protein-coding loci showed spontaneous loss of heterozygosity resulting from ameiotic recombination at many loci (Omilian AR et al 2006 Proc Natl Acad Sci USA 103:18638). ►reproduction, ►mitotic recombination, ►parasexual mechanism

ASF1 (anti-silencing function protein, CIA/CCG1 interacting factor 1): This is a chaperone for newly synthesized histones H4 and H4 and it participates in nucleosome assembly, DNA replication and repair. ►chaperones, ►nucleosomes, ►chromatin, ►RCAF, ►NHEJ, ►histone acetyltransferases; Mousson F et al 2005 Proc Natl Acad Sci USA 102:5975; English CM et al 2006 Cell 127:495, SR motif, structure: Natsume R et al 2007 Nature [Lond] 446:338.

AS-Fish (antisense fluorescent in situ hybridization): The probe labels the sense strand of the DNA and thus it may make possible to label differentially the transcribed and non-transcribed heterologous DNA, introduced by transformation in the cell. ►FISH, ►antisense strand

Ash: The mineral residue of tissues left after igniting the organic material.

Ash Tree: Forest and ornamental trees (*Fraxinus excelsior*, 2n = 46; *F. americana*, 2n = 46, 92, 138).

Ashkenazi: Refers to Jews who lived during the Middle Ages in German lands although they migrated from there to Eastern Europe and other parts of the world. They preserved their ethnic identity and a special gene pool. Therefore, certain hereditary conditions such as Tay-Sachs disease, Gaucher disease, Niemann-Pick's disease, Bloom's syndrome, higher I.Q, etc. occur at increased frequencies in the population compared to some other ethnic groups. The haplotype spectrum based on the non-recombining part of the Y chromosome and microsatellite haplotypes indicate some significant differences from the Sephardic Jews and similarities to some Eastern European Slavic and Turcic (Khazar) ethnic groups. Some likely Khazar introgression appeared among Hungarian Jews because among the invaders of the Carpathian basin the tribe of chieftain Taksony was of Turcic ethnicity and embraced Jewish religion during the seventh-eighth century. ►Sephardic, ►Jews and genetic diseases, ►introgression; Behar DM et al 2003 Am J Hum Genet 73:768.

Asialoglycoprotein Receptor: Normally many soluble glycoproteins have sialic acid residues attached to their end. The sialic acid residues determine whether or not the glycoprotein is circulated in the bloodstream. If the sialic acid is lost the glycoprotein may bind to the plasma membrane of the liver cells (hepatocytes) and become asialoglycoprotein receptors. Glycoproteins attached to these receptors are generally degraded by the lysosomes of the liver. ►sialic acid

Asilomar Conference: In 1975, when recombinant DNA was beginning to be widely used, scientists convened at this place in California to prepare voluntary guidelines for protection against the potential hazards of the application of new techniques. ►containment; Berg P et al 1975 Proc Natl Acad Sci USA 72:1981.

ASK1 (apoptosis signal regulating kinase): This member of the mitogen-activated MAP protein family is activated by TNF-α. It induces apoptosis but it may inhibit TNF-a-induced apoptosis. It stimulates JNK activation, and also interacts with the TRAF family especially with TRAF2- induced JNK activation. ►apoptosis, ►MAP, ►TNF, ►JNK, ►TRAF

ASLV (avian sarcoma-leukosis virus): ►retroviruses

ASMD (anterior segment mesenchymal dysgenesis): This is encoded by the dominant PTX3 gene (10q25) affecting the development of cataract and later midbrain, tongue, incisors, breastbone (sternum), vertebrae and limbs. ►cataract, ►Rieger syndrome, ►eye diseases

ASN.1 (Abstract Syntax Notation): Describes the format in sequence databases to which all other files correspond; asn.all describes the formats of both literature and genetic sequence messages. ►Bioseq, ►gi, ►accession; http://asn1.elibel.tm.fr/.

Asn-Pro-X-Tyr: An amino acid sequence responsible for the internalization of low-density lipoproteins (LDL) of the membranes. LDL.

ASO: Refers to allele-specific oligonucleotide probe. Screening can be carried by semi-automated procedures. ►allele-specific probe

A

ASP Analysis: This analysis is used to estimate linkage in cases when a particular trait is under polygenic control. The co-segregation of multiple markers is followed in individuals who manifest the particular trait and determine which of the markers are most consistently present in these individuals. The analysis still requires the MAPMAKER/SIBS computer program, which evaluates multiple segregating families. ►MAPMAKER, ►QTL, ►interval analysis

Asparagine (α-aminosuccinamic acid): $NH_2COCH_2CH(NH_2)COOH$; its RNA codons are AAU, AAC.

Asparagine Synthetase (AS): Asparagine synthetase of bacteria uses ammonia as an amide donor, rather than glutamine as the mammalian enzyme. Cells expressing the bacterial AS will grow in asparagine-free medium if the glutamine analog, albizzin is present. In AS transfected mammalian cells the gene can be amplified in the presence of β-aspartyl hydroxamate, an analog of aspartate, and thus AS can be used as a dominant amplifiable marker in mammalian cell cultures. The mammalian genes are present in human chromosomes 7q21-q31, 8pter-q21, 21pter-q22. The AS genes do not have TATA and CAAT boxes in the promoter. They are homologous to the hamster *ts11* gene that is required for passing the cell cycle through the G1 stage. ►amino acid metabolism, ►cell cycle, ►house keeping genes, ►CAAT box, ►TATA box, ►AS in leukemia chemotherapy; Richards NGJ, Kilberg MS 2006 Annu Rev Biochem 75:629.

Asparaginyl tRNA Synthetase (ASNRS): This charges the appropriate tRNA with asparagine. In human cells it has been located in chromosome 18. ►aminoacyl tRNA synthetase

Asparagus officinalis (a dioecious monocot, 2n = 20): Refers to sex determination by XX pistillate and XY staminate plants (see Fig. A128). By anther culture YY plants can be obtained that can be vegetatively propagated or by pollination they produce exclusively male progeny. The male plants are of special economic value because their yield/area of edible spears is substantially higher. Almost half of the human populations excrete methanethiol in their urine after consuming this vegetable. The excreter trait appears to be autosomal dominant. The ability to smell this particular odor may also be under dominant control. ►YY asparagus, ►olfactory genetics

Figure A128. Asparagus

Aspartame (Nutra-Sweet): Refers to *N*-L-α-aspartyl-L-phenylalanine-1-methyl ester, an artificial low-calorie food and beverage sweetener; about 160 times as sweet as sucrose. It is not recommended for phenylketonurics because it contains phenylalanine. ►saccharine, ►fructose, ►phenylketonuria

Aspartate Aminotransferase (glutamate oxaloacetate transaminase, GOT1, GOT2): One of the functional forms of this enzyme GOT1, is encoded in human chromosome 10q24.1-q25.1 and it is expressed in the cytosol. A homolog GOT2 is encoded in human chromosome 16q12-q21 and it is expressed in the mitochondria. Pseudogenes of the latter have been located at 12p13.2-p13.1, 1p33-p32 and 1q25-q31. In the liver, the mitochondrial enzyme is largely present whereas the cytosolic enzyme is mainly located in the serum. ►amino acid metabolism, ►asparagine ►synthetase

Aspartate Phosphatase: ►two-component regulatory systems

Aspartate Proteases: The opening up of DNA for the integration of retrotransposable elements. Their protein generally shares the motif D,D45E (aspartic acid, aspartic acid, 35 amino acids, glutamic acid). ►transposase, ►retrotransposons

Aspartic Acid ($HOOCCH_2CH[NH_2]COOH$): This is a negatively charged amino acid. ►amino acids, ►aspartate aminotransferase, ►ancient DNA

Aspartic Acid Racemization: ►ancient DNA

Aspartoacylase Deficiency (aminoacylase-2 deficiency, Canavan disease, ACY2): This enzyme cleaves acylated amino L-acids into an acyl and amino acid group, whereas amino-acylase-1 (ACY-1) similarly cleaves all acylated L-amino acids, except L-aspartate. The autosomal recessive disorder has an early or late onset resulting in debilitating muscle, eye defects, mental retardation and spongy degeneration of the white matter of the brain. A defect in myelin synthesis is the major cause of the frequently fatal diseases (Madhavarao C et al 2005 Proc Natl Acad Sci USA 102:5221). There may be a 200-fold increase of *N*-acetylaspartic acid in the urine. Its incidence is increased among Jews of Ashkenazi descent and in Saudi Arabic populations. The chromosomal location is 17pter-p13. The catalytic site of aspartoacylase reveals close structural similarity to those of carboxypeptidases despite only 10–13% sequence identity between these proteins. Around 100 C-terminal residues of aspartoacylase form a globular domain with a two-strand β-sheet linker that wraps around the N-terminal domain. The long channel leading to the active site is formed by the interface of the N- and C-terminal domains. The

C-terminal domain is positioned in a way that prevents productive binding of polypeptides in the active site. The structures revealed that residues 158–164 may undergo a conformational change that results in the opening and partial closing of the channel entrance (Bitto E et al 2007 Proc Natl Acad Sci USA 104:456). ►amino acid metabolism, ►neuromuscular defects, ►mental retardation, ►eye diseases, ►Jews and genetic diseases, ►carboxypeptidase

Aspartylglucosaminuria (AGA): A chromosome 4 recessive defect of the enzyme aspartylglucosaminidase (4q32-q33) may eliminate an important S—S bridge of the protein resulting in neurological-mental and other defects. Its frequency is higher ($\sim 4 \times 10^{-5}$) in populations of Finnish descent. ►amino acid metabolism, ►disulphide bridge, ►sialidosis; Saarela J et al 2001 Hum Mol Genet 10:983.

AS-PCR: Refers to allele-specific PCR. polymerase ►chain reaction

ASPD (Artificially Selected Proteins/Peptides Database): ►phage display

Asperger Syndrome (Xq22.3, Xq13-q21): This is a form of childhood autism with less severe expression than the adult forms encoded at several autosomal locations. Susceptibility genes have been located to 3q25-q27, 3q24-q21, 17p13, 1q21-q22 and to TBX1 (T-box protein) transcription factor at 22q11.2. ►autism

Aspergillus: Numbering nearly ~185 species, including 20 human pathogens of ascomycetes, *Aspergillus nidulans* (n =8, $\sim 3 \times 10^7$ bp, 9,541 protein-coding genes) is a favorite organism for studies of recombination (see Fig. A129). One meiotic map unit is about 5–10 kbp. It has been extensively used for mitotic recombination. Asexual reproduction is by conidiospores (3–3.5 µm). This is a homothallic fungus and thus does not have different mating types. In the cleistothecium there are up to 10,000 binucleate ascospores in 8-cell linear, ordered asci. Transformation systems are available. It yields about 5×10^3 transformants/µg DNA. *A. flavus* is responsible for the production of aflatoxin, an extremely poisonous toxin that is found on infected plant residues, seeds, etc. *A. fumigatus* ($\sim 2.8 \times 10^7$ bp, 9,926 protein-coding genes) is a soil-born fungus, which causes ear, nose, lung and other infections in humans and animals. *A. oryzae* (3.7×10^7 bp, 12,074 protein-coding genes) is important for food technology (sake, soy sauce and miso [a fermented Japanese soy paste]). The size of protein-coding genes varies from 1,547 (*nidulans*) to 1,389 (*fumigatus*) and 1,1529 (*oryzae*). *A. nidulans* is more closely related to *A. fumigatus* than to *A. oryzae*. *A nidulans* has a known sexual cycle whereas the other two species generally reproduce asexually. All three species display homology of 5000 non-coding regions. The homothallic *A. nidulans* has both the MAT locus and a HMG (high-mobility group) gene. The heterothallic *A. fumigatus* conserved through evolution only HMG but no MAT and the heterothallic *A. oryzae* has only the MAT locus but no HMG. The latter two species have, however, highly homologous sequence to the flanking sequences sex-determination loci of *A. nidulans*. The industrially important *A. nigra* genome has also been sequenced (Pel HJ et al 2007 Nature Biotechnol 25:221). ►aflatoxins, ►mitotic recombination, ►recombination, ►cleistothecium, ►conidia, ►tetrad analysis, ►mating type determination in yeast, ►high-mobility group of proteins, ►nuclear membrane, comparative genomic sequences of *Aspergilli*: Galagan JE et al 2005 Nature [Lond] 438:1105; Nierman WC et al 2005 Nature [Lond] 438:1151; http://www.ncbi.nlm.nih.gov/genome/guide/aspergillus/, scientific and medical information: http://www.fgsc.net/aspergenome.htm.

Figure A129. *Aspergillus nidulans* conidiophore and conidia

Aspermia: Refers to the lack of ejaculating ability of the male.

Asphyxiating Thoracic Dystrophy (Jeune syndrome, 15q13): This is a recessive chondrodysplasia causing constricted thorax and respiratory difficulties and possibly different malformations; it is frequently lethal in the case of infants. It bears similarity to Ellis-van Creveld syndrome. ►Ellis-van Creveld ►syndrome

Aspirin (salicylic acid acetate): An analgesic, anti-fever, anti-inflammatory and anti-coagulant drug (blood thinner) (see Fig. A130).

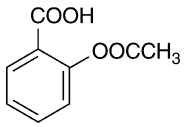

Figure A130. Aspirin

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It inhibits cyclooxygenases, IKK and JNK. The aspirin metabolite salicylic acid inactivates staphylococcal virulence factors and thus acts directly on the bacteria rather than on the host organism (Kupferwasser LI et al 2003 J Clin Invest 112:2221). Aspirin reduces the risk of major cardiovascular disease in both men and women (Ridker PM et al 2005 New England J Med 352:1293). Nitroaspirin increases the function of tumor-antigen-specific T lymphocytes and aids the anti-tumor effect of cancer vaccines (De Santo C et al 2005 Proc Natl Acad Sci USA 102:4185). Some individuals may show hypersensitivity to aspirin and precautions are required in the case of some hearing deficits, gout, hyperthyroidism, some kidney and liver problems, anemia, glucose-6-phosphate deficiency and Hodgkin's disease. Contraindication is warranted for hemophilia, other bleeding diseases, pregnancy, nursing, chickenpox and Rye syndrome. ►salicylic acid, ►cyclooxygenases, ►IKK, ►JNK, ►host-pathogen relations; Kurumbail RG et al 1996 Nature [Lond] 384:644.

Asplenia: One form (Ivemark syndrome) of asplenia is usually sporadic or autosomal recessive and it is associated with the absence or enlargement of the spleen or multiple accessory spleens and cardiac and other organ malformations. Another form of asplenia involves most conspicuously cystic livers, kidneys and pancreas. ►spleen; Nikawa N et al 1983 Am J Med Genet 16:43.

ASPP (apoptosis stimulatory proteins of p53): These are specific activators of tumor suppressor p53. iASPP is an inhibitor of p53 and is thus an oncoprotein. ►p53, ►oncoprotein; Bergmaschi D et al 2003 Nature Genet 33:162.

Assay: Refers to a test for mutagenic effectiveness or efficiency or the velocity of a chemical reaction catalyzed by enzymes or the test of function of any biological process.

Assembly Initiation Complex: The minimal elements required for the completion of the assembly of the viral components. ►bacteriophages

Assignment Test: ►somatic cell hybrids

Assimilation: This is a process for converting nutrients into the cell constituents and also, for blending of an initially different ethnic (cultural) group into the general population. ►genetic assimilation

Association: The joint occurrence of pathological symptoms, which do not have an expected common functional basis. Some of the associated genetic factors may indicate, however, disease risk. ►syndrome, ►PAF; Lohmueller KE et al 2003 Nature Genet 33:177.

Association Constant (K_a): Indicates the association between the components of a complex. The larger the K_a the stronger is the association.

Association Mapping: Identifies chromosomal regions containing disease-susceptibility or other genes on the basis of their association (linkage) with other marker(s) in a population rather than in a pedigree. The association may not necessarily indicate a linkage because selective forces may bias the observations in small populations. Moreover, recent migration or other admixture may lead to a bias. A transmission disequilibrium test may provide a remedy for the spurious association. With the availability of SNP and microsatellite markers genome-wide association between a number of genetic factors and complex disease traits can be attempted (Hirschhorn JN, Daly MJ 2005 Nature Rev Genet 6:95). ►transmission disequilibrium test, ►linkage disequilibrium, ►haplotype block, ►family-based association tests [►FBAT], ►QTL, ►SNIPs, ►triad ►test; Sham PC 2000 Am J Hum Genet 66:1616; Wang WYS et al 2005 Nature Rev Genet 6:109, power and efficiency: de Bakker PIW et al 2005 Nature Genet 37:1217; Yu J et al 2006 Nature Genet 38:203; Laird NM, Lange C 2006 Nature Rev Genet, 7:385.

Association Phase: Refers to the coupling phase in a linkage, a term used in fungal genetics. ►coupling phase, ►repulsion, ►crossing over, ►linkage

Association Site: Periodically distributed, microscopically detectable multiple interstitial association points are also called nodules. The distance between the paired chromosomes is about 0.4 µm. ►zygotene stage, ►meiosis, ►synaptonemal complex, ►recombinational nodule

Association Test: This is basically a 2 × 2 contingency chi square test based on a panel:

where a, b, c, d represent the number of observations (++), (−+), (+−) and (−−), respectively; n = the total number of observations. If b = c = 0, there is no association. The significance of the association is tested $\chi^2 = \frac{n(|ad-be|-0.5)^2}{(a+c)(a+b)(b+d)(c+d)}$ chi square, and the probability of a greater chi square can be determined by a χ^2 table or χ^2chart for 1 degree of freedom. The association test is most useful for studying a homogeneous population. A particular association may not be an indication of a genetic linkage, a physiological or cause-effect relationship but may provide useful information on the relation between two diseases or whether or not the reciprocal crosses are identical. A family-based association test for QTLs has similarity to the linkage disequilibrium approaches (Lange C et al 2002 Am J Hum Genet 71:1330). Single nucleotide polymorphism can be exploited for genome-wide search of SNP and disease

susceptibility association (Van Steen K et al 2005 Nature Genet 37:683). In the direct approach the candidate genes are sequenced and non-synonymous codon changes (SNPs) are most likely to be associated with disease (Cohen JC et al 2004 Science 305:869) although some non-synonymous substitution are neutral regarding function; the structural effect of SNPs may be more critical for disease and 26–32% of the non-synonymous natural SNPs affect function in a deleterious manner (Chaseman D, Adams RM 2001 J Mol Biol 307:683). The SIFT (sorting tolerant from intolerant) computer program can distinguish between neutral and deleterious amino acid changes in a protein sequence (Ng PC, Henikoff S 2003 Nucleic Acids Res 31:381, http://blocks.fhcrc.org/sift.SIFT.html). In the indirect approach, whole-genome associations are sought (Carlson CS et al 2004 Nature [Lond] 429:446). Such studies may rely on heritability estimates, which include the effect of several gene loci as well as the effects of the environment. The variations, however, can be partitioned to components by appropriate experimental design and statistics (see Table A6) (Mountain JL, Risch N 2004 Nature Genet 36:S48). ►linkage disequilibrium, ►association mapping, ►chi square, ►SNIPS, ►heritability, ►partitioning, ►Odds ratio; Lange C, Laird NM 2002 Am J Hum Genet 71:575; Lange C et al 2003 Am J Hum Genet 73:801; Balding DJ 2006 Nature Rev Genet 7:781.

Table A6. Association test

		First Variable	
Association test		+	−
Second variable	+	a	b
	−	c	d

Assortative Mating: Mates are chosen on the basis of preference or avoidance (positive or negative assortative mating), rather than at random, e.g., tall people frequently chose tall spouses; educated, higher economic or social status individuals usually marry within their group. Traits unknown to the majority, like blood groups, usually do not come into consideration in mate selection. Assortative mating may contribute only slightly to the average coefficient of inbreeding (f) in human populations: $\bar{f} = \frac{r}{2n_e(1-r)+r}$ where r = correlation coefficient, n_e = an equivalent number of genes ($n_e = \frac{\sum_{ij}\sigma_i\sigma_j}{\sum_i \sigma_i^2}$). Assortative mating may have some effect on the expression of a quantitative trait and the heritability becomes $h^2 = \hat{h}^2[1 - (1 - \hat{h}^2)A]$ where A is the product of the average heritability and the phenotypic correlation, i.e., $r\,\hat{h}^2$. ►controlled mating, ►mating system, ►inbreeding, ►correlation; Rice TK, Borecki IB 2001 Adv Genet 42:35.

Astacin: This is a zinc-metalloprotease. ►bone morphogenetic protein

Aster: Radiating structures around the two (round) centrosomes are visible in some animal cells (see Fig. A131). ►centrosome, ►centrioles, ►ASAP; figure is redrawn after Cleveland LR 1938 Biol Bull 74:41.

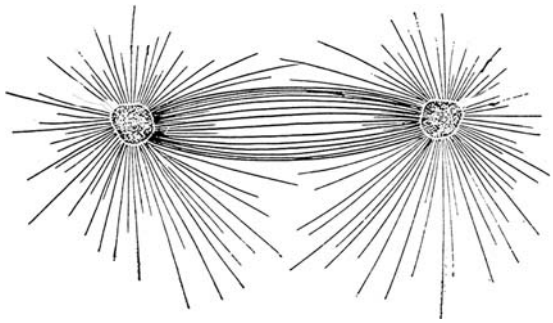

Figure A131. Aster

Asthenozoospermia: Less than 25–50% of the spermatozoa show forward motility. It appears that reduced OXPHOS activity in the mitochondria affects them. Defects in dynein axonemal heavy chain (DNAH1, 3p21.3) may also be concerned. ►OXPHOS, ►dynein, ►cytoplasmic male sterility; Ruiz-Pesini E et al 2000 Am J Hum Genet 67:682; Neesen J et al 2001 Hum Mol Genet 10:1117.

Asthma: This is a respiratory disease due to multiple causes affecting ~155 million people worldwide. Nasal polyps or elevated level of immunoglobulin A (IgA) or IgE may cause some autosomal recessive forms. Key players in the development of asthma are interleukin-13 (IL-13), IL-10 because they guide immature T cells into the development of T_H2 lymphocytes. IL-4 controls the development of B cells (that produce IgE) and IL-5, IL-3 and GM-CSF also play a role through eosinophils that are required for allergic inflammation. Transgenic mouse line genetically devoid of eosinophils lack the inflammatory response (mucus and airways hyperresponsiveness) of asthmatic animals (Lee JJ et al 2004 Science 305:1773). Mast cells and basophils affect the production of histamines, cytokines and chemokines control acute symptoms of asthma. The mast cells respond to IgE and the allergens. The interleukin gene cluster is located in human chromosome 5q31-q33. Genes in human chromosomes 1p32, 2q, 5q31, 6p21, 7p, 8p23, 11q21, 12q12, 13q, 14q24, 15q13 and perhaps other sites appear to be associated with the manifestation of asthma. In different populations different loci may play a major role. The α chain

A

of IL-4 receptor binds IL-13 to the T^H2. Susceptibility to asthma is controlled by a few genes and the heritability has been estimated as ~75%. Asthma—as well as some other anomalies of the immune system—also has a maternal effect. The risk of maternal transmission seems to be fourfold higher. This may be caused either by allelic exclusion, imprinting or by placental transfer or breastfeeding. Indeed, the IgE receptor (FCεRI-β, IL-5) has been mapped to a chromosome (11q13) that commonly affects imprinting. The metalloprotease ADAM33 (20p13) appears to be an important regulator of the disease (Van Eerdewegh P et al 2002 Nature [Lond] 418:426). Glucocorticoids are most commonly used in medication. Immunoglobulin free light chains (κ) mediate hypersensitivity response and the light chain antagonist 9-mer peptide F991 can abrogate the development of airways obstruction, hyperresponsiveness and pulmonary inflammation (Kraneveld AD et al 2005 Proc Natl Acad Sci USA 102: 1578). In asthma-sensitive mice,, endogenous *S*-nitrosothiols (R-S-N=O) are depleted because of increased *S*-nitrososo-glutathione reductase activity. Thus, the enzyme may be a logical target for therapeutic intervention (Que LG et al 2005 Science 308:1618). ►immunoglobulins, ►polyp, ►protease ►inhibitor, ►allergy, ►γδ T cell, ►T cells, ►IL-13, ►IL-10, ►IL-4, ►IL-5, ►IL-►3, ►imprinting, ►allelic exclusion, ►hypersensitive reaction [►animals], ►atopy, ►platelet activating factor, ►eczema ►filaggrin, ADAM; Xu J et al 2001 Am J Hum Genet 68:1437; Niimi T et al 2002 Am J Hum Genet 70:718; Umetsu DT et al 2002 Nature Immunol 3:715; Laitinen T et al 2004 Science 304:300, nitrosothiol pharmacology: Hogg N 2002 Annu Rev Pharmacol Toxicol 42:585, genes; Ober C, Hoffjan S 2006 Genes Immunol 7:95, http://cooke.gsf.de/asthmagen/main.cfm.

ASTRAL: This is a compendium of protein structures. protein structure, structural classification of proteins, SCOP; http://astral.berkeley.edu/.

Astrobiology: This is the study of the possibility of biology in the stars. ►exobiology, ►extraterrestrial life

Astrocyte: Refers to a type of branching cell that supports the nervous system. glial cells (see Fig. A132).

Figure A132. Astrocyte

Astrocytosis: Denotes an increase in astrocyte number because of neuronal loss.

ASV: The avian sarcoma virus of birds is an oncogenic RNA virus that can induce sarcoma in rodents. ►sarcoma

Asymbiotic Nitrogen Fixation: This proceeds by a microorganism without dependence on cohabitation with other organisms such as by members of the soil bacterial species *Azotobacter* and *Clostridium*. ►nitrogen fixation, ►symbiosis

Asymmetric Carbon: This atom has four different covalent attachments. ►covalent bond

Asymmetric Cell Division: This is a requisite for embryonal differentiation and these divisions specify the dorso-ventral and anterior-posterior polarities of the body pattern (see Fig. A133). Several protein factors specify the process. The orientation of the spindle in *Drosophila* involves the localization of the Numb and Prospero proteins in the basal cells and the polarity instructions may come from the product of the *inscruteable (insc), partner of inscruteable (pins)* and other loci. Yeast (Ash1p) and *Caenorhabditis* (SKN-1) also have controls similar to Numb and Prospero and *she* and *par* genes, respectively, are analogous to *inscruteable*. In *Drosophila* epithelium the adherens junctions inhibit asymmetric divisions. Centrosomally located mRNAs may be asymmetrically transmitted during the embryonic cleavage divisions (Lambert JD, Nagy LM 2002 Nature [Lond] 420:682). Cdc2 appears to link the asymmetric division machinery and the cell cycle. In the initial determination of the left-right axis in the embryo, the leftward flow of the extraembryonic fluid propelled by the primary monocilia plays a role in vertebrates from mouse, rabbit and medakafish and probably others too (Okada Y et al 2005 Cell 121:633). Embryonic stem cells have the potential of self-renewal (symmetric development) or differentiation into various types of cells (asymmetric divisions). ►morphogenesis in *Drosophila*, ►polarized differentiation, ►spindle, ►axis of asymmetry, ►left-right asymmetry, ►adherens junction, ►polarCdc2; Grill SW et al 2001 Nature [Lond] 409:630; Knoblich JA 2001 Nature Rev Mol Cell Biol 2:11. Adler PN, Taylor J 2001 Curr Biol 11:R233; Knust E 2001 Cell 107:125; Betschinger J et al 2003 Nature [Lond] 422:326, review: Betschinger J, Knoblich JA 2004 Curr Biol 14:R674; Morrison SJ, Kimble J 2006 Nature [Lond] 441:1068.

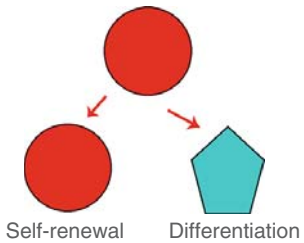

Figure A133. Asymmetric cell division

Asymmetric Heteroduplex DNA: ►Meselson-Radding model of recombination

Asymmetric Hybrid: Some of the chromosomes of one or the other parent are lost. ►somatic hybrids

Asymmetric Inheritance: ►asymmetric cell division

Asymmetric Mutation: ►mutation asymmetry

Asymmetric Replication: At the replication fork DNA synthesis on the leading and lagging strands proceeds in an opposite direction relative to the base of the fork. ►replication, ►replication fork

Asynapsis: Refers to the failure of chromosome pairing. ►desynapsis, ►synapsis

Asymptomatous: This is a disease without any symptoms.

Asymptotic Distribution: This type of distribution is observed in a sample or population when the *n* becomes very large. *Asymptotic relative efficiency* indicates the ratio of sample sizes required to obtain the same accuracy. An *asymptote* is a curve steadily approaching but never intersecting a straight line.

At Hooks: These are DNA minor groove-binding peptides, common in chromatin-associated proteins. The AT hooks generally contain a conserved GRP (glycine-arginine-proline) core surrounded by basic amino acids. They assist other proteins in binding to DNA.

At Least One Hypothesis: Every NK cell in an individual expresses at least one inhibitory receptor molecule specific for one or another self-MHC class I molecule. Consequently, self-tolerance is increased since many NK cells would be capable of destroying any autologous cells that have down-regulated MHC class I molecules. ►killer cells, ►MHC, ►self-tolerance, Valiante NM et al 1997 Immunity 7:739.

Atabrine: This is a preparation of quinacrine, an antimalaria and antihelminthic (intestinal tapeworm) drug. The quinacrine mustard (ICR-100) is a radiomimetic mutagen. ►quinacrines, ►radiomimetic

ATase: ►UTase

Atavism: Refers to the recurrence of expression of traits of ancestors beyond great grandparents. It is based on either recessive, complementary recessive or recombination of genes or special environmental conditions. For some time in the twentieth century it was no longer used in genetic literature. Atavism may, however, have a real basis in the genetic material and may represent in an altered form of ancient genetic sequences that are expressed in an "atavistic" manner if appropriately activated by a developmental program shift. Under such circumstances, from the rudimentary limb buds of the whales occasionally hind limb bones may develop. Hypertrichosis in humans, encoded in chromosome Xq24-q27.1, also represents such an atavistic reprograming. These atavistic changes may not be basically very different from the expression of homeotic genes. (Atavus in Latin means great great grandfather). ►hypertrichosis, ►homeotic genes, ►non-Mendelian inheritance, ►paramutation; Verhulst J 1996 Acta Biotheor 44:59.

Ataxia Telangiectasia (AT): This is one of almost a dozen human ailments involving ataxias: poor coordination of the muscles because of dilations in the brain blood vessels, reduced immunity, elevated level of a-fetoprotein, DNA repair, etc. Its appearance in human diseases is attributed to instability and breakdown of chromosomes 14, 7, 2, 11 and 12 although the major locus (150 kb genomic DNA and 66 exons transcribed into 13 kb RNA) appears to be at chromosome 11q22-q23. Leukemias and other malignancies are very common among these patients. Cultured cells of the affected individuals are highly sensitive to both X-ray and UV damage. Further, standard radiation therapy for malignant tumors may prove fatal in such cases.. The basic defect in AT is either in a DNA-dependent phosphatidylinositol protein kinase (M_r 350K) that controls progression of the cell cycle (p53) or in DNA repair and recombination (its homologs are MEC1, SAD3, ESR1). Alternatively, it has been found that an inositol 1,4,5-trisphosphate receptor (IP^3R1) deficient mouse mutants either die in utero or when born display severe ataxia and die shortly thereafter. The normal allele of AT stabilizes double-strand DNA breaks and promotes apoptosis and the deficiency of this function can explain the symptoms caused by its (ATM) mutation (Bredemeyer AL et al 2006 Nature [Lond] 442:466). It now appears that the mutant AT protein (ATM, 11q22.3) interacts with c-Abl oncogene resulting in radiation-sensitivity and in the arrest of the cell cycle at the G1 phase. An SH3 domain of c-ABL interacts with a DPAPNPPHFP amino acid sequence in ATM. As a consequence of radiation the tyrosine kinase activity of c-Abl is reduced in the ATM cells. Homozygosity of this recessive human gene has a frequency about 5×10^{-5} and the frequency of the carriers, prone to breast cancer and other malignancies, is about 1%. All mutations, which cause ataxia telangiectasia in homozygotes involve ~2.4 increased risk for breast cancer in the heterozygotes (Renwick A et al 2006 Nature Genet 38:873). The *spinocerebellar ataxia* (SCA5) of human chromosome 11 is caused by instability of the CAG trinucleotide repeats. SCAs include more

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than 16 genetically distinct neurodegenerative anomalies. SCA6 involves defects in the α subunits of Ca^{2+} ion channel. SCA1 is in chromosome 6p23.5-p24.2 and has CAG instability resulting in polyglutamine protein misfolding. SCA2 maps to 12q23-q24.1, SCA3 in 14q24.3-qter, SCA4 in 16q. The autosomal dominant cerebellar ataxia type III (SCA11) maps to 15q14-21.3 region. SCA10 is in human chromosome 22. The *autosomal dominant cerebellar ataxia* (ADCA type II) with pigmentary muscular dystrophy is coded in human chromosome 3p12-p21.1, and ADCA-like recessive gene is at 9q14. A nonepisodic dominant form (19q13.4) is due to mutation in protein kinase Cγ (Chen D-H et al 2003 Am J Hum Genet 72:839). *Episodic ataxia* is associated with defects in potassium ion channel or in the α subunits of Ca^{2+} channel functions. Ataxia with oculomotor apraxia (AOA2, 9q34) is a recessive ataxia telangiectasia-like disease, characterized by difficulty in moving the eyes and elevated levels of α-fetoprotein. The basic defect is in DEAxQ-box helicase (senataxin) involved in RNA maturation (Moreira M-C et al 2004 Nature Genet 36:225). X-linked ataxia with deafness and vision loss (*Arts syndrome*, Xq22.1-q24) also involves mental retardation and is apparently caused by mutation in phosphoribosyl pyrophosphate synthetase 1 gene (PRPS1) and impaired purine biosynthesis (de Bouwer APM et al 2007 Amer J Hum Genet 81:507). ►Friedreich ataxia, ►Nijmegen breakage syndrome, ►DNA repair, ►DNA replication in eukaryotes, ►excision repair, ►carcinogenesis, and a number of genetic diseases, which may have ataxic symptoms such as neuromuscular diseases, ►gangliosidoses, ►β-galactosidase, ►Niemann-Pick disease, ►metachromatic leukodystrophy, ►neurofibromatosis, ►olivopontocerebellar atrophies, ►Refsum diseases, ►Usher syndrome, ►Hartnup disease, ►light-sensitivity diseases, ►myotonia, ►cancer, ►cell cycle, ►DNA repair, ►trinucleotide repeats, ►AVED, ►RAD3, ►abl, ►SH3, ►phosphoinositides, ►ion channels, ►p53, ►breast cancer, ►Mre11, ►Mantle cell lymphoma, ►telangiectasia, ►DEAD-box proteins, ►fetoprotein-α; Taroni F, DiDonato S 2004 Nature Rev Neurosci 5:641; Paulson HL et al 2005 Neuron 46:845, autophosphorylation of Atm protein–activation: Pellegrini M et al 2006 Nature [Lond] 443:222, Gros-Louis F et al 2007 Nature Genet 39:80.

Ataxin: The protein responsible for SCA1 ataxia associates with a cerebellar leucine-rich acidic protein and alters the nuclear matrix. The expression of the neurodegenerative disease depends on the phosphorylation of ataxin-1 containing expanded polyglutamine tract by Akt and then its association with protein 14-3-3. Ataxin 3 is involved in deubiquitylation as well as in aggresome formation (Burnett BG, Pittman RN 2005 Proc Natl Acad Sci USA 102:4330). ►ataxia, ►spinocerebellar ataxia, ►trinucleotide repeats, ►Akt, ►protein 14-3-3, ►SCA, ►aggresome, ►ubiquitin; Emamian EE et al 2003 Neuron, 38:375; Chen HK et al 2003 Cell 2003 113:457.

ATCC: American Type Culture Collection maintains cell cultures of prokaryotes and lower and higher eukaryotes.

Ateles (spider monkey): ►cebidae

Atelosteogenesis (5q32-q33.1): Refers to fetal defect in the formation/elongation of fetal skeletal bones due to a defect in the diastrophic dysplasia sulfate transporter. ►diastrophic dysplasia

ATF2 (activating transcription factor): A family of proteins containing homologous basic/leucine-zipper (bZIP) binding domains; it is regulated by the JNK signal transduction pathway. Mutations in ATF2 interfere with the retinoblastoma and E1A oncogene's transcription suppressing activities. ATF6 is a membrane-bound transcription factor, which activates genes of the endoplasmic reticulum (ER). ATF4 is a suppressor of CREB-mediated long-term potentiation. When unfolded proteins accumulate in the ER ATF6 is released by Site-1 and Site-2 proteases. These two enzymes are required for the stress response of ER, lipid biosynthesis and for the processing of SREBPs in response to cholesterol deprivation (Ye J et al 2000 Mol Cell 6:1355). ATF3 is induced by lipopolysaccharide and it is a negative regulator of IL-6 and IL-12b by altering the chromatin structure. It also seems to regulate the Toll-like receptor 4 and thereby inflammatory responses (Gilchrist M et al 2006 Nature [Lond] 441:173). ►retinoblastoma, ►CREB, ►long-term potentiation, ►osteoblast, ►bZIP, ►JNK, ►adenovirus [►E1A], ►SREBP, ►Coffin-Lowry syndrome, ►IL-►6, ►IL-►12, ►Toll; Fuchs SY et al 2000 J Biol Chem 275:12560; Bhoumik A et al 2002 J Clin Invest 110:643.

Athanogene: This generates an anti-apoptotic function. ►BAG1, ►apoptosis

Atherosclerosis: This condition is characterized by hardening and then degeneration of the walls of arteries because of the deposition of fatty acid nodules on the inner walls and obstruction of blood circulation (see Fig. A134).

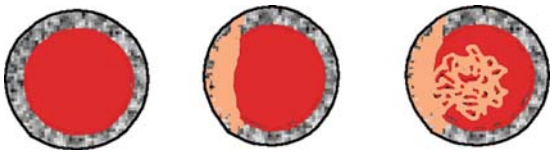

Figure A134. Cross section of an artery with blood (red) at center. Normal artery (at left), foamy plaques accumulate within the smooth muscles of the arterial wall and reduce blood flow because of the constriction of the lumen (in the middle), ruptured plaque may eventually block the blood flow to the heart (right).

In the first phase lipid-filled foam cells (macrophages) appear. In the next phase, fibrous plaques are formed of lipids and necrotic cells, covered by smooth muscle cells and collagen. The final phase lesion involves platelet and fibrous clots (thrombus). This group of vascular diseases is one of the most common causes of heart diseases. The number of deaths annually due to coronary heart disease and stroke are 490,000 and 150,000 respectively in the USA. The underlying genetic mechanisms vary and non-genetic factors play a substantial role. In human atherosclerotic lesions CD40 and its ligand CD40L are expressed. Susceptibility is controlled by 10 to 13 genes in human chromosome 1q24.3-1q25.1 and by 11 gene at the *Ath* locus of mice (Wang X et al 2005 Nature Genet 37:365).

By blocking the latter signaling molecules, atherosclerosis and some autoimmune symptoms may be mitigated. Atherosclerosis develops at a high level of the enzyme ACAT (acylcoenzyme cholesterol acyltransferase). In the case of apolipoprotein E (APOE) deficiency in mouse atherosclerosis, caused by oxidation of arachidonic acid, symptoms can be reduced by oral administration of vitamin E. Monocyte chemoattractant protein (MCP-1), a chemokine, and low-density lipoprotein (LDL) deficiency, and substantially reduced lipid deposition in the arteries are some of the characteristics. MCP-1 apparently recruits monocytes to the arterial epithelium during the earliest stages of the disease. A number of different hereditary and environmental factors contribute to the development of atherosclerosis. The heritability of the genetic factors (high cholesterol, triglycerides, diabetes) may vary from 40 to 80%. High lipoprotein (A) level controlled by several genes has over 90% heritability. Bone marrow-derived vascular progenitor cells can alleviate the symptoms upon injection into mice. Apparently, due to aging the repair capacity of the bone marrow decreases (Karra R et al 2005 Proc Natl Acad Sci USA 102:16789). The immunomicelles provide excellent, validated in vivo enhancement of atherosclerotic plaques. The enhancement seen is related to the macrophage content of the atherosclerotic vessel areas imaged by MRI. The immunomicelles may aid in the detection of high macrophage content associated with plaques vulnerable to rupture (Amirbekian V et al 2007 Proc Natl Acad Sci USA 104:961). The immunomicelles have an average mean hydrated size of 107.3 ± 0.21 nm and average concentration of gadolinium 2.23 mM. Gadolinium is a rare earth metal providing high resolution in magnetic resonance imaging. ►cardiovascular diseases, ►myocardial infarction, ►heart disease, ►sterol, ►HDL, ►LDL, ►CETPl, ►CD40, ►arachidonic acid, ►apolipoproteins, ►vitamin E, ►T-bet, ►monocytes, ►MCP, ►APRF, ►osteoarthritis, ►MRI; Lusis AJ 2000 Nature [Lond] 407:233; Welch CL et al 2001 Proc Natl Acad Sci USA 98:7946; Glass CK, Witztum JL 2001 Cell 104:503; Lusis AJ et al 2004 Annu Rev Genomics Hum Genet 5:189.

α-Thiophosphate-dNTP: Refer to point mutagens when incorporated into gapped DNA by DNA polymerase I. The thiophosphates are not effectively removed by the 3′ → 5′ editing function of the DNA pol I enzyme. ►pol

Atlas Human cDNA: This contains commercially available arrays of cDNAs (Clontech, Palo Alto, CA) on membranes in several quadrants, each specific for 96 genes of different specificity of expression. The membranes can be used for hybridization probes for the identification of genes with unknown function in different tissues or in healthy and diseased conditions. ►microarray hybridization; Sehgal A et al 1998 J Surgical Oncol 67:234, protein atlas: http://www.proteinatlas.org/.

ATM (ataxia telangiectasia mutated, 370 kDa): It involves an altered phosphatidylinositol kinase. ATM kinase may activate p53 in response to radiation stress but if ATM is defective p53 does not respond to e.g., ionizing radiation and in the absence of apoptosis the chances of cancer may increase. ATM or loss of AT increases the chances of oxidative damage to the cell. It is homologous to *MEC1* and *rad53* of yeast and *mei-41* of *Drosophila*. ►PIK, ataxia ►telangiectasia, ►ATR, ►BID, ►p53, ►apoptosis, ►Chk2, ►breast cancer, ►double-strand break, ►X-ray ►repair, ►telangiectasia; Pincheira J et al 2001 Mutagenesis 16:419.

Atom Microscopy: This technique is being developed for imaging atomic structures. The equipment uses

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mono-energetic sodium atoms ejected into a vacuum chamber and carried by noble gases such as argon. The beam is broken up into sub-components on a silicon nitride grid. The phase shift generated by the two beams is then measured.

Atomic Coordinate File: Lists molecular coordinates of macromolecules in three dimensions. ►coordinate

Atomic Force Microscope (AFM): An instrument that can image the surfaces of conductor and non-conductor molecules even in aqueous media. It can reveal molecular structure of surfaces, adhesion forces between ligands and receptors, and other biological processes in real time. It can also be adopted for DNA sequencing. ►STM, ►nanotechnology; Ljubchenko YL et al 1995 Scanning Microsc 9:705; Lyubchenko YL et al 2001 Methods Mol Biol 148:569; Müller DJ et al 2002 Progr Biophys Mol Biol 79:1.

Atomic Radiations: Killed 100,000 and injured 60,000 in Hiroshima (6 August, 1945) and Nagasaki (9 August, 1945) at the end of World War II, and caused substantial increase (about 4 fold or more at the epicenter) of cancer but showed no significant increase in human mutation. The incidence of cancer varied depending on a number of factors such as distance from the epicenter, age, sex (higher in females), by the type of cancers and some unexplained factors (such as geographic location of Hiroshima or Nagasaki).

The cause of the scarcity of mutations is not that these radiations were genetically ineffective rather the human breeding system, avoiding marriage between relatives, did not favor homozygosity of the recessive mutations resulting in lethality. Recent studies of the populations exposed to the radiation caused by the failure of the Chernobyl nuclear power plant (26 April 1986) indicate an increase not only in cancer but also of mutation (see Fig. A135).

Most likely, some of the mutations induced will be maintained in the exposed populations and may contribute to an increase of the genetic load. The total radiation from natural sources (cosmic radiation, disintegration of terrestrial isotopes [uranium, thorium, potassium], etc.), reaching the human gonads was estimated to be 100–125 millirads per year. The atomic bomb tests conducted during the years (1956) to (1965) contributed an average of about 76 millirads and expected to have exerted their effect mainly up to the year (2000) through the short half-life radioactive elements (Cesium^{137}, Strontium^{90}) and have substantially decayed by then. The long half-life Carbon^{14} will continue to pollute by an additional estimated 167 millirads even after year 2000.

The meltdown of the Chernobyl power plant in the Ukraine near the Byelorussian border, in the spring of 1986, exposed nearby populations up to 75 rem, whereas the whole of Byelorussia received about 3.3 rem.

In 1986, in that country, the total number of thyroid cancer in children was 2, and by (1992) it reached to about 60 cases. By (1999) more than 800 children who drank milk from cows exposed to the radiation developed thyroid cancer. The figures are still increasing. The thyroid cancer has been attributed to iodine^{131} released during the fallout. In the human minisatellite DNA the mutation rate doubled and in the feral populations of voles (*Microtus*) the base pair substitution frequency in the mitochondrial DNA was found to be in excess of 10^{-4}, over two orders of magnitude increase above the appropriate control groups. Nevertheless, the rodent populations appeared in good condition and their fertility was also good. This report of 1996, about the high mutation rate at Chernobyl, was retracted by the authors in (1997) (Nature 390:100). In barn swallows an increase of mutations at two microsatellite loci was observed (Nature 389:593). The Hanford Nuclear Reservation, in the state of Washington, exposed nearby populations in excess of 33 rads over a period of three years. The official estimates place 0.025 rads per year as safe for airborne pollution by nuclear weapon plants for the civilians living in the neighboring area and 5 rads for the workers in those plants for the entire body per year. According to some estimates based on irradiation of mice 20–40 rad is the doubling dose of mutation for ionizing radiation. It was estimated that the radioactive fallout from weapon testing may have increased the genetic risks by 2% over the natural background effects and by 8% for leukemia. The effects of atomic radiation on mutation rates in the minisatellite DNA remains controversial because of the difficulties of finding appropriate (concurrent) controls. The mutation rate in these very sensitive DNA sequences is much affected by environmental factors (pollution), age, etc.

When considering the harmful effects of radiation potentially released by atomic power plants, one must consider the harmful pollution generated by the coal-fired industry and the carcinogenic hydrocarbons released by the combustion in wood fireplaces, etc. Also, the shortage of energy may directly or indirectly cause substantial suffering and even death to the genetically more vulnerable part of the population, especially children.

Estimation of the risk is very complicated because of the many modifying factors (angle of the radiation, age, sex, length of exposure, genetic susceptibility to

cancer, life style [smoking, drug use, etc.]) involved. One simple formula for assessing the excess relative risk (ERR) is $1 + \beta z$, where β = ERR and z = radiation dose. Some variations of the following formula based on least squares regression models have also been developed for the estimation of excess risk: $(\text{Cases. PYR})_d = \alpha + \beta\delta + \varepsilon$ where PYR is the dose-specific person years, α denotes the intercept of the regression term, β stands for the contribution of the doses of the radiation as an excess risk and ε is the error [formula after D.A. Pierce]. ►cosmic radiation, ►isotopes, ►radiation hazard assessment, ►doubling dose, ►plutonium, ►nuclear reactors, ►mutation in human populations, ►mutation detection, ►rad, ►rem, ►control, ►correlation, ►public opinion; Dubrova YE et al 2002 Science 295:1037; Williams D 2002 Nature Rev Cancer 2:543; Dubrova YE et al 2002 Am J Hum Genet 71:801; Awa A 2003 Mutation Res 543:1.

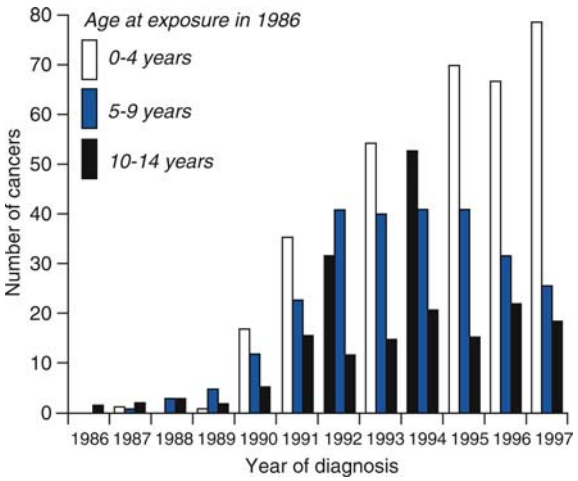

Figure A135. The incidence of thyroid cancer in Belarus following the Chernobyl accident in 1986. (From *Sources and Effects of Ionizing Radiation*. United Nations Scientific Committee Report 2000. vol. II. New York.)

Atopy: A familial allergy, including asthma, hay fever and eczema. The blood serum carries an increased level of immunoglobulin E (IgE). An IgE responsiveness locus was assigned to 11q12-q13. Human chromosome 5q31-q33 harbors an asthma susceptibility region. Atopy is controlled also by epithelial barrier determined by the 370-kDa filaggrin protein, encoded at human chromosome 1q21; semidominant and dominant mutations or loss of this protein predisposes to dermatitis and/or asthma or to both. In about 9% European populations, filaggrin variants occur (Palmer CNA et al 2006 Nature Genet 38:441). ►allergy, ►asthma, ►immunoglobulins, ►ichthyosis, ►Netherton syndrome; Wheatley AP et al 2002 Hum Mol Genet 11:2143.

ATP: Adenosine-5′-triphosphate is a universal carrier of metabolic energy by transferring the terminal phosphate to various acceptors and resulting in ADP (adenosine diphosphate) that is recycled to ATP by either the chemical energy of oxidative phosphorylation or the solar energy of photosynthesis. Besides the thermodynamic role, ATP has also catalytic activity e.g., in nitrogen fixation. ATP provides also binding energy through non-covalent interactions with various molecules in order to lower activation energy. It provides energy for charging tRNA with amino acids, for DNA synthesis, for bioluminescence mediated by the firefly luciferase, it is indispensable in carbohydrate metabolism, it serves as a precursor of cyclic AMP that has major role in signal transduction and protein phosphorylation, etc. The major catabolic pathways (glycolysis, citric acid cycle, fatty acid and amino acid oxidation and oxidative phosphorylation) are coordinately regulated in the production of ATP. The relative abundance of ATP and ADP controls electron transfers in the cell. ATP is generated in the mitochondria and chloroplasts. ATP is the major link between anabolic and catabolic reactions mediated by enzymes. UTP (uridine triphosphate), GTP (guanosine triphosphate) and CTP (cytidine triphosphate) are also important in similar processes but have relatively minor role compared to ATP. ►ATP synthase, ►ATPase, ►cAMP; Pfeiffer T et al 2001 Science 292:504.

ATP Synthase: A ~500 kDa multisubunit protein complex forming ATP from ADP and phosphate (oxidative phosphorylation) on plasma membranes (bacterial, mitochondrial, chloroplast); it is also a motor protein. ►ATP, ►ATPases; Boyer PD 1997 Annu Rev Biochem 66:717: Yoshida M et al 2001 Nature Rev Mol Cell Biol 2:669.

ATPase: Enzymes are required for active transport of chemicals and other functions in the cells. The *P-type* ATPases maintain low Na^+, low $Ca^{2+}$and high K^+ levels inside the cells, generate low pH within cellular compartments and activate proteases and other hydrolytic enzymes of eukaryotes and generate transmembrane electric potentials. Na, K-ATPase has binding sites for cardiac glycosides such as ouabain, digoxin and digitoxin and mediates adrenocorticotropic hormone (ACTH) induced hypertension

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in mice and presumably in humans (Dostanic-Larson I et al 2005 Proc Natl Acad Sci USA 102:15845). The *V-type* (vacuolar) ATPases secure low pH inside lysosomes and vacuoles of eukaryotes. The *F type* ATPases (energy coupling factors, F_1-F_0-ATPase) are located in the plasma of prokaryotes. In the mitochondrial and thylakoid membranes of eukaryotes the *F type* ATPases are actually ATP synthase enzymes generating ATP from ADP and inorganic phosphate. The *DNA-dependent* ATPases are type I restriction endonucleases that depend on Mg^{2+}, ATP and SAM for cutting of DNA strands. After cleavage they function only as ATPases. ►ATP, ►SAM, ►ACTH, ►ouabain, ►digoxigenin, ►digitoxin; Palmgren MG 2001 Annu Rev Plant Physiol Plant Mol Biol 52:817; V-type Na^+ -ATPase structure: Murata T et al 2005 Science 308:654; F-type Na^+ -ATPase structure: Meier T et al 2005 Science 308:659.

A-Tract: Includes four or more AT base pairs in the DNA without a 5′-TA-3′ step. Such elements cause curvature at the helix axis and influence nucleosome packaging and base pair opening due to the C^5 methyl of thymine. Such structures modulate sequence-specific ligand binding and gene expression. (See Wärmländer S et al 2002 J Biol Chem 277:28491).

ATR (ATM - Rad3-related): Is a phosphatidylinositol kinase related to ATM and yeast gene product RAD3. It controls cell cycle checkpoints and double-strand breaks. Phosphorylation of its substrates inhibits DNA replication fork, mitosis and promotes repair, recombination or apoptosis. ►ATM, ►checkpoint, ►PIK, ►*RAD3*, ►sex body; Cortez D et al 2001 Science 294:1713; Zou L, Elledge SJ 2003 Science 300:1542.

Atransferrinemia (3q21): A defect in the synthesis of the iron-regulatory protein transferrin, resulting in hypochromic anemia. ►transferrin, ►anemia

Atrazine (Lasso): ►herbicides, ►photogenes

Atresia: Closure of an organ (e.g., vagina, and it can be surgically corrected to permit procreation), parts of the digestive tract (pyloric atresia), closure of the bile duct (biliary atresia), etc. pyloric stenosis.

Atresia: Mediates the elimination—by apoptosis—of oocytes with mutant mitochondria. Although the primordial germ cells produce millions of oocytes in humans, only a small fraction of them reach the stage of ovulation. Thus, atresia serves as a genetic quality control. In the male germ cells (which do not transmit mitochondria) atresia was not observed. ►apoptosis, ►mtDNA; Krakauer DC, Mira A 1999 Nature [Lond] 400:125.

Atresia, Congenital Aural: A narrowing or closure of the auditory channel due to deletion of human chromosome 18q21–q23 region. Its prevalence is 1×10^{-4} per live birth. (See Veltman JA et al 2003 Am J Hum Genet 72:1578).

Atrial: Adjectivization of atrium. ►atrium

Atrial Septal Defect: An autosomal recessive type developmental heart disease that displays increased recurrence when transmitted through the males although the prevalence is greater in the females. The dominant form encoding a transcription factor is in human chromosome 6. Dominant defects in the NXX2-5 gene (encoded at 5q35) affects cardiac septation and is responsible for congenital heart disease. Gene TBX5 (12q24) is responsible for ventricular septal defects. ►heart diseases

AT-Rich DNA: Common in the repetitive sequences, and is generally not transcribed. Some of the petite colony mutants of yeast mitochondrial DNA contain mainly AT sequences. ►mitochondrial genetics, ►mtDNA

ATRIP: ATR-interacting protein. ►ATR; Cortez D et al 2001 Science 294:1713; Zou L, Elledge SJ 2003 Science 300:1542.

AT-Risk-Motifs (ARM): Increase instability of the genome such as inverted repeats, palindromes, and insertion elements either by illegitimate or homologous recombination or rearrangements. ►repeat inverted, ►palindrome RecA-independent recombination, ►Alu family, ►instability genetic; Gordenin DA, Resnik MA 1998 Mutat Res 400:45.

Atrium: The entrance to an organ. ►atrial

Atropa belladonna: A plant of the *Solanaceae* family (n = 50, 72) is a source of alkaloids. ►henbane

Atrophine-1: Protein is encoded by the human gene DRPLA and affects other trinucleotide repeat genes. ►dentatorubral-pallidoluysian atrophy, ►Huntington's chorea

Atrophy: Under-nutrition or lack of nutrition; wasting away of cells and tissues. ►Kugelberg-Welander syndrome, ►Kennedy disease, ►dystrophy, ►muscular dystrophy, ►neuromuscular diseases, ►spinal muscular atrophy

Atropine: A highly toxic alkaloid. ►henbane

ATRX: A helicase protein encoded at human chromosome Xq13 (>220 kb). It is similar to the RAD54 and the SWI/SNF proteins. It is implicated in psychomotor functions, DNA methylation, regulation of transcription, DNA repair and chromosome segregation. Mutations have been found in cases of

Figure A136. att sites

thalassemia/mental retardation and in the Juberg-Marsidi syndrome. See separate entries for the terms mentioned.

att SITES: At the position where site-specific integration and excision takes place, lysogenic bacteria and temperate phage have consensus sequences (see Fig. A136). The *att* sites are about 150 nucleotides long in l and 25 bp in the bacterium. 15 bp sequences are identical in both.

The underscored sequences (see figure) are then reciprocally recombined and POB′ and BOP′ sequences are generated from the left (attL) and right (attR) sequences. The integration requires the phage-coded INT and the bacterial coded HF proteins. The excision requires an additional protein XIS to be coded by the bacterial gene *xis*. This is probably because it is not exactly the reverse type of process since the original attP and attB elements were not identical except the 15 bps. ►lambda phage, ►integrase; Williams KP 2002 Nucleic Acids Res 30:866.

Attached X Chromosomes: Two X chromosomes fused at the centromere (see Fig. A137). They have been exploited for cytogenetics. Among others, they were first used to carry out half-tetrad analysis in *Drosophila*. Females with attached-X produce eggs but half of them have only autosomes and no X-chromosome. If the attached X-chromosomes carry different alleles of a locus, double dose of the same allele in the eggs can be achieved only if there is a recombination between that gene and the centromere. This is because the first meiotic division is reductional and the second is equational. ►half-tetrad analysis, ►compound X chromosomes; Anderson EG, 1925 Genetics 10:403.

Figure A137. Attached X-chromosomes (→) in the oogonium of an XXY *Drosophila*. (After a drawing by Curt Stern in the 1920s)

Attachment Point *(ap)*: A mappable site in the chromosome of the chloroplast of *Chlamydomonas reinhardi* green alga, representing a hypothetical centromere-like element. It is called *ap* because it attaches to the chloroplast membrane and assists the disjunction of the ring DNA during division. In genetic recombination this is taken as the 0 coordinate of marker segregation. ►chloroplast genetics, ►mapping of chloroplast genes

Attachment Site: ►*att* site

Attention Deficit-Hyperactivity (ADHD): A condition observed in 2 to 5% of elementary school children that causes learning disabilities and emotional problems. Boys have about 5-fold higher chance to be affected than girls. It frequently goes into remission as age progresses but some personality disorders (hyperactivity, antisocial behavior, alcoholism, hysteria) may persist even in adulthood. About 25 to 30% of the parents of affected children had some of the symptoms in childhood. The genetic basis is unclear. The dopamine receptor 4 encoded in human chromosome 11p15.5 may be responsible for the behavioral anomalies but not necessarily for the attention deficit. The heritability is 0.75–0.91. Chromosomal locations 17p11, 15q, 7p and 9q have been implicated (Bakker SC et al 2003 Am J Hum Genet 72:1251). Childhood asthma is strongly associated with ORMDL3, a member of a gene family that encodes transmembrane proteins anchored in the endoplasmic reticulum in human chromosome 17q21 (Moffatt MF et al 2007 Nature [Lond] 448:470). ►affective disorders, ►dyslexia, ►autism, ►behavior genetics; Fisher SE et al 2002 Am J Hum Genet 70:1183; Wilens TE et al 2002 Annu Rev Med 53:113.

Attenuate: Tapered appearance.

Attenuation: A regulatory process in bacteria. ►attenuator region, ►host-pathogen relations, ►tryptophan operon, ►antitermination

Attenuation, Viral: A reduction in virulence achieved by subculturing in a new cell population. In this process, numerous adaptive mutations occur after a period of

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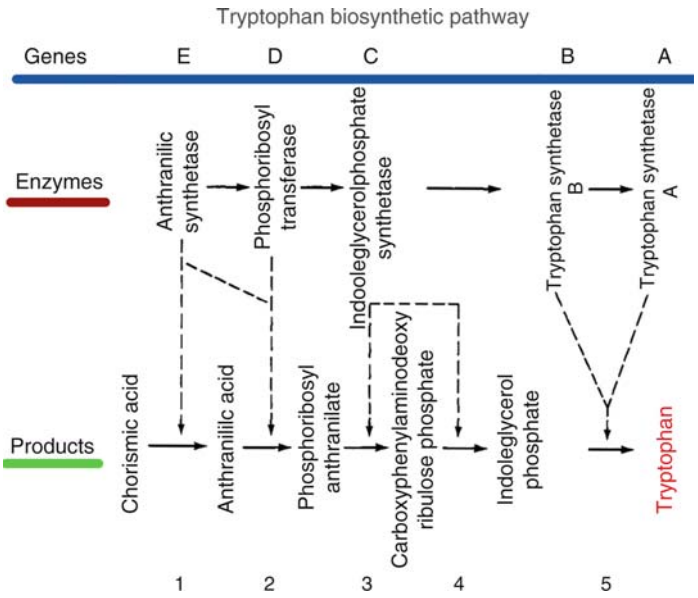


Figure A138. The biosynthesis of tryptophan from chorismic acid in *E. coli* bacteria requires five steps, mediated by five enzymes. The sequence of the encoding genes in the bacterial genetic map corresponds to the sequence of the metabolic steps. This was the first case of recognition of such a ►co-ordinate regulation in bacteria. Primarily, a repressor controls the five genes, and attenuation provides an additional fine-tuning. Some of the enzymes are composed from more than a single functional unit. Indoleglycerolphosphate synthetase catalyzes two synthetic steps as shown in figure

time that permit them to grow well in the original cells but with diminished virulence. These mutations generally occur in the 5′-non-translated region and modify the translation of the viral RNA although attenuating mutations may occur all over the viral RNA genome. attenuator region.

Attenuation, Vaccines: The virus is immunogenic but not pathogenic in the vaccine.

Attenuator Region: Region where RNA polymerase may stop transcription when all the cognate tRNAs are charged. Then the mRNA assumes a special secondary structure and this leads to a temporary cessation of transcription, leading to a reduction of transcription by a factor of 8–10. It is one of the regulatory mechanisms of bacterial amino acid operons. A type of attenuation also regulates the pyrimidine operon of *E. coli*. The operon is induced by low concentration uridine triphosphate. (see Fig. A138; tryptophan biosynthetic pathway).

When the UTP level increases, slippage occurs at the promoter incorporating long stretches of uridylic acid and the RNA polymerase cannot escape the promoter. The cytosine deaminase/cytosine transport locus behaves similarly. The histidine operon does not even use the more common type of operator repressor/inducer system.

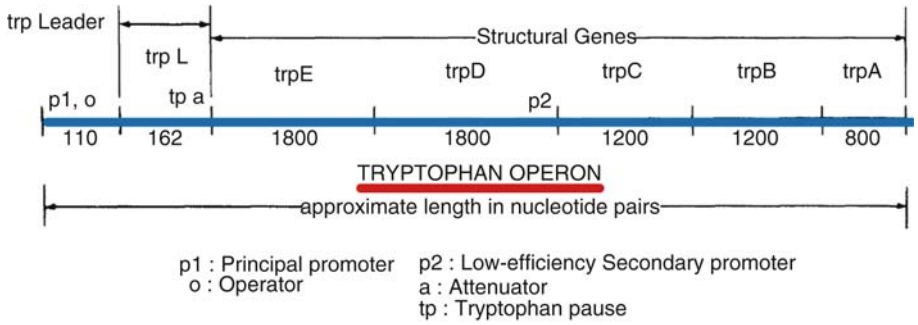
Sucrose, β-glucoside, β-glucan utilization enzymes in bacteria use RNA-binding proteins that inactivate transcription termination and thus promote transcription. The elongation of some lipid biosynthesis RNAs may be also negatively controlled. Attenuation appears to be a widely used mechanism of regulation in bacteria (see Fig. A139) (Merino E, Yanofsky C 2005 Trends Genet 21:260).

(See diagrams of the ►tryptophan operon, ►TRAP, ►tryptophan, ►tryptophan repressor, ►antitermination, ►slippage; Yanofsky C 2000 J Bacteriol 182:1).

Attractin: A human serum glycoprotein-regulating cell mediated immunity and is homologous to the *mg* locus of mouse. It is a low affinity receptor for agouti protein. ►obesity, ►agouti; He L et al 2001 Nature Genet 27:40.

Attrition: The cost of failure in the development of an effective drug. The cost of developing a highly successful therapeutic agent generally exceeds $800 million and the chance of failure is over 90% either because of insufficient efficacy or unacceptable side effects. ►translation

Auberger Blood Group: ►Lutheran blood group



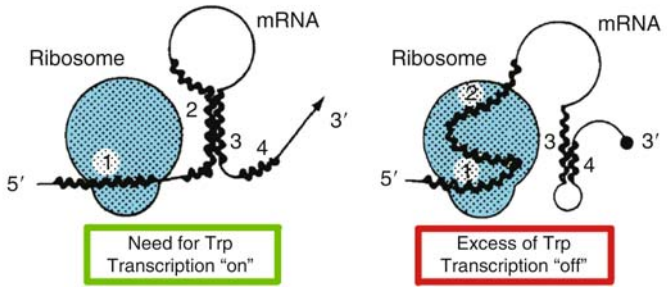


Figure A139. A genetic and molecular map of the tryptophan operon in *Escherichia coli* bacterium. Attenuation may dictate an early termination of transcription. The site of attenuation (*a*) is within the tryptophan leader sequence (*trpL*) and the site of the transcription pause (*tp*) precedes it. Transcription is primarily under the control of the promoter - operator region and the process begins at the left end of the *trpL* site. The RNA polymerase pauses at the *tp* site before proceeding further. In case most of the tryptophanyl tRNAs ($tRNA^{Trp}$) are charged with tryptophan and therefore there is no need for additional molecules of this amino acid, transcription is momentarily terminated at the attenuator (*a*) site. If however the $tRNA^{Trp}$ is largely uncharged because of shortage of tryptophan and active protein synthesis, the transcriptase RNA polymerase passes through the *a* site without interference. This passage is made possible by alterations in the secondary structure of the RNA transcript of the operon. The initial segment of the leader sequence encodes a short tryptophan-rich peptide. In case there is a scarcity in tryptophan, translation on the ribosome is stalled at the tryptophan codons in the leader sequence. During the pause (*tp*), the mRNA transcript assumes a hairpin-like structure by base pairing between segments marked by (2) and (3) and thus the passage through the *attenuator* (*a*) site is facilitated. In case, however, most of the cognate tRNAs are charged, the transcript shows base pairing between segments (3) and (4), resulting in stoppage of transcription until the over-supply is exhausted by protein synthesis. The tryptophan operon also relies on suppressive transcriptional controls. See base sequences of the attenuator at the entry "tryptophan operon". (Modified after Yanofsky C 1981 Nature (Lond.) 289:751)

AUC (area under the curve): See Fig. A140.

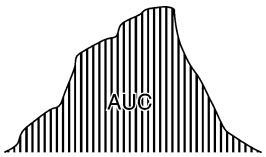


Figure A140. AUC

Auer Bodies: Clusters of granules or bundles of rods in the nuclei of acute promyelocytic leukemia cells. ►leukemias

AUG Codon: In mRNA, AUG is the only one codon that specifies methionine yet there are two different tRNAs for methionine. In a majority of cases in prokaryotes one of the methionine-tRNAs is formylated at the amino group by N^{10}-formyltetrahydrofolate, and this formylmethionine tRNA initiates translation whereas the other methionine-tRNA carries methionine to all other sites in the polypeptide. In eukaryotes the *initiator methionyl-tRNA* is not formylated, the primary structure and conformation of the tRNA specify its initiator attribute. Thus, the overwhelming majority of nascent proteins that start at the NH_2 end with a methionine. In the mature

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protein this methionine may be absent because of processing. ►genetic code

Auger Emission: ^{125}I (iodine) or ^{195m}Pt (platinum) isotopes may emit electrons or Auger positrons (^{64}Cu) when excited by external radiation. When incorporated, these isotopes may deliver high doses within the radius of a cell and can be used to damage tumor cells.

Augmenting Genes: Facilitate viral reproduction although not absolutely essential for it.

AU-Rich Elements (ARE): ARE in the 3′-untranslated region may target the mRNAs of proto-oncogenes, cytokines and lymphokines for rapid degradation. However, these AU-rich mRNAs are stabilized by heat shock, UV, hypoxia, stimulation and oncogenic transformation. ELAV family of proteins, such as HuRs, may bind AREs. ►ELAV, ►HuR; Stoecklin G et al 2001 RNA 7:1578.

Auricles: Small projections at the upper part of leaf sheath in cereals (see Fig. A141). They are of importance for taxonomic characterization.

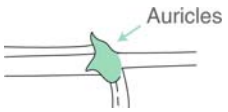

Figure A141. Auricles

Aurones: Plant flavonoids conveying yellow color to flowers. They are synthesized from chalcones by aureusidine synthase (39-kDa copper glycoprotein) and a member of polyphenol oxidases.

Auroras: Are threonine/serine protein kinase(s), regulating the mitotic spindle, chromosome segregation, cytokinesis, etc. Humans have three Aurora kinases, A, B and C. Its activator is the Ajuba protein of the LIM family. Inhibitors have relevance to cancer therapy. Loss of the mitotic checkpoint protein Chfr can ubiquitinate and regulate Aurora. It promotes chromosomal instability (Yu X et al 2005 Nature Genet 37:401). Aurora A and B are associated with and over-expressed in several types of cancer. The inhibitors target serine 10 in histone H3 and may cause tetraploidy. ►LIM domain, ►passenger proteins, ►co-orientation, ►infertility, ►condensin; Taguchi S et al 2002 FEBS Lett 519:59; Keen N, Taylor S 2004 Nature Rev Cancer 4:927.

Austin Disease: ►mucosulfatidosis

Australopithecus: An extinct, fossil (5–1 million year old) of the bipedal Hominidae of the Old World. Its brain size is intermediate—between modern humans and apes. Exact relation to existing species is unclear. ("Austral" means Southern). ►hominidae

Autapomorphy: A condition when a particular trait(s) occurs only in a particular evolutionary line and not in other related species.

Autapsis (adj. autaptic): Are synapses that cells form with themselves. ►synaps

Autism: A human behavioral anomaly involving reticent, self-centered, subjective thoughts and actions, learning and communication difficulties. Its prevalence is 0.02 to 0.05% in the general population, and the recurrence risk in families may be 6–8%. More recent estimates of the prevalence are about 0.06%. The concordance between monozygotic twins appeared 36 to 96% while between dizygotic ones none to 24% was observed. Its incidence is about 4-fold higher in males than females. Because of its behavioral nature, animal models cannot be used efficiently and directly. It is generally associated with mental retardation and other psychological disorders. Although the incidence within affected families is 50 times higher than that in the general population, no single gene could be identified as a causative agent although some role of serotonin transporter has been suspected. Actually even in humans, the diagnosis is somewhat difficult because of the complexity of the traits and differences among the alleles. Several features of the condition overlap some symptoms of other diseases. Autism may be associated with genes in several chromosomes but 7q31 or 1p or 1q23-q24, or 3q25-q27 or 17q11 appear to be the most likely locations of the major factors involved. However, other search have revealed several other putative linkage relations (Liu J et al 2001 Am J Hum Genet 69:327; Bartlett CW et al 2005 Am J Hum Genet 76:688). An aminophospholipid-transporting ATPase situated in the imprinted region 15q11-q13 near the ubiquitin ligase E3A and the Angelman syndrome genes is associated with a small percent of the autisms (Herzing LBK et al 2001 Am J Hum Genet 68:1501; Folstein SE, Rosen-Sheidley B 2001 Nature Rev Genet 2:943). Additional loci have also been identified (Yonan AL et al 2003 Am J Hum Genet 73:886). Using Affymetrix 10K SNP microarrays and 1,168 families with at least two affected individuals implicate chromosome 11p12–p13 and neurexins, respectively, among other candidate loci (The Autism Genome Project 2007 Nature Genet 39:319). De novo copy number variations (CNVs) in the genome were significantly associated with autism ($P = 0.0005$). Such CNVs were identified in 12 out of 118 (10%) patients with sporadic autism, in 2 out of 77 (3%) of patients with an affected first-degree relative, and in 2 out of 196 (1%) of controls. Most de

novo CNVs were smaller than microscopic resolution (Sebat J et al 2007 Science 316:445).

The infantile autism becomes apparent during the first year of life. Apparently it is under polygenic control. In the dominant autism with onset after an initial normalcy (Rett syndrome, RTT, prevalence 1×10^{-4}), the symptoms are shared but progressive dementia, uncoordination and deterioration of all mental functions follow. This view about autism is gradually changing as current studies reveal the other end of the condition that involves preoccupation with details and qualities of a genius. The latter type appears to be coded at Xq28 as MeCpG2. The Rett syndrome affects primarily females. Earlier the short arm of the X had also been implicated. The Xp22.3 region encodes the NLGN4 neuroligin and Xq13 encodes NLGN3 neuroligins, their mutations are associated with autism (Jamain S et al 2003 Nature Genet 34:27). Neuroligins are essential factors for the formation of synapses. ►affective disorders, ►Asperger syndrome, ►attention deficit-hyperactivity, ►disorder, ►mental retardation, ►neurexin, ►MeCpG2; Fombonne E 1999 Psychol Med 29:769; Folstein SE, Mankoski RE 2000 Am J Hum Genet 67:278; Geschwind DH et al 2001 Am J Hum Genet 69:463; Shao Y et al 2002 Am J Hum Genet 70:1058; Yu C-E et al 2002 Am J Hum Genet 71:100; Veenstra-VanderWeele J et al 2004 Annu Rev Genomics Hum Genet 5:379.

Autoallopolyploid: A polyploid in which the genome(s) is/are duplicated from one or more species, e.g., AAAABBBB or AAAABB. ►allopolyploid, ►sesquidiploid

Autoantibody: An antibody formed against the body's own antigens, such as in autoimmune disease. During early B lymphocyte development 55–75% of all antibodies formed may display self-reactivity but most of them are destroyed as the B cells mature (Wardemann H et al 2003 Science 301:1374). ►autoimmune disease, ►B lymphocyte

Autoantigen (self-antigen): A normal cellular protein yet it may be attacked by the cellular immune system. This is similar to what happens in autoimmune disease. ►immune system, ►immune reaction

Autocatalytic Function: Of DNA is the process of replication; also, any reaction that is promoted by its own product. Although self-replication is the most common property of nucleotide chains, peptides and other molecules may be involved in autocatalysis and cross-catalysis (i.e., the formation of other molecules). ►replication, ►heterocatalysis; Paul N, Joyce GF 2002 Proc Natl Acad Sci USA 99: 12733.

Autochthonous: Located at its original site or a graft of an individual at another position within the same body.

Autoclaving: Heating under pressure (1 atmosphere above sea level) by steam, usually at 121 °C, for a minimum of 15 min to kill non-spore-forming bacteria and other cells. ►sterilization, ►filter sterilization

Autocorrelation, Spatial: Compares data (e.g., DNA sequences and haplogroup frequencies) within arbitrary areas in order to study diversity distribution. Measures of overall genetic similarity are evaluated in each distance class and the degree of genetic similarity at the different genetic distances determined. A variable can be autocorrelated either (+) or (−) if its value at a given point in space is associated with its measures at other locations. (Simoni L et al 2000 Amer J Hum Genet 66:262).

Autocrine: Signal production within a cell in response to external stimuli.

Autocrine Stimulation: Cells infected by proto-oncogene carrying virus secrete a growth factor that further stimulates the cell's proliferation. ►proto-oncogenes, ►paracrine stimulation

Autoecious: A parasite that completes its life cycle on the same host.

Autogamy: A process of self-fertilization common in hermaphroditic and monoecious plants; autogamy in the unicellular animals, *Paramecia*, is preceded by meiosis and one the four haploid products survive. This cell then divides into two cells by mitosis. These two identical cells may then fuse and a genetically homozygous diploid zygote is formed. ►allogamy

Autogenesis: ►Lamarckism

Autogenous Control: The own product of genes regulates the coding gene either in a positive or a negative way. In genetic networks the autogenous control appears superior to the non-autogenous system. The autogenous control better prevents false triggering due to transient fluctuations of input (Camas FM et al 2006 Proc Natl Acad Sci USA 103:12718). ►negative control, ►positive control, ►genetic network

Autogenous Evolution: Structures and organelles evolved through differentiation of the cells own system. ►exogenous evolution

Autogenous Suppression: The *Salmonella* RF2 translation termination protein occasionally fails to recognize or misreads the UGA stop codon resulting in readthrough by suppressing termination. ►translation termination, ►readthrough, ►recoding, ►stop codon

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Autograft: The tissue transplantation is within one individual. ►homograft

Autoimmune Disease: The immune system fails to recognize the cell's own antigens and attacks them. In many instances altered glycosylation is responsible for the pathogenesis. Normally the lymphocytes with defects in self-antigen recognition are eliminated by apoptosis. It has been shown that receptor tyrosine kinases (Tyro 3, Axl, Mer) plays an essential regulatory role in the development of the immune response. Normally these receptors control the function of antigen presenting cells by supplying growth-promoting and pro-survival molecules. They also seem to have negative control. Mutation of these receptors may disable the binding of gamma interferon and the inability to clear the dying cells results in overactivity of the macrophages that then attack the body's own cells (Lu Q, Lemke G 2001 Science 293:306). The regulatory $CD4^+$ $CD25^+$ T cells can suppress the autoreactive T cells by engaging the B7 protein molecules on the surface of the target T cells (Paust S et al 2004 Proc Natl Acad Sci USA 101:10398). Mutation in ICOS, an essential co-stimulatory receptor of follicular T cells results in overproduction of IL-21 and fails to repress autoantibody formation. A RING-type ubiquitin ligase can repress these T cells and autoimmunity (Vinuesa CG et al 2005 Nature [Lond] 435:452).

Lupus erythematosus cells (a variety of skin and possibly visceral inflammations) make antibodies against their own DNA and RNA. In insulin-dependent diabetes the insulin producer β cells of the pancreas are attacked by the body's immune system, coded for by the major histocompatibility genes. The Rasmussen's encephalitis, a rare form of epilepsy, and the paraneoplastic neurodegenerative syndrome (PNS), both are caused by autoantibodies against the glutamate receptors of the nervous system. PNS is a rare sign of cancer and often the patient is unaware of the cancer. The symptoms are generally memory loss, sensory deficiency, motor dysfunction or blindness. The most common cause is breast or ovarian or small-cell lung cancer. The tumor cells express proteins that are normally only expressed in neurons. The $CD8^+$ T cells are then activated and the immune lymphocytes somehow cross the blood-brain barrier and evoke neuronal degeneration (Albert ML, Darnell RB 2004 Nature Rev Cancer 4:36). Herpes Simplex virus Type 1 expresses a coat protein which recognizes autoreactive T cells targeting mouse corneal antigens and may cause stromal keratitis (inflammation of the fibrous coat of the eye). Autoimmune diseases include a series of different anomalies (p = prevalence, r = risk of siblings relative to risks in the general population): psoriasis (p: 2.8, r: 6), rheumatoid arthritis (p:1, r: 8), goiter (p: 0.5, r: 15), insulin-dependent diabetes (p: 0.4, r: 1.6), ankylosing spondylitis (p: 0.13, r: 54), multiple sclerosis (p: 0.1, r: 20), lupus erythematosus (p: 0.1, r: 20), Crohn disease (p: 0.06, r: 20), narcolepsy (p: 0.06, r: 12), celiac disease (p: 0.05, r: 60), cirrhosis of the liver (p (0.008, r: 100). Autoimmune diseases have been attributed to increased V(J)D recombination in a class of B (B-1) lymphocytes as a result of increased RAG activity. Several autoimmune diseases (multiple sclerosis, rheumatoid arthritis) are more prevalent in females. The cause is apparently the difference in response to hormones of the T_H1 and T_H2 lymphocytes. Low estrogen level T_H1 cells secrete IL-2, INF-γ and lymphotoxins due to which, multiple sclerosis and rheumatoid arthritis are aggravated. At high estrogen (increased progesterone, testosterone) levels, T_H2 cells promote IL-4, IL-5, IL-6, IL-10. As a consequence, during pregnancy the symptoms of multiple sclerosis and rheumatoid arthritis are mitigated but lupus erythematosus may be aggravated. Immune therapies are being sought for the cure of these diseases (Steinman L 2004 Science 305:212). Autoimmune diseases seem to be clustered in certain families because they share common environment, genes and the interaction of the two. Protein tyrosine-phosphatase (PTPN22, 1p13) is lymphoid-specific and intracellular. Fc gamma RIII receptor may mediate early neutrophil recruitment in immune complex-mediated inflammation and reduced copy number of the gene increases the susceptibility to systemic lupus erythematosus, microscopic polyangiitis and Wegener's granulomatosis (6p21.3). However, the organ-specific Graves' disease or Addison's disease did not show this association (Fanciulli M et al 2007 Nature Genet 39:721). Single nucleotide polymorphism in this gene confers four autoimmune phenotypes: Type 1 diabetes (T1D), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Hashimoto thyroiditis (HT). The Multiple Autoimmune Disease Genetics Consortium survey detected nine "core" diseases, which included at least two autoimmune phenotypes: rheumatoid arthritis, systemic lupus erythematosus, type 1 diabetes, multiple sclerosis, autoimmune thyroid diseases (Hashimoto thyroiditis), Graves disease, juvenile rheumatoid arthritis, inflammatory bowel disease (Crohn disease), psoriasis and primary Sjögren syndrome (Criswell LA et al 2005 Am J Hum Genet 76:561). (See named diseases under separate entries, ►immunotherapy, ►statins, ►PPAR, ►CTLA4, ►AIRE, ►IPEX, ►HLA, ►NF-κB, ►complement, ►B7 protein, ►T cell, ►Sjögren syndrome, ►goiter, ►Hashimoto disease, ►Goodpasture syndrome, ►APECED, ►bullous pemphigoid autoimmune disease, ►hemolytic anemia, ►*Borrelia*, ►V(J)D, ►RAG, ►B cell, ►T helper cell, ►signal transduction, ►interferon,

►antigen presenting cell, ►ICOS, ►interleukins, ►IL-21, ►RING-finger, ►ubiquitin, ►lymphotoxins, ►TGF, ►immunoglobulins, ►monoclonal antibody therapies, ►caspase, ►ALPS, ►epitope spreading, ►apoptosis, ►stem cells, ►T cell vaccination; Marrack P et al 2001 Nature Med 7:899; Leadbetter EA et al 2002 Nature [Lond] 416:603; Malek TR, Bayer AL 2004 Nature Rev Immunol 4:665; Feldman M, Steinman L 2005 Nature [Lond] 435:612 and other articles in the same issue; Gregersen PK, Behrens TW 2006 Nature Rev Genet 7:917).

Autoimmune Lymphoproliferative Disease: ALPS.

Autoimmune Polyendocrinopathy: APECED.

Autoinduction: A type of cell-to-cell interaction in bacteria and other organisms. The cells release small extracellular signaling molecules, which are taken up again by the cells. It adjusts gene expression in the cells responding to a level appropriate for the local density of the signaling cells. The autoinducer signals may be acylated homoserine lactones, Tra proteins, amino acids, short peptides and pheromones. ►autoregulation, ►pheromones, ►quorum sensing, ►tra, ►Tata, ►homoserine ►lactone; Tata JR 2000 Insect Biochem Mol Biol 30:645.

Autoinhibition: Inactive conformation of a receptor in quiescent cells. It is controlled by a variety of mechanisms such autophosphorylation, ligand binding, etc. Schlessinger J 2003 Science 300:750.

Autointerference: The process when defective virions may interfere with the replication of intact ones.

Autologous: Its origin is within the cell or individual; a self-made molecule.

Autologous Transplantation: Used in cancer therapy by implanting e.g., genetically modified bone marrow cells of the same individual. Thereby, the undesirable immune rejection may be avoided. ►immune system, ►gene therapy, ►cancer gene therapy

Autolysis: Is the decomposition of cells and cell content by the action of the natural enzymes of the cells. It takes place generally in injured cells.

Automaton: Is a machine that can react automatically to preset conditions. The biological system can also be considered an automaton, which maintains continuous operations in response to potentially variable conditions. An applied possibility is to devise a DNA computer, which has three main functional parts. The first measures the absence or excess of a particular nucleic acid (RNA) in the cell that indicates e.g., a particular disease. The second part identifies the mRNA and the third part then releases an antisense RNA, which can suppress e.g., small-cell lung carcinoma or prostate cancer. Such device can work under selected laboratory conditions but its clinical applicability is still awaited. ►DNA computer, ►small cell lung carcinoma, ►prostate cancer; Benenson Y et al 2004 Nature [Lond] 429:423.

Automixis: ►Self fertilization

Automutagen: A metabolite of the organism may become mutagenic, e.g., tryptophan.

Autonomous Controlling Element: A plant transposable element carries the transposase function and controls its own movement, e.g., Ac versus Ds in maize, the latter is a defective form of Ac, incapable of moving by its own power unless the autonomous (intact) Ac is present in the cell. ►transposable elements, ►*Ac - Ds*, ►*Spm*

Autonomous Developmental Specification: Maternal information or prelocalized morphogenetic information regulates the initiation of transcription of morphogenetic genes. ►morphogen

Autonomous Parvovirus: Uses the host system for productive replication. Only strain B19 is pathogenic in humans. They display antineoplastic properties in Ehrlich ascites tumors. ►parvoviruses, ►ascites

Autonomously Replicating Pieces: ►macronucleus

Autonomously Replicating Sequences: ►ARS

Autonomy: Cells transplanted into tissues of different genotype, or forming parts of genetically different sectors, still maintain the expression encoded by their genotype, and are not, or barely, affected by the genetically different tissue environment.

Autophagy: Destruction of cytoplasmic particles within a cell by delivering dispensable structures or molecules (in autophagosome vehicles), to lysosomes or to vacuoles (see Fig. A142). Autophagosomes are large (500–100 nm) double-membrane vesicles. Autophagy, a pathway of cell elimination, is different from apoptosis. This process gets rid of and re-utilizes the molecules during adverse conditions (e.g., cell starvation). The same machinery may degrade infective microorganisms. Before autophagy, isolation membranes sequester certain molecules. In resting cells, TOR inhibits autophagy; starvation and rapamycin dephosphorylate, and inactivate TOR, and can lead to the formation of *autophagosomes*. Autophagosomes can fuse with lysosomes and non-degraded proteins and viruses can be transported to the cell surface. Degradation within the lysosomes is also called *microautophagy*. In *macro-autophagy,* the subcellular membranes are altered and part of the cytoplasm is sequestered into double-membrane-surrounded

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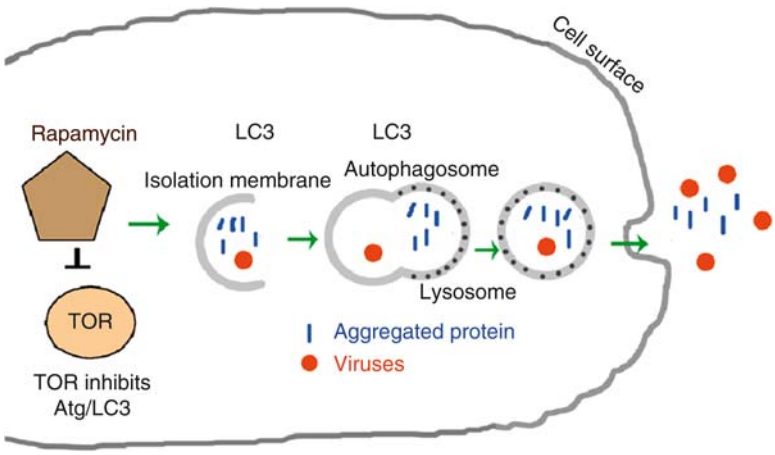

Figure A142. Autophagy

autophagic vacuoles (autophagosomes). Caspase 8 mediates autophagy through ATG7 (an ATP-dependent activator) and beclin 1 (Yu L et al 2004 Science 304:1500). Autophagy may have both advantageous (defensive) and deleterious features for health and disease (Shintani T, Klionsky DJ 2004 Science 306:990). Loss of autophagy in the central nervous system leads to neurodegeneration mice (Komatsu M et al 2006 Nature [Lond] 411:880; Hara T et al 2006 Nature [Lond] 441:885). When the proteasomes cannot handle the load, the non-degraded proteins may aggregate as *aggresomes*. Eventually the aggresomes can also be degraded (Wileman T 2006 Science 312:875). ►lysosomes, ►aggresome, ►ubiquitin, ►apoptosis, ►beclin, ►pexophagy, ►dauer larva, ►trinucleotide repeat, ►TORs, ►rapamycin, ►endoplasmic reticulum-associated degradation; Klionsky DJ, Emr SD 2000 Science 290:1717; Subramani S 2001 Developmental Cell 1:6; Ohsumi Y 2001 Nat. Rev Mol Cell Biol 2:211; Khalfan W, Klionsky DJ 2002 Curr. Opin Cell Biol 14:468; yeast microautophagy; Duybouloz F et al 2005 Mol Cell 19:15, mini review: Yoshimori T 2007 Cell 128:833.

Autophene: Genetically determined trait, which is expressed independently of the position in case of transplantation. ►allophenic

Autophosphorylation: Upon binding a ligand to a receptor it results in rapid phosphorylation of the receptor by its own subunits, e.g., by members of a dimeric molecule generally at tyrosine sites. ►receptor tyrosine kinase

Autoploid (autopolyploid): Autoploid is the presence of more than two complete sets of identical genomes per cell. Autopolyploids may be [auto] tetraploid (2n = 4x), hexaploid (2n = 6x), octaploid (2n = 8x), etc. Autotetraploids in meiosis may pair as quadrivalents, however, at a particular point only two chromosomes synapse (see Fig. A143). In autopolyploids, pairing may be also as two bivalents, one trivalent and univalent, and may form four univalents. When all chromosomes pair as bivalents, it is called selective pairing, and segregation of genes resemble that of diploids with duplicate genes. Autotetraploids

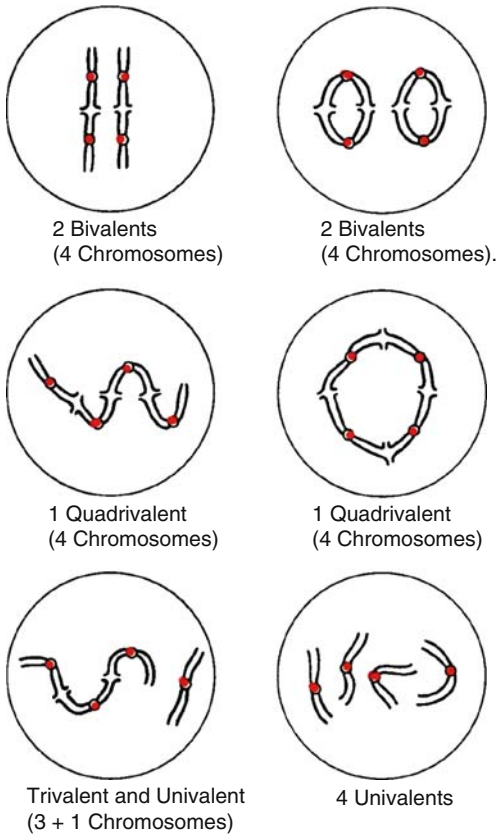

Figure A143. Association of homologs in autotetraploids

may carry a different allele in each of the four chromosomes; therefore, they can produce a larger variety of gametes than diploids. The maximal number of gametic combinations can be determined by the formula (see Table A7 and A8):

$\begin{bmatrix} n \\ x \end{bmatrix}$ where n = the total number of alleles, and x = the number of alleles in a gamete, thus in autotetraploids it becomes $\begin{bmatrix} 4 \\ 2 \end{bmatrix}$ *for octaploids it is* $\begin{bmatrix} 8 \\ 4 \end{bmatrix}$ and these can be rewritten as $\frac{4\times3}{2\times1} = 6$ for autotetraploids and $\frac{8\times7\times6\times5}{4\times3\times2\times1} = 70$ for autooctaploids, and this means that the number of allelic combinations possible with 4 different alleles are 6 types ([4 × 3]/[2 × 1] = 6) of gametes and in an octaploid with 8 different alleles ([8 × 7 × 6 ×5]/[4 × 3 × 2 × 1] = 70), the total number of gametic types is 70.

In case all the four alleles are dominant, AAAA, the individual is a quadruplex, AAAa = triplex, AAaa = duplex, Aaaa = simplex and aaaa = nulliplex. The segregation ratios in F_2 depend on whether there is crossing over between the gene and the centromere, the type of pairing (as indicated above) and the type of disjunction at anaphase II (alpha parameter). The phenotypic proportions in F_2 are determined by the gametic output of the parents or selfed individuals. The gametic output and F_2 segregation of autopolyploids is very difficult to generalize because the genes are rarely linked absolutely to the centromere and the frequency of recombination may vary from 0 to 50%. There are additional variables that may be estimated by the alpha parameter. Segregation ratios at higher level of polyploidy can be predicted only theoretically, the actual results may be quite different, however. ►synteny, ►bivalent, ►trivalent, ►univalent, ►synteny, ►alpha parameter, ►maximum ►equational ►segregation; Haldane JBS 1930 J Genet 22:359; Rédei GP 1982 Genetics, Macmillan, New York; see chromosome association diagram.

Autopodium: The skeletal portion of the hand and foot.

Autoprocessing: Occurs when a sequence of a protein (e.g., the C-terminal) is involved in its processing.

Table A7. Gametic output of autotetraploids

	Absolute Linkage*			Independence from Centromere†		
Parent	AA	Aa	aa	AA	AA	aa
AAAa	1	1	0	13	10	1 (4.2%)
AAaa	1	4	1 (16.6%)	2	5	2 (22.2%)
Aaaa	0	1	1 (50.0%)	1	10	13 (54.2%)

Table A8. Phenotypic segregation ratios in autotetraploids in case the dominance is complete in F_2

	Absolute Linkage*		Independence from Centromere†	
Mating	Dominant	Recessive	Dominant	Recessive
AAAa selfed	1	0	575	1
AAaa Selfed	35	1	19.3	1
Aaaa selfed	3	1	2.4	1
AAAa×AAaa	1	0	107	1
AAAa×Aaaa	1	0	43.3	1
AAAa×aaaa	1	0	23	1
AAaa×Aaaa	11	1	7.3	1
AAaa×aaaa	5	1	3.5	1
Aaaa×aaaa	1	1	1	1.2

*No recombination between gene and centromere (chromosome segregation).

† The distance between gene and centromere is 50 map units or more, and therefore recombination occurs freely as if they (gene and centromere) would not be syntenic (chromatid segregation or maximum equational segregation).

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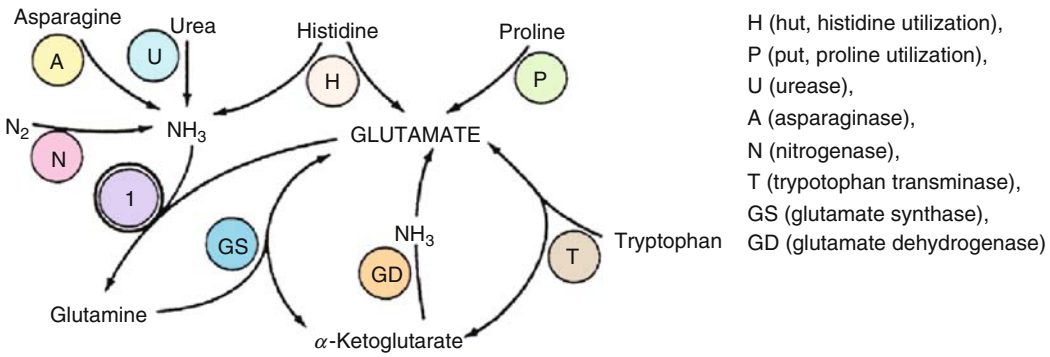

Figure A144. Metabolic steps involved in the regulation and autoregulation of Glutamine synthetase (1)

Autorad: Lab slang for autoradiogram. ►autoradiography

Autoradiography: Labeling technique by which a radioactive substance reveals its own position in a cell or on a chromatogram when brought into contact with photographic film. For cytological analyses, most commonly H^3-labeled thymidine is used because it gives the clearest resolution of chromosomal regions without serious DNA breakage, whereas in molecular genetics the much higher energy P^{32}-labeled compounds are employed usually. ►non-radioactive labels, ►immunoprobes; Taylor JH et al 1957 Proc Natl Acad Sci USA 43:122.

Autoreactive: When the lymphocytes recognize the individual's own molecules and develop an immune reaction to them. ►autoimmune disease

Autoreduplication: self-duplication.

Autoregulation: Occurs when a compound (or system) controls the rate of its own synthesis (see Fig. A144). For, e.g., the bacterium *Klebsiella aerogenes* uses glutamine dehydrogenase to make glutamate from α-keto-glutarate and ammonia, if the concentration of the latter exceeds 1 nM. If the concentration of ammonia is low, glutamate dehydrogenase cannot function to an appreciable extent. In this case, the ammonia + glutamate are converted into glutamine by glutamate synthetase. The active form of glutamine synthetase is non-adenylylated. In the presence of high concentration of ammonia, the enzyme is adenylylated and thus, the activity is reduced by this mechanism of autoregulation. In its non-adenylylated states it represses glutamate dehydrogenase instead. ►regulation of gene activity, ►nitrogen fixation, ►genetic network; Magasanik B et al 1974 Curr Top Cell Reg 8:119; Chandler DS et al 2001 Nucleic Acids Res 29:3012; Isaacs FJ et al 2003 Proc Natl Acad Sci USA 100:7714.

Autosegregation: May take place in an apomictic or vegetatively multiplied organism due to chromosomal loss or somatic mutation. ►apomixis, ►mutation

Autosexing: Identification of sex by genetic markers rather than by the genitalia. Silkworm breeders and poultry producers have exploited this procedure. Homozygosity for the *B* (barring) genes suppresses the appearance of colored spots on the head of the newly hatched chicks, controlled by this sex-linked gene (remember that in birds the males are homogametic). The *B* gene is dominant yet it shows clear dosage effect. In the females that are heterogametic, the spot is evident. Thus, the hens can be separated early from the roosters when the recognition of gender by anatomy is very difficult. Since most of the roosters will be used for meat production and the hens for egg production, they can be fed and managed accordingly. In the silkworm, the male cocoons (chrysalis) produce 25 to 30% more silk than the females and therefore, autosexing may have economic advantage. An electronic device may sort the silkworm eggs according to color (sex). (see Fig. A145; ►chromosomal sex determination, ►sexing)

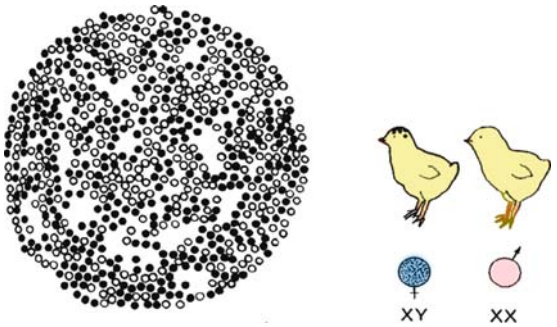

Figure A145. Left: Autosexing in the silkworm. The dominant gene in the Y chromosome permits the distinction between the eggs which will hatch to become a male (pale color) and female (dark). Right: The homozygous male (b/b) chicks are light colored while the hemizygous b/o females develop colored spots on the head. (In the Lepidoptera and birds the males are WW and the females are WZ)

Autosomal Dominant Mutation: Readily detected and identified in many instances because the novel type appears suddenly without precedence in the pedigree. Achondroplasia in humans is frequently cited as such an example. The homozygotes generally suffer perinatal death. Therefore, most of the achondroplasiac dwarfs are heterozygotes and new mutants. These dwarfs are of normal and frequently of superior intelligence. One must not forget that over 70 gene loci are responsible for various types of dwarfing in humans. Autosomal dominant mutation rates (per gamete/generation) in human populations for ten diseases vary from 4 to 100 × 10^{-6}. ►mutation rate, ►achondroplasia

Autosomal Recessive Lethal Assay: A tester stock used for the detection of recessive second chromosomal lethals in *Drosophila.* It is of the following genetic constitution: *Cy L/Pm* where *Cy* (*Curly*) *L* (*Lobe*) and *Pm* (*Plum*) are heterozygous viable but homozygous lethal dominant genes. The *Cy* chromosome generally carries three inversions to prevent the recovery of crossovers. The heterozygotes of either sex are crossed with a mate that carried no mutation in either of the two second-chromosomes before the test. Single F_1 male(s) are then backcrossed with the *Cy L/Pm* female tester. From their offspring *Cy L* individual sibs are mated. From this mating, an F_2 is obtained. If all the survivors are *Cy L*, this indicates that a new lethal mutation occurred in the grandfathers' or grandmothers' 2nd chromosome and therefore *non-Curly* and *non-Lobe homozygous* individuals could not live. The diagram does not show the genotypes in the F_2 (see Fig. A146). ►sex-linked recessive lethal assays

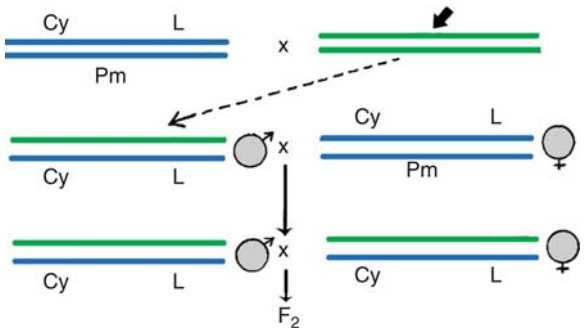

Figure A146. Autosomal recessive lethal assay

Autosome: Autosome is a chromosome that is not a sex chromosome. ►chromosomal sex determination

Autosyndesis: May take place between homoeologous chromosomes in the absence of homoeologous pairing-suppressor genes. ►homoeologous, ►chromosome 5B

Autotoxic Enterogenous Cyanosis: An obsolete name for human familial NADH-methemoglobin deficiency. ►methemoglobin

Autotroph: Can synthesize cellular C- and N- containing molecules from carbon dioxide and ammonia.

Autozygous: A genotype, which is not just homozygous but the alleles at the locus are *identical by descent*. ►allozygous, ►inbreeding coefficient, ►coancestry, ►homozygosity

Autozygosity Mapping: ►homozygosity mapping, ►inbreeding coefficient; Kruglyak L et al 1995 Am J Hum Genet 56:519.

Auxanography: A method for mutant selection. A minimal medium is over-layered with auxotrophic spore or cell suspension and subsequently to different segments of the plate small quantities of various substances that the cells may need for growth are added. Where growth occurs, the cells utilize the compounds added and their nutritional requirement is identified.

Auxilin: 100-kDa brain-specific chaperone with C-terminal homology to DnaJ. Auxilin-bound clathrin mediates also uncoating of clathrin-coated vesicles (Fotin A et al 2004 Nature [Lond] 432:649). ►DnaJ, ►clathrin

Auxins: phytohormones (morphogens) produced by the plant metabolism such as indole-3-acetic acid or of synthetic origin such as α-naphthalene acetic acid or 2,4-dichloro-phenoxyacetic acid (see Fig. A147). They play important role in cell elongation, signal transduction and required supplements for proliferation and regeneration in tissue culture. The transport of auxins in the plant tissues is regulated by chemosmosis aided by various transporter proteins. Auxin is synthesized in the leaves of the plants and it is transported to the stem apex where it plays an important role in the generation of flowers. Auxins also regulate root development. The *pin* family of proteins controls the transport of auxin either to the shoot and/or to the root and is essential for the development/growth of these organs (Kaplinsky NJ et al 2004 Science 306:822). The (►*PLETHORA PLT*) genes are required for *PIN* transcription and for stabilizing auxin at the root tip (Blilou I et al 2005 Nature [Lond] 433:39). The auxin-binding protein (ABP1)—with its crystal structure known—is essential for normal function of auxin (Napier RM et al 2002 Plant Mol Biol 49:373). The auxin-response factor (ARF) and AUX/IAA proteins are involved in regulation of auxin-dependent genes. The latter binds ARF and ARF binds directly to DNA (Hagen G, Guilfoyle T 2002 Plant Mol Biol 49:373; Liscum E, Reed JW 2002 Plant Mol Biol 49:387). These proteins are considered repressor of gene expression.

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Figure A147. Pin-like mutants of *Arabidopsis* do not develop normal flowes at the tip of the stem. (Rédei, unpublished)

H^+ -pyrophosphatase (AVP1) controls auxin distribution and auxin-mediated shoot and root development (Li J et al 2005 Science 310:121). Auxin aides the interaction between the large number of AUX/IAA family of proteins and the ubiquitin ligase SCF, and the TIR1 and three other F-box proteins appear to be auxin receptors and transport inhibitors, which degrades AUX/IAA (Dharmasiri N et al 2005 Nature [Lond] 435:441; Kepinski S, Leyser O 2005 *ibid*. 446). The leucine-rich repeat domain of TIR1 of *Arabidopsis* contains an inositol hexakisphosphate co-factor and recognizes auxin and the AUX/IAA polypeptide substrate through a single surface pocket. Anchored to the base of the TIR1 pocket, auxin binds to a partially promiscuous site, which can also accommodate various auxin analogues (such as naphthalene acetic acid and 2,4-D). Docked on top of auxin, the AUX/IAA substrate peptide occupies the rest of the TIR1 pocket and completely encloses the hormone-binding site (Tan X et al 2007 Nature [Lond] 446:640). Inositol hexakisphosphate (IP6) and inositol heptakisphosphate (IP7) kinase activities generally regulate cell growth and morphology (Mulugu S et al 2007 Science 316:106).

Auxin modulates the response to gibberellin and the latter opposes the nuclear DELLA proteins, which are growth repressors (Fu X, and Harberd NP 2003 Nature [Lond] 421:740). Genes (*iaaH, iaaM*) in the Ti plasmid of *Agrobacterium* have instructions for their production and regulation, and these genes play a role in crown gall formation (in cooperation with cytokinins). An auxin response element first identified in the octopine synthase (*ocs*) gene of *Agrobacterium tumefaciens* (AuxRe [named *as-1* in cauliflower mosaic virus]) is an enhancer and it is present in many genes. The *ocs/as-1* consensus consists of a more or less well-conserved 20- bp direct repeat with a 4 base spacer: TGACGTAAGCGCTGACGTAA. These elements respond to various auxins, salicylic acid, methyljasmonate and many other diverse compounds. The binding transcription factors have basic leucine zipper (bZip) motifs. Indole-3-acetic acid is biosynthesized mainly from tryptophan (aminotransferase) through indole-3-pyruvate (decarboxylase). ►plant hormones, ►crown gall, ►Ti plasmid, ►embryogenesis somatic, ►ARF1, ►SCF, ►chemosmosis, ►bZip, ►SAUR, ►sirtuin, ►phosphoinositides; Guilfoyle TJ, Hagen G 1999 In: Reynolds PHS (ed) Inducible gene expression in plants. CABI, New York, p 219; Sabatini S et al 1999 Cell 1999:463; Zhao Y et al 2001 Science 291:306; Gray WM et al 2001 Nature [Lond] 414:271; Leyser O 2002 Annu Rev Plant Biol 53:377.

Axiom: Is a self-evident statement, which does not require proof; a basic tenet, e.g., nucleic acids represent genetic material.

Auxonography: ►auxotrophy

Auxotroph: A mutant that requires nutritive(s) not needed by the wild type (prototroph) (see Fig. A148). Auxotrophic mutations have been extensively used for the study of biochemical pathways and for the identification enzymes catalyzing particular metabolic steps. In genetic analysis, auxotrophs facilitate selective techniques in backmutation, recombination, transformation, etc. A pyridoxine deficiency, causing seizure in humans, has been identified.

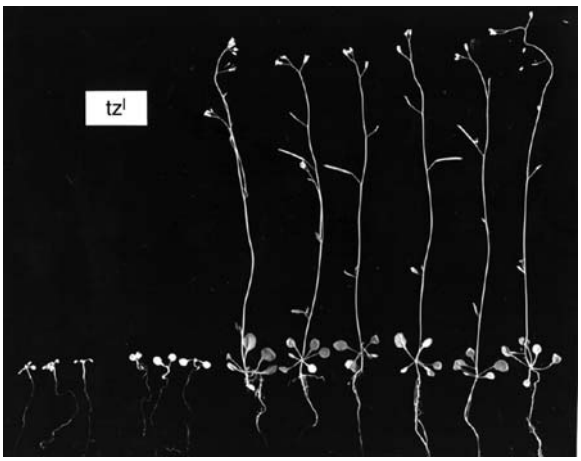

Figure A148. Left: Thiazole auxotrophs of *Arabidopsis* on basal medium; Right: on thiamine medium. (From GP Rédei, unpublished)

True auxotrophic animal mutations are exceptional and are also rare in higher plants. In *Arabidopsis,* over 200 mutations were obtained in the thiamine pathway without any obligate auxotrophy for other metabolites. The scarcity of auxotrophic mutations may be

due to redundancy of the genomes, alternative metabolic pathways and to compensatory effects in large genetic networks. ►pyridoxine, ►autotroph, ►redundancy, ►genetic network; Rédei GP 1982 Genetics, Macmillan, New York.

AuxRE (auxin response element): ►ARF1, ►auxin

Avastin (Bevacizumab): Avastin is a monoclonal antibody drug targeting vascular endothelial growth factor (VEGF) to reduce the blood supply (angiogenesis) for cancer cells. ►angiogenesis, ►VEGF, ►monoclonal antibody, ►biomarkers

AVED (ataxia with vitamin E deficiency): Caused by mutation in the large subunit of microsomal triglyceride transfer protein (encoded in human chromosome 8q13). Although the intestinal absorption of α-tocopherol is normal, the hepatic secretion into the blood is defective. The condition is very similar to Friedreich ataxia. ►Friedreich ataxia

Avena: A genus of grasses (oats) with basic chromosome numbers x = 7 and form an allopolyploid series, 2n, 4n, 6n.

Average: Arithmetic mean, i.e. the sum of all measurements (x) divided by the number of measurements (N): $\bar{x} = \frac{\sum x}{N}$. ►mean, ►median, ►mode

Average Inbreeding Coefficient: α.

Avian: Pertaining to the taxonomic class of *Aves*. (sing. *Avis,* bird[s]). ►chicken; http://www.grcp.ucdavis.edu/publications/doc20/full.pdf.

Avian Erythroblastosis (erbB): Viral oncogene (prevents maturation of the red blood cells in fowl) has its cellular homolog as a proto-oncogene in several eukaryotes. It is a protein kinase, phosphorylating primarily tyrosine residues. The normal allele specifies a plasma membrane receptor of epidermal growth factor (EGF). ►erythroblastosis ►fetalis

Avian Influenza Virus: ►influenza

Avian MC29 Myelocytomatosis: A viral oncogene (*myc,* causes carcinoma, sarcoma and myelocytoma [a kind of leukemia]). It is present as a cellular proto-oncogene in vertebrates and its homologs are also present in plant cells. ►oncogene, ►proto-oncogene, ►carcinoma, ►sarcoma, ►leukemias

Avian Myeloblastosis: ►MYB oncogene

Avian Sarcoma Virus: ►ASV

Avidian: A computer generated "artificial life form" useful for simulating genetics and evolutionary processes in a virtual environment of cybernetics. ►genetics digital, ►cybernetics

Avidin: A ca. 68,000 M_r protein of four subunits, each having strong affinity to biotin. It binds strongly to any molecule complexed with biotin such as nucleic acids, and biotin containing enzymes. It is widely used for non-isotopic labeling of nucleic acids. Originally, it was found and isolated from raw egg white. Eating raw eggs may cause biotin deficiency (cooking inactivates it). It is isolated also from *Streptomyces avidinii* under the name streptavidin. ►biotinylation, ►genomic subtraction

Avidity: ►antibody

Avirulence: The lack of competence for causing pathological effects by an infectious agent.

Avogadro Number: The number of molecules (= 6.02×10^{23}) in a gram molecular weight, a constant for all molecules.

Avoidance Learning: This is a classical test of animal behavior. In a two-compartment box one is electrically wired to provide test animals, an electric shock after a light turns on. After a learning period, some of the animals immediately move to the safe compartment when they see the light signals and learn that the shock comes from one compartment. The learning ability of inbred mice strains is genetically different. In some, about half of the individuals "learn," in others only 10% associates the light signal with the shock. In *Drosophila* olfactory sensory neurons mediate the avoidance of CO_2 emitted by stressed flies (Suh GSB et al 2004 Nature [Lond] 431:854). ►behavior genetics

Avuncular: Ancestral relatedness such as existing between nephews/nieces and uncles/aunts.

Awn (arista): Awn is a part of the glume present in some monocot plants (wheat). It supposedly has a role in photosynthesis, water regulation of the kernel and in seed dispersal. ►glume; Elbaum R et al 2007 Science 316:884.

Axenic: The pure culture of organisms or cells without any contamination by other (micro) organisms. ►aseptic culture, ►tissue culture

Axenfeld-Rieger Anomaly (FKHL7/FOXC1, 6p25): Anterior eye segment defect and glaucoma caused by mutation in the human homolog of the *Drosophila* forkhead gene, FOXC1 (see Fig. A149). Additional loci at 4q25 (PITX2, a bicoid-related protein), 13q14, and 16q22-q24 (FOXC2 forkhead-like).
►forkhead, ►bicoid, ►glaucoma; Priston M et al 2001 Hum Mol Genet 10:1631; Lines MA et al 2002 Hum Mol Genet 11:1177.

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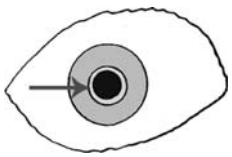

Figure A149. In the Axenfeld-Rieger syndrome within a reduced size iris, a light-colored ring (the sphincter muscle) is conspicuous around the pupil

Axial Elements: The lateral elements of the tripartite synaptonemal complex. ►synaptonemal complex

Axillary: Formed in the axil, the upper surface of the area between the leaf petiole and stem.

Axin: A protein-controlling body axis formation. Mutant axin may interfere with the normal developmental pathway and cause cancer, especially when the mismatch repair is defective. It is homologous to conductin. ►conductin, ►Wnt, ►DNA ►repair

Axis of Asymmetry: Axis through which objects or molecules form mirror images. In the body of the majority of organisms three axes are recognized: anterior–posterior (front–hind), dorsal–ventral (back–abdominal) and left–right. Recently, genes controlling asymmetry of the body have been identified. It had been known for a long time that changing the placement of internal organs has multiple deleterious consequences ►situs inversus viscerum. It has been shown now in the *lefty* mouse mutant that the expression of the transforming growth factor (TGFβ) family plays the role of a morphogen in controlling asymmetry by expressing only in the left half of the gastrula. This asymmetry is transient and sets on before lateral asymmetry becomes visible. Similar genetically-controlled mechanisms have also been discovered in chickens and other organisms. ►morphogen, ►TGF, ►activin, ►Kartagener syndrome, ►asymmetric cell division, ►situs inversus visceri; Lall S, Patel NH 2001 Annu Rev Genet 35:407.

Axl: A receptor tyrosine kinase, which is human myeloid leukemia transforming protein. ►leukemias

Axon: A long nerve fiber that, generally in a bundle surrounded by a myelin sheath, communicates impulses between the central and the peripheral nervous system. Organelles and molecules can be transported along the nerve axons outward from the cell or back to the cell. ►neurogenesis, ►netrin, ►Slit, ►Robo, ►comm, ►neuropilin, ►axotomy; Kamal A et al 2000 Neuron 28:449; axonal transport; Stokin GB, Goldstein LSB 2006 Annu Rev Biochem 75:607.

Axon Guidance: Axons grow and move through the embryonal body toward their targets and allow for synaptic connections of the neurons. Many proteins guide their advance. Some axons follow the same path, and bundle together by a process called fasciculation. Brain wiring and axon guidance can be monitored with the aid of the *PLAP* (placental alkaline phosphatase) vector equipped with an IRES site 5′ to the *PLAP* gene. The vector includes another part carrying *β-galactosidase* and *neomycin phosphotransferase* (*G418*^{r}). This portion of it is expressed by virtue of its fusion to neural body cell-specific promoter. Transformants can be selected on neomycin media. The *β-gal* gene marks the cell body by blue color on X-gal medium; the *PLAP* gene is expressed exclusively in the dendritic part of the neurons. Thus, the wiring pattern of the brain can be monitored without laborious chemical purification. The Netrin, Slit, Semaphorin and Ephrine families of proteins—besides being involved with axons—contribute to the development of many other organs too by regulating transcription and translation of morphogenetic genes (Hinck L 2004 Developmental Cell 7:783). ►axon, ►Parkinson disease, ►neuron, ►IRES, ►G418, ►β-galactosidase, ►X-gal, ►semaphorin, ►netrin; Leighton PA et al 2001 Nature [Lond] 410:175; Lin MZ, Greenberg ME 2000 Cell 101:239; Stein E, Tessier-Lavigne M 2001 Science 291:1928; Patel BN, Van Vactor DL 2002 Curr. Opin Cell Biol 14:221; Dixon BJ 2002 Science 298:1959; Zhu F-Q et al 2004 Neuron 42:897.

Axoneme: Cylindrical structures of microtubule doublets and about 250 attached polypeptides that are the major part of cilia, flagella and sperm. Two rows of the motor protein dynein are situated along the microtubules. ►microtubule, ►dynein, ►cilia; Nicastro D et al 2006 Science 313:944.

Axoplasm: The cytoplasm of axons. ►axon, ►cilia

Axotomy: Lesion of axons; may affect expression of genes. ►regulation of gene activity

5-Azacytidine: A pyrimidine analog (and suspected carcinogen) that interferes with methylation of DNA bases and may even restore the function of genes silenced by methylation (see Fig. A150). 5-azacytidine covalently binds cytosine methyltransferase enzymes and dramatically reduces methylation of cytosine in the DNA (Santi DV et al 1984 Proc Natl Acad Sci [USA] 81:6993). It may affect differentiation and development because hypomethylated genes are preferentially transcribed. It is noteworthy that some small eukaryotic genomes (yeast, *Drosophila*) do not contain methylcytosine yet their genomes are regulated during development. ►methylation of DNA, ►housekeeping genes, ►fragile X, ►trichostatin

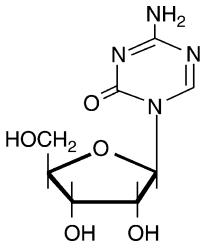

Figure A150. Azacytidine

Azaguanine: A toxic analog of guanine, it is readily incorporated into RNA or DNA (see Fig. A151). ►HAT medium

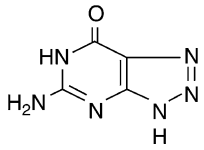

Figure A151. Azaguanine

8-Azaguanine Resistance: A commonly used marker in mammalian cell cultures; the resistance is based on a deficiency of the enzyme azaguanine-hypoxanthine phosphotransferase and therefore, this toxic purine cannot be processed by the metabolism. ►HAT medium

Azaserine (O-diazoacetyl-L-serine): An alkylating, antitumor, antifungal and mutagenic agent. The oral LD50 for rodents is 150–170 mg/kg. ►LD50

Azathiopurine (azathioprine): An anticancer, immunosuppressive drug (see Fig. A152). It is also a receptor of ultraviolet light A and increases the cells sensitivity to oxidative damage brought about by UV. Therefore, people who underwent azathioprine therapy may have increased risk for skin cancer (O'Donovan P et al 2005 Science 309:1871). ►thiopurine-*S*-methyltransferase [TPMT]

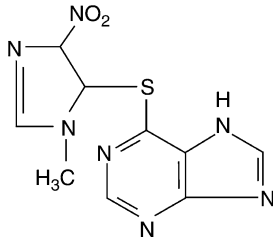

Figure A152. Azathiopurine

6-Azauracil: An antineoplastic pyrimidine analog; its nucleotide is inhibitory to orotidylic-acid decarboxylase and may repress the synthesis of orotidylic acid pyrophosphorylase, key enzymes in the de novo pathway of nucleotide synthesis. ►TIIFS

Azide: A compound with a NH_3; sodium azide, a respiratory inhibitor, is a strong mutagen for certain organisms at low pH but not for others. Nitrogenase enzymes may reduce azides to N_2 and NH_4. ►nitrogenase

Azidothymidine: ►AZT

Azoospermia: Human gene AZF (azoospermia factor) appears to be the expression of the DAZ (deleted in azoospermia) site and it has been assigned to human chromosome Yq11. At the AZF site three long palindromic sequences encoding 11 transcription units have been identified (Kuroda-Kawaguchi T et al 2001 Nature Genet 29:279). At Yq11.2, in the vicinity of AZF, is the DFFR (*Drosophila* fat-facet related), another spermatogenesis control gene. The frequency of the DAZ causes sterility is about 1.25×10^{-4} in men. There is no sperm in the ejaculate although the testes may produce sperm. This gene is substantially (42%) homologous to the *Drosophila* gene *boule* (*bol*) controlling meiotic G2 - M transition. Mouse gene *Dazla* is 33% homologous to DAZ. Both the mouse and the *Drosophila* genes are, however, autosomal yet they also involve male sterility. It has been shown recently that the human AZF gene was originally in the short arm of human chromosome 3 (where highly homologous sequences still exist), and it was transposed to the Y chromosome, amplified and pruned. The human Y chromosome encodes an RNA recognition motif, which is active particularly in the testes and the deletion of this motif may cause azoospermia. Histological analysis revealed that *Brek–/–* germ cells (deficient in a brain-enriched kinase) differentiated normally until the round-spermatid stage, but failed to undergo the normal change in morphology to become elongated spermatids. Testicular somatic cells appeared normal in these mice. Expression of Brek in testis was restricted to the germ cells, suggesting that the maturations of germ cells in *Brek–/–* mice are affected in a cell-autonomous manner. Brek seems to be essential for a late stage of spermatogenesis and may help to identify new targets for reproductive contraceptives and treatments against infertility (Kewa S et al 2006 Proc Natl Acad Sci USA 103:19344). ►holandric genes, ►*twine*, ►*pelota*, ►*boule* ►[*bol*], ►RBM, ►agonadism, ►oligospermia, ►CBADV, ►infertility; Hackstein JHP et al 2000 Trends Genet 16:565; Xu EY et al 2001 Proc Natl Acad Sci [USA] 98:7414.

Azorhizobium: ►nitrogen fixation

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Azotobacter: ►nitrogen fixation

AZT (azidothymidine, also called zidovudin): A thymidine analog with an azido (N_3) substitution of the 3′-OH group (see Fig. A153); it may slow down the reverse transcriptase activity of HIV virus by preferentially selecting this analog that has only minor effect on DNA polymerase of the mammalian cells. Unfortunately, some bone marrow damage is associated with the drug and this limits its usefulness in protecting against the full-scale development of AIDS. Mutations in the HIV reverse transcriptase may result in resistance against the drug by removing the AZTMP that blocks transcription. Eventually it may also debilitate the cells by the inhibition of DNA polymerase γ. It should be remembered that the Aschheim-Zondek test for pregnancy is also abbreviated as AZT. ►acquired immunodeficiency, ►AIDS, ►HIV, ►mtDNA; Lim SE, Copeland WC 2001 J Biol Chem 276:23616.

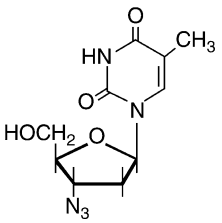

Figure A153. AZT

Azurocidin: ►antimicrobial peptides

Historical vignettes

The Cambridge (Massachusetts) City Council were not the first to disapprove of recombinant DNA. Joshuah Sylvester (1563–1618) answers the "New objection of Atheists, concerning the capacitie of the Ark":

"O profane mockers! if I but exclude
Out of this Vessel a vast multitude
Of since-born mongrels, that derive their birth
From monstrous medly of *Venerian* mirth:
Fantastick Mules, and spotted Leopards,
Of incest-heat ingendred afterwards:
So many sorts of Dogs, of Cocks, and Doves,
Since, dayly sprung from strange & mingled loves,
Wherein from time to time in various sort,
Dedalian Nature seems her to disport:
If plainer, yet I prove you space by space,
And foot by foot, that all this ample place,
By subtill judgement made and *Symmetrie*,
Might lodge so many creatures handsomely,
Sith every brace was *Geometricall*:
Nought resteth (*Momes*) for your reply at all;
If, who dispute with God, may be content
To take for current, Reason's argument."

– *The Complete Works of Joshuah Sylvester*, Vol. I, ed. Rev. Alexander B Grosart, printed for private circulation, 1880, p. 136

Ayala FJ 2007 Proc Natl Acad Sci [USA] 104 (Suppl. 1):8567

"On 1 July 1858, three papers were read by the [Linnean Society] society's undersecretary, George Busk, in the order of their date of composition: Darwin's abbreviated abstract of his 230-page essay from 1844; an 'abstract of abstract' that Darwin had written to the American botanist Asa Gray on 5 September 1857; and Wallace's essay, 'On the Tendency of Varieties to Depart Indefinitely from Original Type; Instability of Varieties Supposed to Prove the Permanent Distinctness of Species' (1858; ref 10).

The papers generated little response and virtually no discussion, their significance apparently lost to those in attendance. Nor was it noticed by the president of the Linnean Society, Thomas Bell, who, in his annual address the following May, blandly stated that the past year had not been enlivened by 'any of those striking discoveries which at once revolutionize' a branch of science."