Křenová – Otová: How to practise …

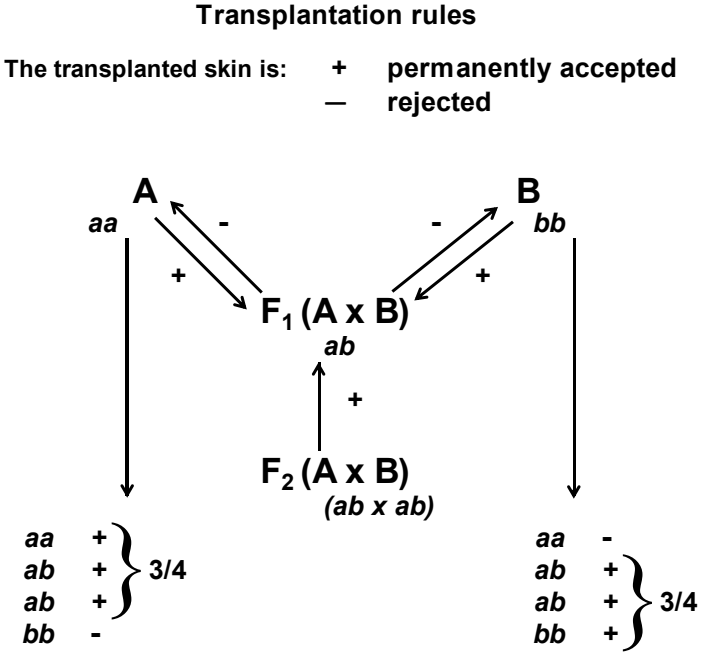
Chapter 14 Immunogenetics

p. 154 (150 old ed.), Task 1a: In parental generation, P1 and P2 individuals are members of two congenic strains differing in alleles of one histocompatibility locus (system) only. The genotype of P1 individual is ***aa*** and the genotype of P2 individual is ***bb***. According to the Mendelian rules, the genotype **in F1** generation is ***ab*** and genotypes **in F2** generation are ***aa***, ***ab*** and ***bb*** in 1:2:1 ratio.

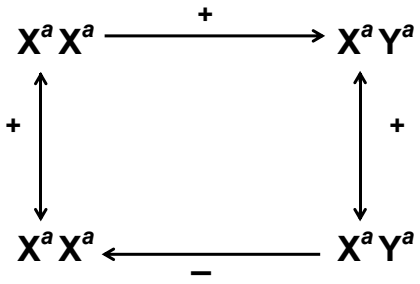
Task 1b: In parental generation, P1 and P2 individuals are members of two congenic strains and they differ in alleles of one histocompatibility locus (system) only. So, for transplantation purposes, they are **allogeneic**.

Task 1c: The fate of the transplanted skin graft depends on the genetic relationship between the donor and the recipient. Skin grafts are tolerated by the recipient when the donor is syngeneic from the point of view of (the immune system of) recipient. (A special case is the autologous grafting, *i.e.* the transfer of skin from one place to another on the same individual.) The skin grafts are rejected by recipient when the donor is allogeneic from the point of view (of the immune system) of the recipient.

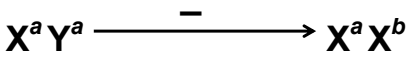
Task 1d: According to the Mendelian rules, the genotype in F1 generation is *ab* and genotypes in F2 generation are *aa*, *ab* and *bb* (in 1:2:1 ratio). After transplantation of skin from P1 (strain) individual with *aa* genotype to F2 recipients, there are 3/4 of F2 individuals with genotype *aa* (1/4 of total) or *ab* (2/4 of total) and from the point of view of their immune system the donor graft is syngeneic. So, these recipients accept the *aa* skin grafts. And, there are 1/4 of F2 individuals with genotype *bb* (1/4 of total) and from the point of view of their immune system the donor graft is allogenic; they are going to reject the *aa* skin grafts. In the situation where the graft donor is a P2 strain individual (genotype *bb*) the reasoning is analogous, only "mirror" reversed (see diagram).



p. 155 (151 old ed.), Task 2a: Skin grafts transferred from one individual (donor) to another (recipient) within one inbred strain are considered syngeneic and should survive permanently. The exception is (subacute) rejection of the skin grafts transferred from the males to females of the same inbred strain. It is explained by the polymorphism of proteins produced by genes on the Y chromosome and expressed on cell surface (as peptides bound to MHC)of male donor skin (the so-called H-Y antigen), which is recognized by the immune system of recipient females as foreign, non-self (unknown) and this initiates an immune (transplantation) rejection response in these recipient females.



Task 2b: Skin grafts from males of parental strain (fathers) transplanted onto F1 hybrid females (daughters) are rejected for the same reason – the incompatibility in the H-Y antigen seen from (F1 female) recipient immune system perspective. (*N.B .:* female / daughter inherits the X chromosome from their fathers.)



p. 155 (151 old ed.), Task 3: Predicted results of bone marrow transplantation between two congenic rat strains differing in alleles of one histocompatibility locus, strain A (genotype *aa*) and strain B (genotype *bb*), and their crosses, are shown in the table. **+** GvHD is expected, recipient (host) dies (untreated GvHD could even kill the recipient); **—** recipient (host) survives, *i.e.* it means the GvHD is not expected in the individual donor-recipient combination.)

Adult donors of lymfoid cells		**Type of recipient**		**Lethality in recipients (GvHR)**		
Donor	***Genotype***	**Recipient**	***Genotype***	**Neonate**	**Adult (healthy)**	**Adult lethally irradiated**
A	***aa***	**A**	***aa***	**-**	**-**	**-**
B	***bb***	**B**	***bb***	**-**	**-**	**-**
A	***aa***	**B**	***bb***	**+**	**-**	**+**
B	***bb***	**A**	***aa***	**+**	**-**	**+**
F_1 (A x B)	***ab***	**A**	***aa***	**-**	**-**	**-**
F_1 (A x B)	***ab***	**B**	***bb***	**-**	**-**	**-**
A	***aa***	**F_1 (A x B)**	***ab***	**+**	**+**	**+**
B	***bb***	**F_1 (A x B)**	***ab***	**+**	**+**	**+**
F_2 (A x B)	***aa***	**F_1 (A x B)**	***ab***	**+**	**+**	**+**
	ab		***ab***	**-**	**-**	**-**
	ab		***ab***	**-**	**-**	**-**
	bb		***ab***	**+**	**+**	**+**
A	***aa***	**F_2 (A x B)**	***aa***	**-**	**-**	**-**
	aa		***ab***	**+**	**+**	**+**
	aa		***ab***	**+**	**+**	**+**
	aa		***bb***	**+**	**-**	**+**
B	***bb***	**F_2 (A x B)**	***aa***	**+**	**-**	**+**
	bb		***ab***	**+**	**+**	**+**
	bb		***ab***	**+**	**+**	**+**
	bb		***bb***	**-**	**-**	**-**

Answers: All of the above events/results may come into consideration after **curative bone marrow transplantation** (BMT) in adult lethally irradiated (or other way immunosuppressed) individuals (patients, last column): most frequently (fully) allogeneic (from unrelated donor) BMT or semi-allogeneic (e.g. from family members or from donors out of the family but tested as "haploidentical"). *N.B.:* i) BMT in neonates is relatively rare therapeutic procedure and, comparing to neonates in *muridae* (mice, rats), in humans there is not such (short) period of neonatal immaturity of immune system, and ii) healthy adults do not need BMT.

GvHD could be avoided or suppressed i) by selecting the appropriate donors (testing the HLA compatibility, Inter/National BM Donors Registries) or ii) by immunosuppression of donor BM cells and, after BMT, of recipient.

p. 157 (153 old ed.), Task 4: Risks of fetomaternal incompatibility (the hemolytic disease of neonates, HDN, is the most severe situation) are shown in the 2 tables separately for anti-D incompatibility and incompatibility for antigens of CcEe series.

Case	FATHER's Rh genotype	MOTHER's Rh genotype	Result
I.	c**D**e/c**d**e	c**D**e/C**d**e	No risk, mother is Rh+
II.	C**D**e/C**D**e	C**d**e/c**d**e	Incompatibility in 100% cases, mother is Rh-, fetus Rh+
III.	c**D**e/c**d**e	c**d**E/C**d**e	Incompatibility in 50% cases, mother is Rh-, fetus either Rh+ or Rh-
IV.	c**d**e/c**d**e	c**D**E/c**D**e	No incompatibility, no risk, Rh+ mother

N.B.: in case I; father's Rh genotype should be correctly typed as cDe/cde.

Case	FATHER's Rh genotype	MOTHER's Rh genotype	Result
I.	**c**D**e**/**c**d**e**	**c**D**e**/**C**d**e**	No incompatibility, no risk
II.	**C**D**e**/**C**D**e**	**C**d**e**/**c**d**e**	No incompatibility, no risk
III.	**c**D**e**/**c**d**e**	**c**d**E**/**C**d**e**	No incompatibility, no risk
IV.	**c**d**e**/**c**d**e**	**c**D**E**/**c**D**e**	No incompatibility, no risk

N.B.: in case I; father's Rh genotype should be correctly typed as cDe/cde.

There is no risk of feto-maternal incompatibility in the antigens coded by the alleles C/c and E/e in any of the given parental combinations. In cases I-III, mothers are heterozygotes **Cc** – so, fetal red blood cells having paternal **C** or **c** (fathers are **CC** or **cc**) are compatible. In case IV, both father and mother are homozygotes **cc** – so, fetus will have the **c** antigen (only), like mother has. In cases I and II, both father and mother are homozygotes **ee** – so, fetus will have the **e** antigen (only), like mother has. In cases III and IV, mothers are heterozygotes **Ee** – so, fetal red blood cells having paternal **e** (fathers are **ee**) are compatible.

Answer 4a): The Rh factor is a specific protein found on the surface of human red blood cells. Most people are Rh-positive, but a small percentage of people are Rh-negative. This means they lack the Rh protein (but it doesn't affect their health). However, this non-pathogenic Rh polymorphism becomes important during pregnancy. Rh incompatibility occurs when a woman is Rh-negative and her fetus/baby is Rh-antigen positive. If this is the case, then the immune system of the mother will approach the Rh-positive protein as something that is foreign (non-self), and produce an immune response against it. If blood cells from Rh+ baby cross the bloodstream of Rh-negative mother, which can happen during pregnancy, labor, and delivery, her immune system will make antibodies against her baby's red blood cells. These antibodies produced by sensitized Rh-negative mother can pass across the placenta to attack baby's red blood cells. Antibodies could destroy foreign substances including the cells expressing them. This can lead to hemolytic anemia (HA) in the baby. HA is a condition in which red blood cells are destroyed faster than the body can replace them. Without enough red blood cells, the fetus/baby will not get enough oxygen. This can lead to serious problems. Severe hemolytic anemia may even be fatal to the child.

In the most severe form, Rh incompatibility can lead to *hydrops fetalis* with severe anemia, edema, central nervous system damage, and fetal death. Because the maternal antibodies remain in the neonate's circulatory system after birth, erythrocyte destruction can continue. This causes hyperbilirubinemia *icterus neonatorum* (neonatal jaundice) shortly after birth. Without replacement transfusions, in which the child receives Rh-negative erythrocytes, the bilirubin is deposited in the brain, a condition termed kernicterus. Kernicterus produces cerebral damage and usually causes death (*icterus gravis neonatorum*). Infants who do not die may have mental retardation, cerebral palsy, or high-frequency deafness. Medication can help with this condition to ensure that both mother and her baby are healthy.

Answer 4b): These antibodies against the baby's Rh-positive blood usually don't cause problems during a first pregnancy. This is because the baby often is born before many of the antibodies develop. However, the immune system memory cells stay in maternal body once she has been sensitized. Typically, such massive sensitization can come after the delivery, because when the placenta is separated, maternal and fetal blood can be mixed in large quantities and infused into the mother's circulation. Thus, Rh incompatibility is more likely to cause problems in second or later pregnancies (if these babies are Rh-positive).

Answer 4c): HDN or *fetal erythroblastosis* (as a result of Rh incompatibility) can be prevented with application of anti-Rh antibodies (anti-D immunoglobulins, Ig), as long as the antibody preparation is given at the correct times. Once the Rh antibodies are formed by immune system of Rh-negative mother, this application of "passively" transferred immunoglobulin preparation will no longer help. Thus, an Rh-negative woman must be treated with anti-Rh Ig during and after each pregnancy or after any other event that allows her immunization with Rh-positive blood cells (e.g. AMC). Early prenatal care also can help prevent some of the problems linked to Rh incompatibility. For example, new methods make it possible to find out in Rh-negative women at the end of the first trimester whether their fetus is Rh-positive (cell-free DNA from maternal serum that contains a fraction of DNA from placenta that is positive for RhD gene) and whether the pregnancy is at risk for the condition. And if it is at risk, the pregnancy can be closely monitored for maternal anti-D antibodies. After the birth, the baby will be watched for signs of hemolytic anemia and provided treatment as needed.

Answer 4d): Fetal damage (HDN or EF) was seen and described in medical literature in less than 10% of Rh-incompatible pregnancies and rarely is a problem during the first pregnancy; the first pregnancy initiates sensitization. As has already been said, HDN affects the second and subsequent pregnancies. Anti-Rh antibodies are formed only in response to the presence of incompatible (Rh-positive) red blood cells (RBCs) to the blood of an Rh-negative mother. Usually this exposure occurs as Rh positive fetal blood is mixed with the mother's blood at the time of (first or previous) delivery. In some cases, Rh-positive RBCs in the maternal organism are blocked (or even destroyed) due to incompatibility in the ABO system and the pre-existence of natural anti-A or anti-B antibodies before anti-Rh sensitization can occur.

It should he noted that HDN caused by Rh incompatibility occurs in only 5% of pregnancies after five or more pregnancies (among other things because of early miscarriages).

Nowadays, the situation is much more optimistic. Blood typing in mothers and infants reveals those who are at risk. Indirect Coombs test reveals antibodies in mothers, and direct Coombs test reveals antibodies bound to fetal erythrocytes. In utero testing is now available. Immunoprophylaxis with anti-D(Rh) immunoglobulin for at-risk mothers has been very successful.

p. 158 (153 old ed.), Task 5: An Rh-negative mother can have an Rh-negative child with an Rh+ man if he is a heterozygote *Dd* (left panel). If both parents are Rh+ they can have an Rh-negative child if both they are heterozygotes *Dd* (right panel).

		Rh+ man	
		D	***d***
Rh- mother	***d***	***Dd***	***dd***
	d	***Dd***	***dd***

		Rh+ man	
		D	***d***
Rh+ mother	***D***	***DD***	***Dd***
	d	***Dd***	***dd***

p. 158, Task 6 (absent in old ed.): Primers used in this PCR are amplifying fragments both in CcEe and D subregions of the locus. Because of missing elfo bands in position of 186 bp, specific for the D product, we may conclude that DNA samples in lane 1, 4 and 5 are from Rh-negative fetuses and the others (2^{nd}, 3^{rd}, 6^{th}, 7^{th}, 8^{th} lane) are at risk of developing *fetal erythroblastosis*

p. 159, Task 7 (p.153, T. 6, old ed.): Partly answered in Task 4, p. 157 (153 old ed.) as d). The complex ABO phenotype means: individuals of A blood group have natural anti-B antibodies (agglutinins) in their serum (or plasma), individuals with B blood group have anti-A antibodies, individuals of O blood groups have both of them, whereas AB individuals have none. And this is the 1st situation (left panel): fetuses with AB mother and O father will be of A or B blood group and in blood of their AB mother there are no agglutinins being able to block (hide) fetal RBC before active recognition of Rh antigens by maternal immune system and its sensitization against D antigen.

In opposite situation (right panel), fetuses growing in O mothers and having AB fathers will be of A or B blood group, too, but in the blood of their O mother there will be anti-A and anti-B agglutinins present and being able to interact with fetal RBC and interfere with active sensitization maternal immune cells against D antigen.

		O father	
		O	***O***
AB mother	***A***	***AO***	***AO***
	B	***BO***	***BO***

		AB father	
		A	***B***
O mother	***O***	***AO***	***AO***
	O	***BO***	***BO***

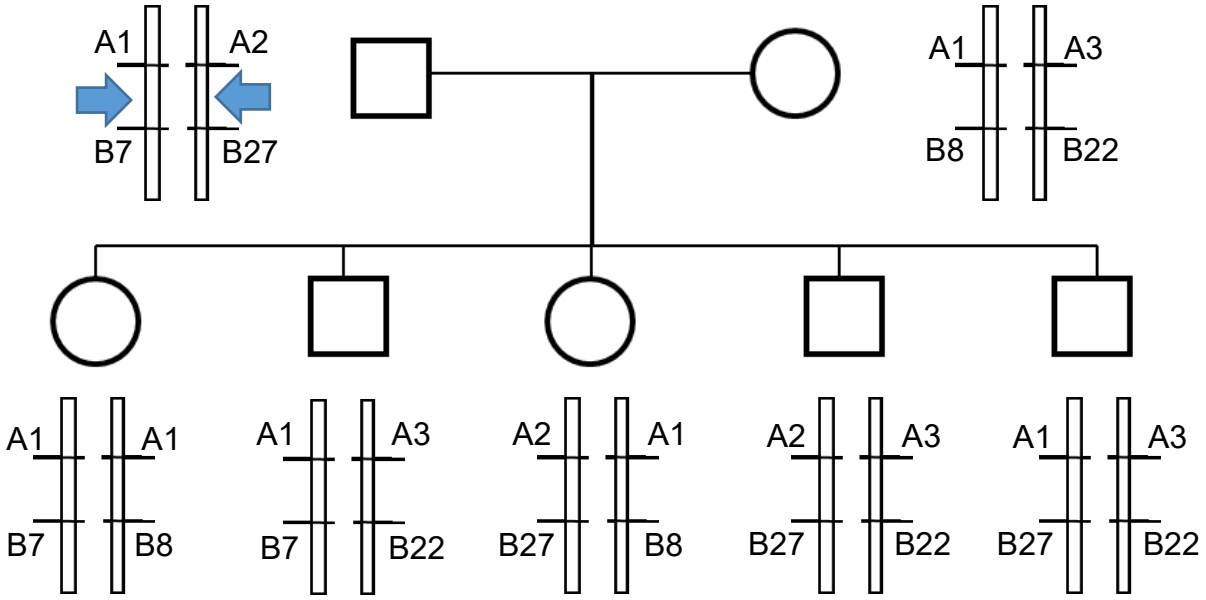
p. 159, Task 8 (p.153, T. 7, old ed.): A+ men (with A blood group and Rh-positive phenotype) born from AB- and O+ parents are double heterozygotes *AO* and *Dd* (left panel). Since the ABO system and Rh system are coded by genes from different chromosomes, they are not linked, and such male will produce 4 types of gametes (*A D*, *A d*, *O D*, and *Od*; right panel).

		O Rh+ (*DD* or *Dd*) parent	
		O D	***O D or d***
AB Rh- parent	***A d***	***AO Dd***	***AO Dd or AO dd***
	B d	***BO Dd***	***BO Dd or AO dd***

A+ men (of A blood group and Rh-positive) with *AO Dd* genotype			
Gametes			
A D	***A d***	***O D***	***O d***

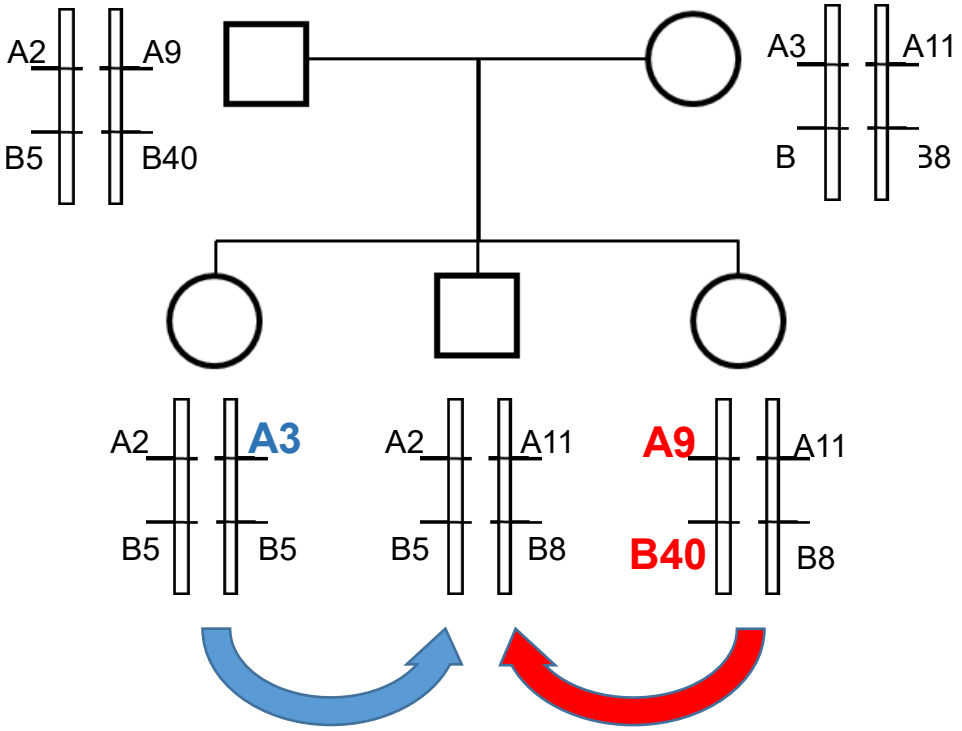
p. 159, Task 9 (p.154, T. 8, old ed.), answer a): Yes, we can deduce the haplotypes of individual members of the family. In the pedigree on Figure No. 14/2, an immunophenotype of each family member is indicated under each symbol. The advantage here is that the oldest daughter is homozygous for the A1 allele, and her haplotypes are A1 B7 and A1 B8. By comparing with the immunophenotypes of both parents, we can see that the first haplotype originates from the father and the other is inherited from the mother. Subsequently, we can determine the second haplotype in each parent – A2 B27 in the father and A3 B 22 in the mother. Furthermore, we can see how these haplotypes segregate in other offspring of the couple.

answer b): Yes, we can reveal the recombination event within HLA region. In the youngest son, one haplotype (A3 B22) is clearly the maternal one, but the second (A1 B27) represents a recombination between the two paternal haplotypes. A putative position of this recombination event is demonstrated by the pair of blue arrows.



p. 160, Task 10 (p.154, T. 9, old ed.), answer a): Yes, we can deduce the haplotypes of individual members of the family; the procedure is similar to that used in previous task. In the pedigree on Figure No. 14/3, an immunophenotype of each family member is indicated under each symbol. First, we set the haplotypes in the oldest daughter (which is homozygous for the B5 allele) as A2 B5 and A3 B5. By comparing with those of both parents, we can see that the first haplotype is inherited from the father and the other originates from the mother. Subsequently, we can determine the second haplotype in each parent – A9 B40 in the father and A11 B 8 in the mother. Furthermore, we can see how these haplotypes segregate in other children of the couple.

answer b): The middle son ("needing renal transplantation") shares one haplotype (A2 B5, paternal) with his older sister, and the second (A11 B8, maternal) with his younger sister. Because his older sister is a homozygote for B5 allele, her tissue (kidney) HLA antigens represent a single antigen barrier (A3) for transplantation in comparison to two antigenic differences to his younger sister. Thus, the older sister could be (from this point of view) better donor for organ transplantation.



p. 160, Task 11 (p.155, T. 10, old ed.): The subject of immune recognition and immune responses of graft recipient are, in addition to HLA antigens, also (polymorphic, non-self) products of non-MHC (non-HLA) histocompatibility loci expressed in the graft. Even at full donor-recipient compatibility in HLA antigens, higher number of these "minor" alloantigen incompatibilities can be expected for non-related grafts compared to related donors. In relatives, a limited number of alleles of individual histocompatibility loci (H-loci) segregate, and therefore the compatibility in many or even most H-loci is more likely, e.g. in between siblings, in contrast to non-related individuals (recipients of cadaverous non-related grafts).

p. 161, Task 12 (p.155, T. 11, old ed.): If father and mother (of the family) differ at all four alleles localized in both A and B (sub)loci of HLA system, in other words, they differ in each of two haplotypes, then

answer a): individual parent and child could share one HLA haplotype (if there was no crossing over) or none (in case of crossing over);

answer b): they could share two HLA antigens (even in case of cross-over);

answer c): two children (siblings) in such a family could share none or one or two HLA haplotypes;

answer d): two children (siblings) in such a family could share 0 or 2 or 4 HLA antigens (in case of no crossing over, look at answer e) for the option for crossing over admittance);

answer e): the result sub d) would be modified when a cross-over between subloci A and B would occur - two such sibs could share 0 or 1 or 2 or 3 or 4 HLA antigens.

p. 161, Task 13 (p.155, T. 13, old ed.): HLA B27 is a class I surface antigen encoded by the (human) major histocompatibility complex (MHC); it presents antigenic peptides to T cells. The prevalence of HLA-B27 varies markedly in the general population (about 8% of Caucasians, 4% of North Africans, 2-9% of Chinese, and 0.1-0.5% of people of Japanese descent). In Lapland (Northern Scandinavia), 24% of people are HLA-B27 positive.

answer a): Gene/genetic/HLA association. HLA-B27 is strongly associated with ankylosing spondylitis (AS), and other inflammatory diseases: inflammatory bowel disease (and ulcerative colitis associated spondyloarthritis), reactive arthritis (Reiter's Syndrome), psoriasis (and psoriatic arthritis), other types of seronegative spondyloarthropathy, and certain eye disorders (such as acute anterior uveitis and iritis).

answer b): The relationship between HLA-B27 and diseases has not yet been fully elucidated. The theories (as to the mechanism) how HLA-B27 initiates and influences diseases can be divided between antigen-dependent and antigen-independent categories.

Antigen-dependent theories consider a (very) specific (i.e. different to the other HLA-B alleles) combination of antigen peptide sequence and the binding groove of HLA-B27. The **arthritogenic peptide hypothesis** suggests that HLA-B27 has a unique ability to bind antigens from a microorganism that trigger a CD8 T-cell response that then cross-reacts with a HLA-B27/self-peptide pair. The **molecular mimicry hypothesis** is similar, however it suggests that cross reactivity between some bacterial antigens and self-peptide can break tolerance and lead to autoimmunity.

Antigen-independent theories refer to the unusual biochemical properties that HLA-B27 has. The **misfolding hypothesis** suggests that slow folding during HLA-B27's tertiary structure folding and association with β2 microglobulin causes the protein to be misfolded, therefore initiating the unfolded protein response (UPR) - a pro-inflammatory endoplasmic reticulum (ER) stress response. This mechanism has been demonstrated both in vitro and in vivo models, but there is little evidence of its occurrence in human pathology. The HLA-B27 **heavy chain homodimer formation hypothesis** suggests that B27 heavy chains tend to dimerise and accumulate in the ER, once again, initiating the UPR. Then, B27 heavy chains and dimers on cell surface can bind to

regulatory immune receptors (e.g. the killer cell immunoglobulin-like receptor family), promoting the survival and differentiation of pro-inflammatory leukocytes in disease.

answer c): While 90% of people with ankylosing spondylitis (AS) are HLA-B27 positive, only a small fraction of people with HLA-B27 ever develop AS. People who are HLA-B27 positive are more likely to experience early onset AS than HLA-B27 negative individuals. Thus, HLA(-B27) does not appear to be the unique mediator in development of AS; there are (many) other genes being discovered that also play the role in AS and other spondyloarthropathies. Additionally, many environmental factors (triggers) may also play a role in susceptible individuals.

answer d): Monozygotic (MZ) twin (identical for presence of HLA-B27 molecule) **discordance in AS** (or morbus Bechterev, MB, see the text) support the answer sub c). If in MZ twins the heritability is not approaching to 1.0 there are evidently other non-genetic factors playing the role in etiology and pathogenesis of the disease.

answer e): Relative risk or risk ratio (RR) is the ratio of the probability of an event occurring (e.g. developing a disease) in an exposed group to the probability of the event occurring in a comparison, non-exposed group. The calculation of RR conferred by an HLA antigen / haplotype / genotype is usually done by method of relative incidence (RI) as follows:

RI = ad / bc (a, b, c, d are the entries in the **2x2 table**)

		Risk factor		***Totals***
		present	**absent**	
Disease	**Patients**	**a**	**b**	**a + b**
	Controls	**c**	**d**	**c + d**
Totals		**a + c**	**b + d**	**N = a + b + c + d**

Conventionally, RR is used in HLA and disease studies instead of relative incidence. To confuse the terminology further, the cross-product ratios described as RI actually gives what is called odds ratio (OR) in epidemiology. More precisely, the RR in a prospective epidemiological study is defined differently (this is the real RR as it is used in epidemiologic studies]. In the **2x2 table**, the proportion of persons with the risk factor (B27 allele in this case) having the disease is a/(a+c), and the corresponding proportion for those lacking the risk factor is b/(b+d). Because relative risk is obtained by dividing the risk of development of disease among subjects with the risk factor by the risk of development of disease among subjects without the risk factor:

RR = (a/(a+c)) / (b/(b+d)) which equals to RR = a(b+d) / b(a+c)

Because in instruction to Task 13 some data are missing (and given data expressed as %), our 2x2 table is incomplete and our estimate of RR will be very approximate. RR is calculated as 103.5.

		HLA-B27		***Totals***
		present	**absent**	
AS (ankylosing spondylitis)	**Patients**	**0.90**	**0.10**	**1.0**
	Controls	**?**	**?**	**??**
Totals (Czech population)		**0.08**	**0.92**	**1.0**

Comment: in original studies from 80´s, this RR was computed as app. 87 times more likely. For more detailed reading, we can recommend a very recent report: Lin, H. & Gong, YZ.: Association

of HLA-B27 with ankylosing spondylitis and clinical features of the HLA-B27-associated ankylosing spondylitis: a meta-analysis. Rheumatology International, August 2017, Volume 37, Issue 8, pp 1267–1280.

(Rheumatol Int (2017) 37: 1267. https://doi.org/10.1007/s00296-017-3741-2)

p. 161, Task 14 (p.155, T. 14, old ed.): HLA loci and alleles which could discriminate, that the boy (son) was born from **donated egg** *in vitro* fertilized by sperm of **husband** and the embryo then transferred into recipient (wife) uterus and not after "natural" *in vivo* fertilization of wife´s egg, are **highlighted** in the table.

Subjects	HLA antigens			
	HLA-A	HLA-B	HLA-C	HLA-D
Foster mother (wife)	1, 24	35	3, 4	4, 6
Father (husband)	**2**	**18**, 44	2, **7**	4, 6
Boy (son)	**2** (i.e. **2**/**2**)	**7**, **18**	**7** (i.e. **7**/**7**)	6
Donor of the ovum	**2**, 29	**7**, 44	**7**	4, 6

Answer to questions at the bottom of p. 164; the Task 15 starts on p. 162 (p.156, old ed.): partly corresponding to Task 11 on p. 160 (T. 10 on p.155, old ed.). So: We cannot test the match (compatibility) in minor non-HLA histocompatibility loci between donors and recipients, it is not possible in (human) clinical transplantology (compared to experiments on genetically defined models in mice and rats). But we can increase this match by using some specific type of donors, which means healthy relatives (typically parents or siblings). Because (we repeat): In relatives, a limited number of alleles of individual minor non-HLA loci segregate, and therefore the compatibility in these is more likely (in contrast to non-related cadaverous, e.g. kidney transplants). Transplantations from healthy donors (besides other, because there is shortage of unrelated organs) is currently experiencing renaissance, but it brings (as it did at the beginning of the transplantation era) some ethical issues, e.g.: no one should be forced to donate organs.

ADDENDUM

Task 12 on p. 155 in old ed. (absent in NEW ed.): similar tasks will be in tests (;-D).