Translation and Analysis of Veterinary Texts

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TRANSLATION AND ANALYSIS OF VETERINARY TEXTS

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Abstract

This thesis deals with the translation of veterinary texts from English into Croatian and vice versa. The English text is a chapter from the textbook on virology, while the Croatian text was extracted from a veterinary handbook. The topic of both texts is immunology, more precisely, the immune response to viral infections and autoimmune diseases. The introductory part of the thesis covers general characteristics of scientific texts, as well as those of the veterinary science. The introduction is followed by the translations and the individual analyses of each of them. The texts are analyzed at the level of syntax, vocabulary, grammar and style, and the entire process of translation of particularly challenging words is also explained. The thesis ends with a conclusion which briefly covers presented solutions to the issues encountered.

Keywords: analysis, Croatian language, English language, translation, veterinary medicine

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1. Introduction

"Translation is an activity that aims at conveying meaning or meanings of a given linguistic discourse from one language to another."[1] Translators need to have extensive knowledge of the languages they are translating from and into because it is important to convey the same meaning without the text sounding unnatural in the target language. There are numerous types of translations and each of them has its own characteristics and features. For example, literary translations can be especially challenging because the translator needs to have a knack for conveying the meaning while still conforming to the rules of the target language. On the other hand, legal and scientific texts are written in a straightforward manner and have to be translated as closely as possible. Being a translator is one of the most demanding, as well as most important jobs one can do. Translators do not only translate New York Times bestsellers, but important medical, legal, engineering, architectural texts which help in spreading the knowledge.

One of the translation domains is specialized translation which includes the fields of technology, engineering, pharmacology, economy, as well as of veterinary medicine. Veterinary medicine or veterinary science deals with "the prevention, control, diagnosis, and treatment of diseases affecting the health of domestic and wild animals and with the prevention of transmission of animal diseases to people".[2] Veterinary medicine has contributed both to animal as well as human health through the development of certain surgical techniques which were then applied to humans. Veterinarians work in agencies charged with the protection of the environment, food and drug safety, public health, food-animal inspection, humane treatment of animals and imported animals' health. They also control human and animal disease outbreaks.[3]

Scientific texts, which include human and veterinary medicine, are precise, clear, concise, logical, succinct and objective. The clarity is achieved by omission of descriptive and decorative elements which might lead to misinterpretation. The text needs to be brief, without uneccessary redundancy, complicated phrases and sentences and vague adjectives. Precision

[1] Retrieved from https://www.oxfordhandbooks.com/view/10.1093/oxfordhb/9780199239306.001.0001/oxfordhb-9780199239306-e-009 Accessed August 2021
[2] Retrieved from https://www.britannica.com/science/veterinary-medicine Accessed August 2021
[3] Ibid.

is important because other scientists reading the text need to be able to, for example, repeat an experiment.[4]

When it comes to the translation of scientific texts, it is often challenging, especially of those regarding human and veterinary medicine. Medical texts include a large number of different areas such as oncology, surgery, pharmacology, obstetrics etc. The most commonly translated texts include research papers, textbooks for students, science books, reports, case studies, as well as brochures, consent forms, information leaflets etc.[5]

During the translation process, it is important to know the audience, i.e., whether the text is used for communication between two or more experts or between experts and non experts. Medical texts generally include specific terminology, long sentences, use of third person and passives, nominalization, abbreviations etc. Regarding the terms used in medicine, one term can have multiple meanings which depend on the country and the region. However, the use of the Latin language which is used around the world makes things a little easier. Another language which is a basis for medical terminology is Greek. Also, medicine features a large number of eponyms, i.e., names derived from the famous researchers or celebrity patients, for anatomical parts (*Fallopian tubes)*, names of procedures (*Heller mytonomy*), diseases (*Parkinson's disease*), symptoms and signs (*Babinski sign*) etc. These can pose a problem because the terms in the source and target text might not be eponymous.[6]

Another distinctive feature of medical texts is the frequent use of acronyms, clipped forms and initialisms. Since the English language is seen as *lingua franca*, acronyms (in their original English form) are used by professionals as well as patients. They are very useful and practical in case of an emergency situation, and they are used for facilitating communication since the full form of the word can be long and impede communication. Although they are extremely common, they can be hard to translate since one acronym can stand for several different medical terms.[7] For example, *Tx* stands for "therapist, therapy, traction, transcription, transfer, transfuse, transplant, transplantation, or treatment"[8], while *TBA* stands for "to be absorbed, to be added, to be administered, to be admitted, to be announced, to be

[4] Retrieved from https://canvas.hull.ac.uk/courses/370/pages/scientific-writing-style Accessed August 2021
[5] Ageicheva, A. O., and I. V. Rozhenko. "MEDICAL TEXTS TRANSLATION PECULIARITIES." *Young* 69.5.1 (2019)., p. 1
[6] Ibid., p. 2
[7] Ibid., p. 2
[8] Retrieved from https://www.ismp.org/resources/medical-abbreviations-have-contradictory-or-ambiguous-meanings Accessed August 2021

arranged, or to be assessed".[9] Some of the most frequent methods of translating abbreviations include their transcription, descriptive translation or transliteration.[10]

Medical terminology is often polysemous or synonymous. There is a large number of synonyms in medicine, some of them being *hepatitis B* or *serum hepatitis, bronchial pneumonia* or *bronchopneumonia, chronic lymphocytic thyroiditis* or *Hashimoto's thyroiditis* etc.[11] When it comes to polysemy, one of the well-known examples is the noun *inflammation* which can have different meanings in different contexts. In English, the term is explained as "a local response to cellular injury that is marked by capillary dilatation, leukocytic infiltration, redness, heat, pain, swelling, and often loss of function and that serves as a mechanism initiating the elimination of noxious agents and of damaged tissue"[12] or as "a fundamental pathologic process consisting of a dynamic complex of cytologic and chemical reactions that occur in the affected blood vessels and adjacent tissues in response to an injury or abnormal stimulation caused by a physical, chemical, or biologic agent […]"[13] The synonym of *inflammation* would be *inflammatory response* or *inflammatory reaction*. The Croatian equivalent is *upala* which has two different definitions: "reakcija tkiva ili organa koja nastaje zbog oslobađanja polipeptida uslijed djelovanja nokse, pri čemu nastaje skupljanje leukocita uz stijenke"[14] (transl. tissue or organ reaction which is the result of the release of polypeptides due to the activity of noxa, leading to the accumulation of leukocytes along the walls) and "reakcija tkiva na oštećenje bilo kojega uzroka s ciljem uklanjanja ili ograničavanja štetnoga čimbenika"[15] (transl. tissue reaction to damage of any cause with the aim of eliminating or limiting the harmful factor). The synonym for the second definition is *upalni odgovor, upalna reakcija* or *inflamacija.*[16] The process of selecting the right translation for a polysematic word can be a challenging one.

Medical translation includes two interconnected steps, i.e., the information extraction from the source text and the selection of the translation methods and means. Information extraction is closely related to informative translation which includes the transfer of

[9] Retrieved from https://www.ismp.org/resources/medical-abbreviations-have-contradictory-or-ambiguous-meanings Accessed August 2021
[10] Ageicheva, A. O., and I. V. Rozhenko. "MEDICAL TEXTS TRANSLATION PECULIARITIES." *Young* 69.5.1 (2019)., p. 2
[11] Ibid., p. 2-3
[12] Pisanelli, Domenico M., et al. "Coping with medical polysemy in the semantic web: the role of ontologies." *MEDINFO 2004*. IOS Press, 2004, p. 416
[13] Ibid.
[14] Retrieved from http://struna.ihjj.hr/naziv/upala/13119/#naziv Accessed August 2021
[15] Retrieved from http://struna.ihjj.hr/naziv/upala/26066/#naziv Accessed August 2021
[16] Ibid.

information and has no esthetic impact on the recipient. During translation, it is important to double-check medical terms, especially those which sound similar in the source and target language. The sentences in the text are often peculiarly written and can feature numerous definitions which in turn leads to limited understanding.[17]

Although the abovementioned characteristics show that the translation of medical texts is demanding, the terms actually have a fixed structure, i.e., a root, a prefix, a suffix and a combining vowel. The root represents the basis of the meaning and it indicates either body parts or a system. For example, the root *faci* refers to illnesses, procedures and processes concerning the face, the root *enceph* refers to illnesses, procedures and processes concerning the brain, while *rhin* refers to the ones concerning the nose. The prefix specifies direction, type, quantity, quality or location and it is optional. For example, levels can be expressed with the following prefixes: *hyper-* indicates that something is above normal, *hypo-* indicates that something is below normal, while *eu-* means that the levels are normal. The suffix specifies a test, procedure, status, function, disorder or specialty. For example, in terms of procedures and tests *-scopy* refers to viewing (e.g., colonoscopy), *-otomy* means cut in (e.g., lobotomy), while *–ectomy* is the removal of (e.g., vasectomy). Finally, the combining vowel facilitates the pronunciation and it is normally the letter 'o'. In the word *hypothermia* (the condition in which the body temperature is below normal), the root is *therm*, meaning *heat*, the prefix is *hypo-*, meaning below normal, and the suffix *–ia* refers to a condition.[18]

One of the branches of medicine and the topic of this thesis is veterinary medicine. The veterinary science is an unknown field for medical writers as well as for medical translators. One of the most important aspects of translating veterinary texts is knowing the target audience which are mostly veterinary surgeons and pet owners. The first group includes professionals who have degrees in parasitology, equine medicine, immunology, anaesthesiology, animal nutrition, dermatology etc. They can work in industry, including diagnostic, nutrition and pharmaceutical companies, academia, government, research organisations or clinics. In case they are the target audience, the texts can be extremely demanding. On the other hand, pet owners include people who own horses, dogs, cats, ferrets, fish, or any other small animals. The texts this group is interested in are mostly web pages which describe various diseases, leaflets, and pet food brochures. The contents of these

[17] Ageicheva, A. O., and I. V. Rozhenko. "MEDICAL TEXTS TRANSLATION PECULIARITIES." *Young* 69.5.1 (2019)., p. 3
[18] Retrieved from https://openmd.com/guide/medical-terminology Accessed August 2021

documents are not as challenging. However, it is important to adapt the language to their level of knowledge, i.e., it needs to be simplified while still conveying the important information.[19]

The third audience is farmers who do not have a degree, but have a lot of practical knowledge which they have obtained through taking care of their animals. In this case, the translator needs to find a balance between the terminology used for professionals and pet owners since the use of lay terminology can be seen as offensive.[20]

Synonimity and polysemy are a problem in veterinary medicine as well. One of the examples given by the author of the article "Exploring veterinary science, a little-known translation specialization" is *veterinary surgeon*. While this is a term of preference in the United Kingdom, in the United States it is *veterinarian*. Furthermore, if they are imployed in clinics, they are called *clinicians*, *practicioners* or *veterinary physicians*. When it comes to the translation of these terms, all of them can in the majority of languages be translated using one term. In Croatian it would be *veterinar*.[21]

In veterinary medicine translation, an important aspect is knowing the context of the source text because it helps the translators to produce better texts in the target language. The result is improved communication and happier clients. Although following the latest trends on the market is a challenging task, it is also a rewarding one because it ensures a greater number of clients and helps to build a lasting relationship with them.[22]

Following the original text's format and structure is another important segment of translating these types of texts. The author of the article called "Exploring veterinary science, a little-known translation specialization" mentions the product information for medical products. These documents have specified templates, published by European Medicines Agency, which list standard sentences and terminology for each part of the document. When it comes to information about the administration of the medicine, the dosage and container it comes in, the terminology is predetermined and listed in the documents which are published by the European Directorate for the Quality of Medicines and Healthcare. During the translation, the translator needs to use both the official document on the product information

[19] Romero, Anna. "Exploring veterinary science, a little-known translation specialisation." *Medical Writing* 23.3 (2014): 182-185., p. 182-3
[20] Ibid., p. 183
[21] Ibid., p. 183
[22] Ibid., p. 183-4

as well as the one with the predetermined terminology. If not, the translation will not comply with the rules and will be worthless to the client.[23]

Overall, medicine and veterinary science are considered to be one of the most challenging fields of translation. It is crucial to know your audience in order to use the proper terminology which has to be adapted to their knowledge level. The translator needs to do in-depth research in order to avoid any possible mistakes. This especially refers to the abovementioned challenges regarding synonymy, polysemy and acronyms.

[23] Romero, Anna. "Exploring veterinary science, a little-known translation specialisation." *Medical Writing* 23.3 (2014): 182-185., p. 184-5

2. First text: “Immune Response to Viral Infections”

The chosen text is a chapter extracted from the book called *Veterinary Virology*, written by Frederick Murphy, E. Gibbs, Marian Horzinek and Michael Studdert. The book deals with zoonotic viruses and the diseases caused by them. It thoroughly explains the pathogenesis, epidemiology, control, prevention and eradication of viral diseases, as well as giving insight into the properties of different viruses that can afflict animals. When it comes to the audience, it can be useful to veterinary students, as well as to microbiologists, virologists and veterinarians.[24]

The translated chapter deals with immunity, i.e., cellular and subcellular components of the immune system, immune response, immunologic memory, as well as immunity to reinfection and recovery from viral infections. Although it gives a detailed overview, description and explanation of immunological mechanisms and each of its components, it still contains numerous terms which would be unknown to anyone who is not pursuing a career in veterinary science. Thus, the text would be too complex for anyone who is interested only in knowing something more about viruses and immunity.

The original text includes figures and diagrams which thoroughly describe certain processes such as the inflammatory response, the interaction between MHC proteins and certain types of molecules, the descriptions of exogenous and endogenous pathways, the basic structure of immunoglobulins etc. These figures were not included in the final version of the translation due to various issues with the layout of the document. Another problem were the translations of the descriptions within the images which were challenging to place and an expert would be needed in order for the translated version of the text to have the same layout as the original.

[24] Retrieved from https://www.elsevier.com/books/veterinary-virology/murphy/978-0-12-511340-3 Accessed August 2021

2.1. Translation

POGLAVLJE 8

Imunosni odgovor na virusne infekcije

Kralježnjaci su kao odgovor na stalne prijetnje prodora zaraznih agensa, uključujući i viruse, razvili složeni skup obrambenih mehanizama koji se jednim imenom zovu – imunosni sustav. Tijekom prvog doticaja s virusom, imunosni sustav domaćina prepoznaje određene virusne makromolekule (proteine, ugljikohidrate), zvane *antigeni*, kao strane. Oni potom izazivaju nekoliko vrsta odgovora s ciljem uklanjanja virusa iz tijela i sprječavanja reinfekcije. B-limfociti (humoralni imunosni odgovor) odgovaraju na podražaj antigena proizvodeći i lučeći *imunoglobuline* ili *protutijela*. T-limfociti (stanični imunosni odgovor) odgovaraju lučenjem citokina koji reguliraju imunosni odgovor usklađivanjem djelovanja raznih vrsta stanica uključenih u proces, uključujući proizvodnju protutijela koju obavljaju B-limfociti. T-limfociti također imaju izravne efektorske funkcije, kao što su citotoksične funkcije. Obje vrste limfocita nose izrazito specifične molekulske receptore koji prepoznaju zasebna područja virusnih proteina, poznate kao *antigenske determinante* ili *epitopi*.

Imunosni odgovori svojstveni antigenima zajedno s urođenim obrambenim mehanizmima zaustavljaju mnoge virusne infekcije prije nego li nanesu štetu organizmu. Rezultat je blagi oblik bolesti ili čak subklinička infekcija. Ovo poglavlje posvećeno je ulozi imunosnog odgovora u oporavku od virusne infekcije i otpornosti na reinfekciju. Kasnija poglavlja obrađuju slučajeve u kojima imunosni sustav nije toliko učinkovit, u kojima je imunosni odgovor zapravo štetan i ima ulogu važnog elementa u patogenezi bolesti te slučajeve u kojima virus uspijeva izbjeći imunosni sustav i potiče perzistirajuću infekciju.

Stanične komponente imunosnog sustava

Stanice imunosnog sustava uključuju B-limfocite i T-limfocite, stanice monocitno/makrofagne linije, dendritične stanice i prirodne stanice ubojice (NK). Na površini

limfocita nalaze se receptori za antigene, koji su osnova imunološke specifičnosti. Svaki T ili B-limfocit ima receptore koji su specifični za pojedini epitop. Nakon vezivanja T ili B-limfocita s antigenom, stanici se šalje signal za dijeljenje, s ciljem formiranja većeg broja klonova stanica (*klonalno širenje*). B-limfociti diferenciraju se u plazma stanice, tj. zrele stanice koje proizvode i izlučuju protutijela. T-limfociti izlučuju topljive faktore poznate kao *limfokini* ili *interleukini*, koji su predstavnici velike skupine molekula sličnih hormonima, a nazivaju se *citokini*. Navedene molekule reguliraju stanične aktivnosti uključene u imunosni odgovor. Neke T i B-stanice regresiraju u stanje malenih dugovječnih limfocita odgovornih za *imunološku memoriju*. Dok protutijela i receptori na B-stanicama prepoznaju epitope na stranim antigenima u njihovoj izvornoj konformaciji, receptori na T-stanicama prepoznaju malene peptide koji se stvaraju cijepanjem virusnih proteina. Taj se proces odvija samo ako su im strani peptidi predstavljeni zajedno s membranskim glikoproteinom poznatim kao *proteini glavnog sustava tkivne podudarnosti (MHC).*

Antigen-specifični receptori

Antigen-specifični receptori na površini B-limfocita modificirane su molekule imunoglobulina sačinjene od četiri polipeptida, dva laka (L) i dva teška (H) lanca, a nazivaju se površinski imunoglobulini (sIg). Oni su modificirani na C-terminalnom kraju teških lanaca kako bi imali transmembransku domenu koja ih učvršćuje u staničnoj membrani gdje obavljaju funkciju receptora. Prije primarne antigene stimulacije, molekule sIg su sIgM. Nakon promjene razreda imunoglobulina (vidi niže u tekstu), Ig koji mijenja razred postaje sIg receptor za antigene.

Antigen-specifični receptor na T-limfocitu (TCR) poprilično je jedinstven. Sačinjen je od dva polipeptidna heterodimera, a iako je nalik imunoglobulinu, kodiran je potpuno drugačijim skupom gena. Dva polipeptida najuobičajenijih antigen-specifičnih receptora na T-limfocitima nose oznake α/β. Druga populacija T-limfocita nosi drugačije antigen-specifične receptore oznake γ/δ.

Specifično prepoznavanje i vezivanje sIg ili antigen-specifičnih receptora na T-limfocitima na epitop izaziva, provođenjem signala kroz staničnu membranu limfocita, široki raspon efektorskih procesa koji napadaju i uklanjaju virus i/ili virusom zaražene stanice. Rezultirajući niz međustaničnih reakcija i izlučivanje citokina pojačava imunosni odgovor s ciljem prilagodbe jačini virusne infekcije te stvaranja dugotrajne memorije koja omogućava imunosnom sustavu brži (sekundarni ili anamnestički) odgovor na reinfekciju istim virusom.

B-limfociti

Neke od pluripotentnih hematopoetskih matičnih stanica koje se stvaraju u fetalnoj jetri, a kasnije u koštanoj srži, diferenciraju se u B-limfocite u Fabriciusovoj bursi u ptica ili u njenom ekvivalentu, koštanoj srži u sisavaca. Karakteristika im je prisutnost antigen-specifičnih receptora na površini te receptora za C3 komponentu komplementa i receptora za Fc regiju imunoglobulina. Tijekom ontogeneze, nekoliko stotina naslijeđenih V (varijabilnih) lakih i teških lanaca imunoglobulinskih genskih segmenata prolaze kroz somatsku rekombinaciju. Tu su i višestruke kopije J (veznih) genskih segmenata u slučaju lakih lanaca te J i D (raznolikih) genskih segmenata u slučaju teških lanaca koji se također somatski rekombiniraju s varijabilnim genima. Somatska mutacija (vidi niže u tekstu) također pridonosi povećanju raznovrsnosti protutijela kako bi se proizvelo potencijalno više od 10^7 jedinstvenih vrsta.

Pojedini B-limfocit i njihovi potomci izražavaju jedan skup imunoglobulinskih gena koji su specifični za jedan epitop. Tijekom razvoja, za takve stanice postoje tri moguća ishoda: (1) mogu reagirati s vlastitim antigenom i biti eliminirane, (2) mogu biti nevijabilne i biti eliminirane, ili (3) mogu reagirati sa stranim antigenom i proliferirati.

U odnosu na T-stanice, sIg receptori B-stanica prepoznaju antigene u njihovom izvornom i topljivom stanju, a ne kao kompleks MHC-peptid na površini stanica, stoga B-stanice direktno djeluju na virusni protein ili virion. Kada specifični klonovi B-stanica, koji su nositelji receptora komplementarnih bilo kojem od nekoliko epitopa na antigenu, vežu taj antigen, oni, nakon primanja odgovarajućih signala od pomagačkih T-stanica, reagiraju dijeljenjem i diferencijacijom u plazma stanice koje izlučuju protutijela.

Svaka plazma-stanica izlučuje jednu vrstu protutijela koje odgovara određenom V (varijabilnom) području sIg receptora koji izražava. To protutijelo u početku pripada IgM razredu, ali somatska genska rekombinacija (translokacija) zatim izaziva promjenu razreda vezivanjem varijabilnog genskog segmenta s različitim konstantnim domenama teškog lanca. Razni citokini igraju važnu ulogu u promjeni izotipa. Stoga, nakon nekoliko dana, IgG, IgA, a ponekad i IgE protutijela iste specifičnosti, počinju prevladavati u imunosnom odgovoru. U ranoj fazi imunosnog odgovora, kada su prisutne velike količine antigena, B-stanice koje reagiraju na antigen mogu biti aktivirane čak i ako njihovi receptori odgovaraju epitopu s relativno slabim afinitetom. Rezultat je stvaranje protutijela koje veže antigen niskog afiniteta. Kasnije, kada preostane samo mala količina antigena, odabiru se B-stanice, razvijene hipermutacijom unutar gena varijabilne regije, koje potom proizvode receptore koji vežu

antigen visokog afiniteta (*afinitetna maturacija*), a afinitet izlučenog protutijela se sukladno tomu povećava.

T-limfociti

T-limfociti dobili su ime po tomu što ovise o timusu u kojemu sazrijevaju iz pluripotentnih hematopoetskih matičnih stanica. Unutar timusa dolazi do pozitivne selekcije onih stanica koje mogu prepoznati odgovarajuće peptide na površini stanica te do negativne selekcije kojom se uklanjaju T-stanice koje posljedično prepoznaju vlastite antigene koji su potencijalni nositelji autoimunosnih bolesti. Samo 1 ili 2% nastalih limfocita napuštaju timus i nastanjuju sekundarna limfoidna tkiva. Prema funkciji, T-limfociti dijele se na dvije podskupine: *pomagački T- limfociti (Th),* koji se dodatno dijele na Th1 i Th2 stanice, i *citotoksični T-limfociti (Tc) (CTL).* Općenito se smatra da Th stanice imaju regulacijsku funkciju dok Tc stanice imaju izravnu efektorsku funkciju, tj. funkciju ciljane stanične lize. Pomno ispitivanje klonova T-stanica pokazuje da jedna vrsta može vršiti i regulacijske i efektorske funkcije te lučiti niz različitih limfokina.

Pomagački T-limfociti

Pomagačke T-stanice nose površinski biljeg poznat kao CD4. One prepoznaju virusne peptide u kombinaciji s MHC proteinima razreda II, najčešće na površini *stanica koje prezentiraju antigen* (APC). Oni potom luče citokine koji se aktiviraju i zatim aktiviraju i druge stanice, uključujući ostale Th, Tc i B-limfocite, pomažući u tom procesu limfocitima Tc da postanu citotoksični te pomažući B-stanicama u proizvodnji protutijela.

Stanice Th1 (*upalne* T-stanice) stanice su koje u pravilu (1) luče citokine IL-2, IFN-γ i TNF-β [ali i čimbenik rasta kolonija granulocita i makrofaga (GM-CSF) i IL-3]; (2) posreduju u izazivanju odgođene preosjetljivosti; i (3) potiču proizvodnju IgG2a. Stanice Th2 u pravilu (1) luče IL-4, IL-5 i IL-6 (ali i GM-CSF i IL-3); (2) pružaju pomoć u izazivanju odgovora odgođene preosjetljivosti, ali ne izazivaju je direktno; i (3) kod nekih vrsta životinja potiču prijelaz iz proizvodnje IgG2, koju vrše B-stanice, u proizvodnju IgG1. Pojedinačni CD4+ klonovi T-stanica znatno se razlikuju s obzirom na određene kombinacije citokina koje proizvode; obično se u kroničnim perzistentnim infekcijama pojavljuju dvije prethodno opisane dominantne vrste.

Stanice Th1, tj. stanice koje izražavaju CD4 (kao i neke koje izražavaju i CD8), luče limfokine koji pokreću upalni odgovor i znatno pojačavaju imunosni odgovor privlačeći na

mjesto virusne infekcije i monocite/makrofage i ostale T-stanice. Navedeni limfokini samostalno se aktiviraju, uzrokujući time aktivaciju, proliferaciju, diferencijaciju stanica koje ih luče, ali i lučenje drugih citokina. Ovaj odgovor osnova je za odgovore odgođene preosjetljivosti koji su poznati kao dio patogeneze mnogih virusnih infekcija. Do istog odgovora dolazi i kada se antigen ubrizga interdermalno – ovo je osnova kožnih testova pri čemu se izaziva lokalna reakcija kod prethodno zaraženih životinja.

Dokazano je da neke T-stanice mogu negativno regulirati druge odgovore T-stanica i/ili B-stanica, zbog čega se nekad smatralo da postoji dodatna vrsta stanica koje su se ranije nazivale supresorske T-stanice. Međutim, pokazalo se da je kloniranje T-stanica koje pokazuju ovo svojstvo otežano te se danas smatra da su supresorske funkcije karakteristika Th i Tc stanica. T-stanice mogu suzbiti razna oružja imunosnog sustava na brojne načine; npr. izravnom interakcijom s limfocitima ili proizvodnjom imunosupresivnih citokina.

Citotoksični T-limfociti

Citotoksični T-limfociti nose površinski biljeg CD8 i imaju antigenske receptore na T-limfocitima koji prepoznaju virusne peptide na površini virusom zaraženih ciljnih stanica u kombinaciji s MHC proteinima razreda I. Aktivacija i kasnija citoliza ciljnih stanica uzrokovana Tc stanicama zahtijevaju izravan kontakt Tc stanice i ciljne stanice na način koji podsjeća na sinapsu (ovaj se kontakt naziva „poljubac smrti“). Granule unutar citoplazme Tc stanice polariziraju se prema staničnoj membrani ciljne stanice te se njihov sadržaj otpušta. Luči se monomerni protein perforin koji se potom polimerizira kako bi oblikovao ~17-merne gljivaste strukture koje se ugrađuju u staničnu membranu ciljne stanice, stvarajući poru koja dovodi do stanične lize. Perforin je strukturom i funkcijom vrlo sličan proteinu C9 koji je odgovoran za lizu posredovanu komplementom (vidi niže u tekstu). Postoje i dokazi da i Tc i NK-stanice otpuštaju granule specifične za pojedine limfocite koje su odgovorne za serinsku esterazu (granzimi). Navedene granule izazivaju apoptozu u ciljnim stanicama.

Efektorski odgovor T-stanica uglavnom je kratkotrajan: kod određenih akutnih infekcija, aktivnosti Th i Tc stanica dosežu vrhunac otprilike tjedan dana nakon početka virusne infekcije, a nestaju nakon 2 ili 3 tjedna. Zasad nije poznato može li se to pripisati uništavanju zaraženih stanica s posljedičnim uklanjanjem antigenskog podražaja ili supresorskoj funkciji T-stanica.

γ/δ T-limfociti

Potpuno drugačiji razred T-stanica s drugačijom vrstom antigenskih receptora na T-limfocitima, koji se sastoji od polipeptidnih heterodimera oznake γ i δ (umjesto uobičajenih α

i β lanaca) nalazi se uglavnom u epitelnim tkivima poput kože, crijeva i pluća. U miševa i ljudi, ovaj razred čini neznatan udio (oko 5%) sveukupne populacije T-stanica. Ove stanice raspolažu relativno ograničenim imunološkim repertoarom, odražavajući vrlo ograničenu uporabu varijabilnih (V) gena. Međutim, sve je veći broj dokaza da su ove T-stanice uključene u imunosne odgovore na virusne infekcije koje ulaze na mjestima na kojima su lokalizirane, a postoje i dokazi da mogu prepoznati antigen bez restrikcije molekulama MHC. Ova obilježja pokazuju da bi ove stanice mogle biti važnije nego li se ranije mislilo, ali njihova točna uloga i važnost u specifičnim infekcijama zasad nije utvrđena. U svinja, preživača i kokoši, γ/δ stanice čine oko 30% T-limfocita te su šire raširene unutar tijela.

Monociti, makrofagi i dendritične stanice

Monociti, zahvaljujući svojoj mobilnosti i sposobnosti samonavođenja, te makrofagi i dendritične stanice, zahvaljujući svojim ključnim položajima unutar raznih tkiva (npr. alveolarni makrofagi u plućima, Kupfferove stanice u jetri, Langerhansove dendritične stanice u koži), važni su inicijatori imunosnog odgovora na virusnu invaziju. Uključeni su u ranu fazu odgovora domaćina na infekciju: (1) monociti ulaze u tkivo te se diferenciraju u makrofage, (2) makrofagi često postaju dominantne stanice unutar žarišta infekcije 24 sata nakon virusne invazije, a (3) dendritične stanice obavljaju aferentne imunosne funkcije na svim površinama tijela te u ključnim organima, kao što su limfni čvorovi, slezena i jetra, u kojima se odvija većina fagocitnog uklanjanja stranih čestica. Sve tri vrste stanica imaju na svojim površinama receptore za Fc i C3b imunoglobulin, što potiče fagocitozu imunokompleksa, tj. viriona prekrivenih protutijelima. Služeći kao „profesionalne“ stanice za izražavanje antigena, one kontroliraju utjecaj nad brzinom, jačinom i dinamikom imunosnog odgovora.

Makrofagi zatim izražavaju eferentan element imunosnog odgovora: citokini koje izlučuju aktivirane T-stanice dovode dodatne monocite u žarište infekcije te ih aktiviraju dok se diferenciraju u makrofage. Aktivirani makrofagi imaju povećanu kemotaktičnu aktivnost, fagocitnu aktivnost i moć razgradnje.

Prirodne stanice ubojice

Prirodne stanice ubojice (NK-stanice) heterogena su grupa velikih granularnih limfocita CD3, CD16+, CD56+ nepoznatog porijekla koji imaju sposobnost ubijanja virusom zaraženih i tumorskih stanica. Temelj za njihovu selektivnost u odabiru virusom zaraženih stanica povezan je s podregulacijom sinteze i izražavanja MHC proteina razreda I („missing self“

hipoteza), a to je rano obilježje mnogih virusom zaraženih stanica. One ne pokazuju imunološku specifičnost za određene virusne antigene, ali ni memoriju, ni ograničenost glavnim sustavom tkivne podudarnosti ni ovisnost o protutijelima. One su važan mehanizam rane obrane budući da je njihova aktivnost uvelike povećana unutar prvog ili drugog dana virusne infekcije. Virusom izazvana aktivacija NK-stanica posredovana je interferonima, sinergijski djelujući s IL-2, dok same NK-stanice luče razne citokine, uključujući interferon γ i čimbenik tumorske nekroze α.

Substanične komponente imunosnog sustava

Glavni sustav tkivne podudarnosti

Kako bismo shvatili obradu i prezentiranje antigena, trebamo prvo ponešto znati o strukturi i unutarstaničnoj proizvodnji MHC proteina. Tijekom procesa ontogeneze, pozitivna selekcija T-stanica koje sazrijevanju u timusu posredstvom „vlastitih" MHC molekula rezultira zrelim T-stanicama koje mogu prepoznati strane peptide, ali samo ako se nalaze unutar pukotine za vezivanje peptida vlastitih molekula MHC proteina – ne ako su slobodni u izvanstaničnom prostoru i ne ako su povezani sa stranim MHC molekulama. Ovaj se fenomen naziva *MHC restrikcija*.

Postoje dva razreda MHC molekula, razred I i razred II; njihova je struktura prikazana na Slici 8.3A. Dva razreda T-limfocita, točnije Th i Tc, definiraju se svojim interakcijama s proteinima MHC razreda I i MHC razreda II, pojedinačno. Putevi kojim se stanice koriste u obradi i predočavanju peptidnih antigena Th i Tc stanicama bitno se razlikuju: za peptide u kombinaciji s molekulama MHC razreda II oni se nazivaju *egzogeni putevi*, dok se za peptide koji se predočavaju u kombinaciji s molekulama MHC razreda I nazivaju *endogeni putevi.*

MHC je genski lokus koji kodira tri proteina MHC razreda I te do 12 proteina MHC razreda II, a svaki od njih se pojavljuje u 50 do 100 alternativnih alelnih oblika. Glikoproteini razreda I mogu biti izraženi na staničnim membranama većine stanica (iznimka su neuroni). Usprkos tome što nisu konstitutivno izraženi, glikoproteine razreda II uglavnom izražavaju „profesionalne" stanice za predočavanje antigena. Na distalnom vrhu oba razreda proteina MHC nalazi se pukotina na koju se peptid veže i predočava. Vezanje peptida određeno je samo dvjema ili trima hidrofobnim aminokiselinama, pod nazivom *usidreni ostatak* (eng. anchor residue), unutar određenog peptida i sukladno tome određeni MHC protein može vezati brojne različite peptide, a neki se peptidi mogu vezati na nekoliko različitih MHC

molekula. Dužina peptida koje predočuju molekule razreda I najčešće iznosi 9 aminokiselina (u rasponu između 8 do 11-mera), dok su peptidi koji se vežu na proteine razreda II dužine od 13 do 18 aminokiselina. U slučaju razreda II, pukotina za vezivanje peptida je otvorena na krajevima, dok je pukotina razreda I zatvorena. Specifične aminokiseline koje stvaraju džepove na dnu pukotine bilo kojeg MHC proteina određuju raspone peptida koji se mogu vezati. Antigenski receptor odgovarajućeg klona T-stanice potom prepoznaje kompleks pMHC-a s apsolutnom preciznošću. Ostatci aminokiselina koje se ne vežu na MHC pukotinu su hidrofobni, okrenuti prema van, te pozivaju na prepoznavanje putem receptora za antigen na T-limfocitima.

Premda postoji znatan polimorfizam MHC gena među individualnim životinjama, bilo koja individualna jedinka ima ograničen broj različitih MHC proteina, a bilo koji peptidni antigen veže se samo za određene MHC molekule. U slučaju da su određeni pMHC kompleksi važni u procesu izazivanja obrambenog imunosnog odgovora na ozbiljnu virusnu infekciju, životinje kojima nedostaju odgovarajući MHC proteini biti će genetski podložnije toj bolesti. Dodatan uzrok povećane podložnosti leži u mogućem nedostatkuT-limfocita, koji nose receptore za taj određeni kompleks pMHC, u repertoaru T-stanica individualne životinje.

Predočavanje antigena putem stanica koje izražavaju MHC-II: egzogeni put

Samo ograničeni broj stanica, pod imenom stanice za predočavanje antigena, obrađuje i predočava antigene u kombinaciji sa T-stanicama MHC razreda II. Stanice za predočavanje antigena uključuju dendritične stanice, monocite/makrofage, a u kasnijoj fazi imunosnog odgovora, i B-limfocite. Dendritične stanice, uključujući Langerhansove stanice kože, dendritične stanice limfnih čvorova, crvene pulpe i rubnih područja slezene, nose to ime jer tvore duge procese nalik prstima koji se isprepliću s limfocitima i time omogućuju predočavanje antigena. Za razliku od dendritičnih stanica, makrofagi u mirovanju luče relativno niske razine proteina MHC razreda II, ali se ta razina povećava nakon aktivacije, posebice one pomoću interferona γ. Nakon primarne aktivacije, B-limfociti postaju važne stanice za predočavanje antigena, a posebno su važni tijekom kasnijih stadija infekcije i tijekom reinfekcije. Memorijske B-stanice predstavljaju vrlo učinkovitu vrstu stanica za predočavanje antigena. Virusni antigen, ili sam virion, veže se na specifične receptore imunoglobulina na B-limfocitu te prolazi kroz proces endocitoze, cijepa se u peptide koji su predočeni na površini B-stanice u kombinaciji s proteinima MHC razreda II. Navedeni peptidi obično predstavljaju drugačije epitope od onih istog antigena kojeg B-stanica prepoznaje za proizvodnju protutijela. CD4+ Th stanice kojima B-stanice predočavaju antigene, odgovaraju

lučenjem citokina koji B-stanice potiču na stvaranje protutijela. Ova *srodna* interakcija, koja uključuje blisko udruživanje T i B stanica, omogućuje vrlo učinkovitu isporuku „pomagačkih faktora“ (citokina) od Th stanice do relevantne senzibilizirane stanice B.

Virus ili virusni proteini koje su stanice za predočavanje antigena preuzele iz vanjskih izvora ulaze u egzogeni put; postupno prolaze kroz rane endosome sve do kasnih (kiselih) endosoma i primarnih lizosoma gdje ih proteolitički enzimi cijepaju. Neki od nastalih virusnih peptida mogu vezati polipeptide α i β MHC razreda II, kako bi formirali trimerni kompleks koji se potom prenosi do stanične membrane gdje ih prepoznaju CD4+ T-stanice, što dovodi do odgovora Th stanica.

Predočavanje antigena putem stanica koje izražavaju MHC-I: endogeni put

Skoro sve stanice mogu nakon infekcije virusom biti potaknute na sintezu proteina MHC razreda I; iznimka su neuroni. Nakon sinteze, polipeptidi α- i β-mikroglobulina MHC razreda I prenose se do endoplazmatskog retikuluma gdje se okupljaju kako bi formirali stabilnu cjelinu u kombinaciji s molekularnim nadzornim proteinom imena kalneksin. U stanicama zaraženima virusom, neki od virusnih proteina se u citoplazmi razgrađuju (cijepaju) posredstvom velikog (26S) proteosomskog kompleksa koji sadrži LMP (eng. LMP-containing proteasome complex) - kaže se da ovi virusni proteini ulaze u endogeni put. Nastali peptidi se zatim prenose prijenosnim molekulama (TAP ili *transporter associated with antigen processing)* u endoplazmatski retikulum, gdje se okupljaju s molekulama MHC razreda I kako bi formirali stabilan trimerni kompleks koji potom prolazi kroz Golgijev aparat do površine stanice i predočuje se Tc stanicama. I LMP i TAP proteini kodirani su za funkcioniranje unutar kompleksa MHC gena.

Citokini

Citokini su proteini male molekularne mase nalik hormonima koji stimuliraju ili inhibiraju proliferaciju, diferencijaciju i/ili sazrijevanje stanica imunosnog sustava (Tablica 8.1). Od pravih se hormona razlikuju na nekoliko načina, uključujući to da ih proizvode nespecijalizirane stanice. Mnoge od njih proizvode T-limfociti (limfokini) ili monociti/makrofagi (monokini) te, tako što koordiniraju aktivnosti raznih tipova stanica uključenih u proces, služe za regulaciju imunosnog odgovora. Stoga, iako citokini nisu antigen-specifični, njihovom proizvodnjom i djelovanjem često upravljaju antigeni.

Citokini mogu djelovati na stanicu koja ih je proizvela (autokrin) ili na stanice u neposrednoj blizini (parakrin), posebice na dodirnim površinama stanica, pri čemu može doći do usmjerene sekrecije te se vrlo niske koncentracije mogu pokazati učinkovitima ili mogu djelovati na udaljenije stanice (endokrini). Osjetljive ciljne stanice nose receptore za određene citokine. Jedan citokin može proizvesti mnoštvo bioloških učinaka, nerijetko djelujući na više od jedne vrste stanica. Nadalje, različiti citokini mogu imati slične učinke iako možda putem različitih postreceptornih puteva transdukcije signala, dovodeći do sinergizma. Djelovanje citokina uvelike je redundantno, vjerojatno zbog potrebe za obrambenim mehanizmima koji neće podbaciti; učestalo se koriste *knock-out* miševi koji ne podliježu određenim izazovima virusa, a u čijim je genima izbrisan jedan citokinski gen.

Citokini pozitivno ili negativno reguliraju ciljne stanice, a različiti citokini mogu biti antagonisti jedni drugima. U pravilu citokin koji luči određena vrsta stanice aktivira drugu vrstu stanice kako bi ona lučila drugačiji citokin ili kako bi izrazila receptore za određeni citokin, i tako dalje u nekoj vrsti lančane reakcije. Zbog zamršenosti kaskade citokina, rijetko je moguće pripisati taj biološki proces *in vivo* jednom citokinu.

Citokini mogu na različite načine utjecati na virusnu patogenezu: (1) jačanje imunosnog odgovora, npr. jačanje citotoksičnih T-stanica čimbenikom tumorske nekroze α ili interferonom γ, koji pozitivno regulira izražavanje MHC-a; (2) regulacija imunosnog odgovora, npr. izotopi protutijela koje mijenjaju interleukini 4, 5, 6 ili interferon γ; (3) suzbijanje imunosnog odgovora, npr. interleukin 10 sprječava sintezu interferona γ; (4) inhibicija umnažanja virusa pomoću interferona; i (5) pozitivna regulacija izražavanja virusnih gena.

Tablica 8.1
Citokini: Izvori, svrha i djelovanje[a,b,c]

CITOKIN	GLAVNI IZVOR	GLAVNA SVRHA/DJELOVANJE
IL-1α, β	Monociti/makrofagi, B-stanice, dendritične stanice	Proliferacija T-stanica, izražavanje receptora IL-2, protutijelo, vrućica
IL-2	Th1 tanice	Proliferacija i diferencijacija T-stanica
IL-3	T-stanice, NK-stanice, mastociti	Matične stanice i mastociti; hematopoeza, oslobađanje histamina
IL-4	Th2 stanice, mastociti, NK-stanice	Proliferacija i diferencijacija B-stanica, T-stanica i makrofaga; promjena iz IgM u IgG1 i IgE; nadregulira izražavanje MHC razreda II
IL-5	Th2 tanice, mastociti	Proliferacija i diferencijacija B-stanica i eozinofila; promjena razreda u IgA
IL-6	Th2 stanice, makrofagi,	Proliferacija B-stanica, plazma stanice hepatocita;

	druge stanice	potpomaže diferencijaciju u plazma stanice; sinteza proteina akutne faze (vrućica)
IL-7	Stanice koštane srži i timusne stromalne stanice	Proliferacija pre-B i pre-T stanica; povećava izražavanje IL-2 i njegovih receptora
IL-8	Makrofagi, endotelne stanice	Kemotaksija, adhezija i dijapedeza neutrofila
IL-9	Th stanice	Neke Th stanice; djeluje kao mitogen koji u nedostatku antigena podupire proliferaciju
IL-10	Th2 stanice	Inhibira stvaranje citokina putem makrofaga čime indirektno smanjuje stvaranje citokina putem T-stanica
IL-11	Stromalne stanice koštane srži	Stanice pre-B, stanice plazmocitoma, megakariociti, hepatociti; rast i diferencijacija
IL-12	Makrofagi, B-stanice	Sinergijski djeluje s IL-2 u svrhu stimuliranja diferencijacije Tc stanica; proliferacija NK-stanica
IL-13	Th stanice	Makrofagi; inhibira aktivaciju i otpuštanje upalnih citokina
IL-15	T-stanice, crijevni epitel, NK-stanice i aktivirane B-stanice	Rast i proliferacija crijevnog epitela i T-stanica; komitogen
IL-16	T-stanice (prvenstveno Tc stanice), makrofagi, eozinofili	Th stanice, kemotaksa, izražavanje MHC razreda II, suzbijanje proliferacije izazvane antigenima
TNF-α, β	Makrofagi, Th1 stanice, Tc i mastociti	Antivirusno; proliferacija i diferencijacija T-stanica, B-stanica, makrofaga, NK-stanica, fibroblasta; vrućica; citotoksično, potiče kaheksiju
TGF-β	Trombociti, makrofagi, limfociti, mastociti	Inhibira proliferaciju T-stanica, B-stanica i matičnih stanica i potiče povećanu proizvodnju IL-1, čime inhibira upalu i stimulira zacjeljivanje rana; potiče promjenu razreda u IgA
IFN-α, β	Leukociti, druge stanice	Antivirusno; vrućica
IFN-γ	Th1, Tc i NK-stanice	Antivirusno; aktivacija Th2 stanica, makrofaga i NK-stanica; promjena iz IgM u Ig2a; blokira promjenu razreda iz IgE u IgG1 potaknutu citokinima IL-4; pozitivna regulacija MHC i Fc receptora
GM-CSF	T-stanice, makrofagi, endotel	Hematopoeza, granulociti, monociti

a Citokini su pleiotropični, tj. jedna molekula ima nekoliko različitih i naizgled nepovezanih fenotipskih učinaka.
b U ovom sažetom pregledu navedene su samo neke od glavnih aktivnosti najproučavanijih citokina.
c IL, Interleukin; TNF, čimbenik tumorske nekroze; TGF, transformirajući čimbenik rasta; IFN, interferon; CSF, faktor stimulacije kolonija

Protutijela

Krajnji rezultat aktivacije i sazrijevanja B-stanica jest proizvodnja protutijela koja reagiraju izričito s epitopima koje su u početku prepoznali njihovi recetori. Protutijela se dijele na četiri

glavna razreda: dva monomera, IgG i IgE, i dva polimera, IgM i IgA. Svi imunoglobulini određenog razreda imaju sličnu strukturu, ali uvelike se razlikuju prema nizu aminokiselina koje sadrže antigenska vezna mjesta, što određuje njihovu specifičnost za antigensku determinantu. Najčešći imunoglobulin koji se nalazi u serumu, IgG, sastoji se od dva teška i dva laka lanca, a svaki se lanac sastoji od *konstantne* i *varijabilne* regije. Lanci su povezani disulfidnim vezama. Papainsko cijepanje razdvaja molekule na dva jednaka *Fab fragmenta,* koji sadrže mjesta za vezivanje antigena, te na *Fc fragment* koji sadrži mjesta za razne efektorske funkcije kao što su fiksacija komplementa, vezivanje na fagocite i prijenos kroz posteljicu i kolostrum.

Imunološka specifičnost molekule protutijela ovisi o njezinoj mogućnosti vezanja isključivo na određeni epitop. Mjesto vezivanja, tj. *žlijeb za vezanje protutijela* nalazi se na amino-terminalnom kraju molekule. Varijabilne regije lakih i teških lanaca sastoje se od oko 107 aminokiselina unutar kojih se nalaze tri hipervarijabilne regije, pod nazivom *CDR (complement determining) regije,* raštrkane među četirima konzerviranim regijama zvanima *FR (framework) regije*. Kada se peptidi saviju kako bi formirali trodimenzionalnu funkcionalnu strukturu imunoglobulina, šest CDR regija (po tri iz lakih i teških lanaca) nalazi se u žlijebu za vezanje antigena. Varijabilnost CDR regija odgovorna je za neograničeni raspon različitih epitopa koje ove molekule prepoznaju. (Slični principi osnova su stvaranja antigene raznolikosti prisutne u varijabilnim regijama T staničnog receptora.)

Protutijela usmjerena protiv epitopa na površini viriona, neutraliziraju infektivnost; također mogu djelovati kao opsonini, olakšavajući makrofagima aktivni unos i uništavanje viriona. Osim toga, protutijela se mogu pričvrstiti za površinu zaražene stanice, dovodeći do njezina uništenja aktivacijom klasičnih ili alternativnih puteva komplementa ili naoružavanjem i aktivacijom stanica koje nose Fc receptor kao što su NK-stanice, polimorfonuklearni leukociti i makrofagi (citotoksičnost posredovana NK-stanicama ovisna o protutijelima).

Imunoglobulin G

Glavni razred protutijela u krvi jest imunoglobulin G (IgG) koji se pojavljuje u četiri podrazreda: IgG1, IgG2, IgG3 i IgG4. Nakon sistemske virusne infekcije, IgG se godinama nastavlja sintetizirati te je glavni posrednik u zaštiti protiv reinfekcije. Podrazredi imunoglobulina G razlikuju se po konstantnoj regiji teških lanaca, a stoga i po biološkim svojstvima kao što su fiksacija komplementa i vezanje na fagocite.

Imunoglobulin M

Imunoglobulin M (IgM) je razred protutijela s visokim afinitetom. Radi se o pentameru koji se sastoji od pet IgG ekvivalenata, s 10 Fab fragmenata, a time i 10 mjesta za vezivanje antigena. Budući da se IgM zamjenjuje IgG, u imunosnom se odgovoru razvija rano pa su određena protutijela razreda IgM simptom nedavne (ili kronične) infekcije. U fetusu se mogu pronaći niske razine imunoglobulina M dok se imunološka sposobnost razvija u drugoj polovici trudnoće. S obzirom na to da IgM kod nijedne vrste ne prelazi kroz posteljicu iz ženke u fetus, prisutnost IgM protutijela za određeni virus kod novorođene životinje može biti znak intrauterine virusne infekcije.

Imunoglobulin A

Imunoglobulin A (IgA) je dimer s četiri Fab fragmenta. Prolazeći kroz epitelne stanice, IgA dobiva fragment J (J sa značenjem 'pripajanje' /joining/ u engleskom jeziku; zove se i sekretorni dio) kako bi postao *sekretorni IgA*, koji se kroz epitel izlučuje u respiratorni, crijevni i urogenitalni trakt. Sekretorni IgA je otporniji na proteazu od ostalih imunoglobulina te je glavni imunoglobulin na mukoznim površinama, a kod nekih vrsta životinja, i u mlijeku i kolostrumu. Upravo zato su protutijela IgA važna u obrani od infekcija respiratornog, crijevnog i urogenitalnog trakta, a odgovori protutijela IgA mogu se učinkovitije izazvati oralnom ili respiratornom nego li sistemskom administracijom antigena, što je od velike važnosti u razvoju i načinu davanja nekih cjepiva (vidi Poglavlje 13).

Imunoglobulini D i E

IgD i IgE su manje zastupljene vrste imunoglobulina, a čine manje od 1% sveukupnih razina imunoglobulina: (1) većina imunoglobulina D vezana je za površinu B-limfocita, no njegova funkcija nije poznata; (2) IgE, kojeg proizvode subepitelne plazma stanice u respiratornom i crijevnom traktu, snažno se veže na mastocite i reagira s određenim vrstama antigena (alergeni). Stimulira otpuštanje medijatora anafilakse poput serotonina i histamina.

Komplement

Sustav komplementa sastoji se od oko 30 serumskih proteina, koji mogu biti aktivirani kako bi „kompletirali“ imunosni odgovor. Uz klasični put aktivacije komplementa, koji ovisi o prisutnosti kompleksa antigena i protutijela, postoji i alternativni put neovisan o protutijelima. Oba su važna kod virusnih infekcija.

Aktivacija komplementa klasičnim putem može dovesti do uništenja viriona ili virusom zaraženih stanica, ali i do upale. Uništavanje viriona rezultat je opsonizacije, jačanja

neutralizacije ili lize virusne ovojnice. Aktivacija komplementa koja slijedi nakon interakcije protutijela s virusnim antigenima unutar tkiva, dovodi do upale i nakupljanja leukocita. Čini se da se aktivacija komplementa putem alternativnih puteva događa uglavnom nakon infekcija virusima u ovojnici koji sazrijevaju „pupanjem“ kroz staničnu membranu. Alternativni put može se pojaviti odmah nakon virusne invazije tijela jer ne zahtijeva protutijelo.

Imunološka memorija

Nakon prvog kontakta s antigenom i klonalnog širenja limfocita, nastaje populacija dugovječnih *memorijskih stanica* koje nemaju ograničen životni vijek. Memorijske T-stanice prepoznatljive su po posebnim površinskim biljezima (osobito CD45RO) i samonavodećim molekulama (*adhezini*) koje se povezuju posebnim putevima recirkulacije. Prilikom ponovnog doticaja s istim antigenom, čak i godinama kasnije, memorijske stanice odgovaraju brže i snažnije nego prilikom prvog susreta. Prilikom ponovnog doticaja s antigenom, memorijska B-stanica pokazuje i *anamnestički (sekundarni) odgovor*, uz proizvodnju veće količine specifičnih protutijela.

Malo je podataka o mehanizmu dugotrajnosti imunološke memorije T- i B-limfocita u odsustvu dokazive kronične infekcije. S vremena na vrijeme stanice mogu restimulirati prvobitni peptidni antigeni koji se na duže vrijeme zadržavaju u obliku kompleksa MHC-peptid na folikularnim dendritičnim stanicama u limfoidnim folikulama ili zamjenskim antigenima u obliku slučajnih križno-reaktivnih antigena ili antiidiotipskih protutijela. Memorijski T- i B-limfociti mogu godinama preživjeti bez diobe, točnije do ponovne stimulacije nakon reinfekcije.

Imunosni odgovori na virusnu infekciju

Pregled glavnih značajki imunosnog odgovora na tipičnu akutnu viralnu infekciju prikazan je na Slici 8.1. Kao što je prikazano, najmanje tri fenomena pridonose oporavku od infekcije: (1) uništenje zaraženih stanica, (2) stvaranje interferona i (3) neutralizacija infektivnosti viriona. Ubrzo nakon infekcije, makrofagi fagocitiraju dio virusnih čestica. Uneseni virusi, osim u slučaju određenih virusa koji mogu rasti unutar makrofaga, se uništavaju. Njihovi se proteini cijepaju u kratke peptide koji se predočuju na površini makrofaga u kombinaciji s proteinima MHC razreda II. Ovu kombinaciju prepoznaje odgovarajući klon CD4+ limfocita. Th1 limfociti odgovaraju klonalnom proliferacijom i otpuštanjem limfokina, koji na to mjesto privlače krvne monocite i potiču ih na proliferaciju i diferencijaciju u aktivirane makrofage, koji su temelj upalnog odgovora. Th2 limfociti odgovaraju lučenjem drugačijeg

skupa limfokina koji, nakon vezanja virusnog antigena, potiču odgovarajuće klonove B-stanica na diobu i diferencijaciju u plazma stanice. Aktivacija Tc stanica događa se nakon prepoznavanja virusnih peptida u kombinaciji s MHC razreda I na površini zaraženih stanica. U odnosu na odgovor protutijela koji doseže vrhunac nešto kasnije (nakon 2 do 3 tjedna), odgovor Tc stanica najčešće doseže vrhunac oko tjedan dana nakon infekcije. Aktivnost NK-stanice najveća je nakon 2 dana, a aktivnost interferona doseže vrhunac kada i titar virusa.

Sinteza protutijela uglavnom se odvija u slezeni, limfnim čvorovima, limfatičnim tkivima probavnog sustava (GALT) i limfoidnom tkivu povezanom s bronhom (BALT). Slezena i limfni čvorovi primaju virusne antigene putem krvi ili limfnog sustava i sintetiziraju protutijela koja su većinom ograničena na razred IgM u ranom stadiju odgovora i na podrazred IgG u kasnijem. Međutim, submukozna limfoidna tkiva kao što su krajnici i Peyerove ploče, primaju antigene izravno od prekrivajućih epitelnih stanica i uglavnom stvaraju protutijela razreda IgA.

Imunosna citoliza virusom zaraženih stanica

Uništavanje zaraženih stanica osnovna je značajka oporavka od virusnih infekcija te je rezultat bilo kojeg od četiri različita procesa koji uključuju citotoksične T-stanice, citotoksičnost posredovanu komplementom ovisnu o protutijelima, citotoksičnost posredovanu stanicama ovisnu o protutijelima ili NK-stanice. Budući da se neki virusni proteini, ili peptidi koji potječu iz njih, pojavljuju u staničnoj membrani prije nego li je ijedan virion proizveden, stanična liza u ovoj fazi zaustavlja umnožavanje virusa prije nego li se otpusti značajan broj novih viriona.

Čak i u slučaju niskih koncentracija protutijela, citotoksičnost posredovana komplementom ovisna o protutijelu može se lako demonstrirati *in vitro.* Čini se da je kod ovog fenomena posebno važan alternativni put aktivacije komplementa. *Citotoksičnost posredovana stanicama ovisna o protutijelima (ADCC)* posredovana je leukocitima koji nose receptore Fc: makrofagima, polimorfonuklearnim leukocitima i drugim vrstama stanica ubojica. Međutim, NK-stanice aktiviraju interferoni ili ih izravno aktiviraju virusni glikoproteini. Oni ne demonstriraju imunološke posebnosti, ali preferencijalno liziraju virusnom zaražene stanice. Također, u prisutnosti protutijela, makrofagi mogu fagocitirati i razgraditi virusom zaražene stanice.

Neutralizacija virusne infektivnosti

Nasuprot T-stanicama, B-stanice i protutijela u pravilu prepoznaju *konformacijske* epitope, tj. ključni talozi koji dolaze u doticaj s antigenskim veznim mjestom na molekuli protutijela ne nalaze se nužno jedni pokraj drugih u sekvenci aminokiselina, već dolaze u blisku apoziciju kao rezultat savijanja jednog ili više polipeptidnih lanaca kako bi se postigla izvorna konformacija. Ova vrsta epitopa B-stanica obično se nalazi na površini proteina, često na istaknutim izbočinama ili petljama, i u pravilu predstavlja relativno varijabilne regije molekule, razlikujući se među sojevima te vrste virusa.

Dok se određeno protutijelo bilo kojeg razreda može vezati na bilo koji dostupan epitop na površinskom proteinu viriona, samo ona protutijela koja se vežu s prilično visokim afinitetom za određeni epitop na određenom proteinu vanjske kapside ili ovojnice viriona, mogu neutralizirati virusnu infektivnost. Ključni protein najčešće je onaj koji sadrži ligand kojim se virion veže na receptore stanice domaćina. Mutacije unutar ključnih epitopa na takvim proteinima omogućuju virusu da izbjegne neutralizaciju koju vrši protutijelo, a postepena pojava mutacija kod većine navedenih epitopa dovodi do pojave novog soja (genetski/antigenski otklon; vidi Poglavlje 4).

Neutralizacija se ne sastoji samo od oblaganja viriona protutijelima niti blokiranja vezivanja za stanicu domaćina. Osim u slučaju prisutnosti vrlo visoke koncentracije protutijela pri čemu su većina ili sva dostupna antigena mjesta na površini viriona zasićena, neutralizirani virioni još uvijek se mogu vezati na podložne stanice. U tim slučajevima u jednome trenutku, nakon adsorpcije i ulaska, dolazi do sprječavanja neutralizacije. Prema jednoj hipotezi, virion je obično na kontroliran način, kojim se održava njegova infektivnost, neobložen unutar stanice, dok kompleks virion-protutijelo može biti uništen lizosomskim enzimima. Na primjer, čini se da u slučaju pikornavirusa neutralizirajuće protutijelo izobličuje kapsidu, dovodeći do gubitka određenog kapsidnog proteina, pri čemu virion postaje izložen napadima enzima. Kod virusa influence, suptilnije promjene u molekuli hemaglutinina mogu spriječiti fuziju koja prethodi otpuštanju nukleokapside s virusne ovojnice.

Oporavak od virusne infekcije

Stanična imunost, protutijela, komplement, fagociti, interferoni, i drugi citokini uključeni su u oporavak od virusne infekcije – u većini slučajeva nekoliko ovih oružja imunosnog sustava djeluje zajednički ali to ovisi o pojedinoj kombinaciji domaćina-virusa.

Uloga T-limfocita

Limfociti i makrofagi obično prevladavaju u staničnoj infiltraciji virusom zaraženih tkiva; u odnosu na bakterijske infekcije, polimorfonuklearnih limfocita nema mnogo. Smanjenje broja T-stanica putem neonatalne timektomije ili liječenjem antilimfocitnim serumom povećava podložnost pokusnih životinja na većinu virusnih infekcija. Na primjer, miševi koji imaju smanjeni broj T-stanica, a zaraženi su virusom ektromelije, ne pokazuju uobičajenu infiltraciju mononuklearnih stanica u jetru, razvijaju izraženu nekrozu jetre i ugibaju, bez obzira na proizvodnju antivirusnih protutijela i interferona. Titari virusa u jetri i slezeni zaraženih miševa mogu biti uvelike smanjeni adoptivnim prijenosom imunih T-stanica dobivenih od miševa koji su se oporavili od bolesti. Navedeni proces ograničen je na MHC razreda I, a uključuje Tc stanice i može spasiti život.

Sljedeći pristup koji se koristi za „seciranje“ imunosnog odgovora eksperimentalno zaraženih visokosrođenih miševa, jest potpuno uklanjanje imunosnog potencijala (korištenjem rendgenskog zračenja, citotoksičnih lijekova itd.), a zatim zasebno vraćanje individualnih komponenata. U danas prihvaćenom modelu, citotoksični T-limfociti definirane funkcije i specifičnosti, koji su spremni za borbu protiv virusa, a klonirani su u kulturi i potom preneseni u zaražene životinje, spasili su živote miševa zaraženih virusom limfocitnog koriomeningitisa, virusom influence i drugim virusima. U pravilu, CD8+ T-stanice pružaju bolju zaštitu od CD4+ T-stanica. Nadalje, u odnosu na normalne miševe, transgenični miševi kojima nedostaju CD8+ T-stanice skloniji su morbiditetu i mortalitetu nakon virusnih izazova. Bez obzira na to, dokazano je da CD4+ T-stanice igraju važnu ulogu u oporavku, kao i citokini koje luče, a posebice interferon γ i IL-2.

Iako se determinante T-stanica i epitopi B-stanica na površini proteina virusa ponekad preklapaju, imunodominantne Tc determinante često se nalaze na relativno očuvanim proteinima smještenim u unutrašnjosti viriona ili na nestrukturnim virusom kodiranim proteinima koji se pojavljuju samo u virusom zaraženim stanicama. Upravo zato odgovori T-stanica uglavnom imaju širi raspon specifičnosti od odgovora neutralizirajućih protutijela te pokazuju križnu reaktivnost između sojeva i serotipova. Kada se gen koji kodira protein, koji ne uspijeva proizvesti neutralizirajuće protutijelo (npr. NP, M ili S protein virusa influence) sjedini s genomom virusa vakcinije, T-stanice koje su izazvane nakon infekcije tim virusom mogu adoptivno prenijeti potpunu zaštitu na netestirane miševe koji nisu preboljeli virus influence.

Uloga protutijela

Kod općih bolesti koje su karakterizirane viremijom pri čemu virioni slobodno cirkuliraju plazmom, cirkulirajuće protutijelo igra važnu ulogu u oporavku. Podatci o životinjskim i zoonotskim bolestima nisu dostupni, ali dostupni su korisni podatci o ljudskim bolestima: ljudska novorođenčad s težim oblikom primarne agamaglobulinemije bez komplikacija se oporavlja od infekcije virusa ospica, ali imaju 10 000 puta veće šanse od normalne novorođenčadi da razviju paralitičku bolest nakon cijepljenja oslabljenim cjepivom protiv poliovirusa. Ta novorođenčad ima normalan odgovor interferona i imunosni odgovor posredovan stanicama, normalne fagocitne stanice i normalan sustav komplementa, ali ne mogu proizvoditi protutijela, koja su neophodna da bi se spriječilo širenje poliovirusa na središnji živčani sustav kroz krvotok.

Iako postoje poprilično dobri dokazi da protutijela igraju važnu ulogu u oporavku životinja od infekcija pikonavirusom, togavirusom, Flavivirusom i parvovirusom, nije potvrđeno da protutijelo djeluje isključivo neutraliziranjem viriona. Zapravo, pokazalo se da određena monoklonska protutijela koja ne vrše neutralizaciju mogu spasiti živote miševa zaraženih raznim virusima, vjerojatno ADCC-om, lizom zaraženih stanica pomoću komplementa ovisnih o protutijelu (eng. antibody complement-mediated lysis) ili opsonizacijom viriona za makrofage.

Spoznaje o eksperimentalnoj i prirodnoj (urođenoj) imunodeficijenciji

Jedan od pristupa razumijevanju mehanizama koji su uključeni u oporavak od virusne infekcije, a koji nije podložan laboratorijskom ispitivanju, jest jednostavno kliničko promatranje virusnih infekcija kod životinja ili djece koja boluju od primarne imunodeficijencije. Primjerice, atimični (*goli*) miševi, koji su rođeni s nedostatkom T-stanica, izrazito su podložni mnogim virusnim infekcijama. U nekim porodicama arapskih konja, prisutan je potpun ili skoro potpun nedostatak B- i T-limfocita. Karakteristične su limfopenija i hipogamaglobulinemija, koje ždrjebad čine izrazito podložnima infekcijama, a posebice infekciji konjskoga adenovirusa tipa 1. Postoji i nekoliko vrsta deficijencije B-limfocita zbog koje su novorođene životinje sklone vrlo teškim infekcijama. Među njima su primarna agamaglobulinemija čistokrvnih konja, selektivna deficijencija B-stanica koje proizvode IgM u ždrjebadi, deficijencija IgG2-sintetizirajućih stanica u nekih pasmina goveda i disgamaglobulinemija u određenih linija kokoši pasmine White Leghorn. Nadalje, postoje i stanja koja su karakterizirana deficijencijom T-stanica uzrokovanom hipoplazijom timusa.

Sekundarne agamaglobulinemije i hipogamaglobulinemije u ždrjebadi, prasadi, janjadi, a posebno teladi, koje karakterizira neuspjeh prijenosa protutijela putem kolostruma (vidi niže u tekstu), od različitog su podrijetla i važnosti, ali velikog praktičnog značaja.

Imunost na reinfekciju

Iako veliki broj isprepletenih fenomena pridonosi oporavku od virusne infekcije, čini se da je mehanizam stečenog imuniteta na reinfekciju istim virusom mnogo jednostavniji. Prva je linija obrane protutijelo koje se, ako se stekne aktivnom infekcijom virusom koji uzrokuje sustavne infekcije, nastavlja godinama sintetizirati, pružajući snažnu zaštitu od reinfekcije. Stupanj stečenog imuniteta općenito dobro korelira s titrom protutijela u serumu. Nadalje, prijenos samog protutijela, bilo umjetnom pasivnom imunizacijom ili prijenosom majčinih protutijela sa ženke na fetus ili mlado, pruža izvrsnu zaštitu od mnogih virusnih infekcija. Stoga je prihvatljivo zaključiti da su protutijela najutjecajniji čimbenik imunosti stečene prirodnom infekcijom ili cijepljenjem. Ako je odgovor protutijela nedovoljan, ponovno se pokreću mehanizmi koji pridonose oporavku, a glavne su razlike u tome da protutijela smanjuju količinu infektivnog virusa te da senzibilizirani memorijski T- i B-limfociti izazivaju brži sekundarni odgovor.

U usporedbi sa serumskim IgG odgovorom, sekretorni IgA odgovor u pravilu traje kratko. Sukladno tome, otpornost na reinfekciju respiratornim virusima i nekim enteričkim virusima obično je vremenski ograničena. Na primjer, reinfekcija istim serotipom virusa parainfluence ili respiratornog sincicijskog virusa nije rijetkost. Štoviše, reinfekcija u periodu slabljenja imuniteta pogoduje odabiru "neutralization-escape" mutanata, što rezultira pojavom novih sojeva virusa poput virusa gripe nastalih kao rezultat antigenskog otklona. Budući da postoji mala ili nikakva križna zaštita između antigenski različitih sojeva virusa, napadi respiratornih infekcija ponavljat će se tijekom cijelog života.

Imunosni odgovor na prvu infekciju virusom može imati prevladavajući utjecaj na naknadne imunosne odgovore na antigenski povezane viruse jer drugi virus često izaziva odgovor koji je usmjeren uglavnom protiv antigena izvornog virusnog soja. Na primjer, odgovor protutijela na naredne infekcije različitim sojevima virusa influence A uvelike je usmjeren na antigenske odrednice određenog soja virusa kojim je ta individualna jedinka bila zaražena prvi put. Taj fenomen, pogrešno nazvan "izvorni antigeni grijeh", pojavljuje se kod infekcija enterovirusima, reovirusima, paramiksovirusima i togavirusima. Izvorni antigeni grijeh ima važan utjecaj na interpretaciju seroepidemioloških podataka, a posebice za razvoj djelotvornih strategija cijepljenja.

Pasivni imunitet

Postoje brojni dokazi o učinkovitosti protutijela u sprječavanju infekcija. Na primjer, umjetna *pasivna imunizacija* (ubrizgavanje protutijela) privremeno štiti od infekcije psećim štenećkom, mačjom panleukopenijom, svinjskom kolerom i mnogim drugim virusnim infekcijama (vidi Poglavlje 13). Nadalje, urođena pasivna imunizacija, tj. prijenos majčinih protutijela sa ženke na mladunče, prvih nekoliko mjeseci štiti mladunče od većine infekcija koje je ženka preboljela.

Urođeni pasivni imunitet

Urođeni pasivni imunitet važan je iz dva glavna razloga: (1) neophodan je za zaštitu mladih životinja tijekom prvih tjedana ili mjeseci njihova života, a štiti ih od bezbroj mikroorganizama, uključujući viruse koji su prisutni u okolišu u kojem su životinje rođene, a (2) protutijela dobivena od majke sprječavaju aktivnu imunizaciju mladunčeta i stoga se moraju uzeti u obzir prilikom određivanja rasporeda cijepljenja (vidi Poglavlje 13).

Prijenos majčinskih protutijela

Majčinska protutijela ženke mogu se u ptica prenijeti putem žumanjka, u primata posteljicom, a u ostalih sisavaca putem kolostruma i/ili mlijeka. Različite se vrste sisavaca, ovisno o strukturi posteljice, uvelike razlikuju po glavnim načinima prijenosa majčinskih protutijela (Tablica 8.2). U onih vrsta kod kojih su krvožilni sustavi ženke i fetusa odvojeni relativno malim brojem (jedan do tri) slojeva posteljice, protutijela razreda IgG (ali ne i IgM) mogu prodrijeti kroz nju te se majčinski imunitet prenosi se uglavnom tim putem. Međutim, posteljica većine domaćih životinja mnogo je složenija (pet do šest slojeva) te se pretpostavlja da djeluje kao prepreka čak i za IgG; u ovih vrsta, majčinski imunitet prenosi se na mladunče putem kolostruma i, u mnogo manjoj mjeri, putem mlijeka.

Tablica 8.2
Prijenos urođenog pasivnog imuniteta u sisavaca

		Broj placentalnih slojeva				
Vrsta	Vrste placente	Majčinska	Fetalna	Prenatalni prijenos (putem placente	Poslijenatalni prijenos (putem crijeva)	„Zatvaranje crijeva“ (dani)
Goveda, svinje, konji	Epiteliokorijalna	3	3	0	+++	2
Ovce, koze	Sindezmokorijalna	2 ili 3	3	0	+++	2

Mačke, psi	Endoteliokorijalna	1	2 ili 3	+ -	+++	2
Miševi, štakori	Hemokorijalna	0	3	++	+	16-20

Različite se vrste životinja razlikuju po određenim razredima ili podrazredima imunoglobulina koji se preferencijalno prenose na mladunče putem kolostruma (Tablica 8.3), ali u većine domaćih životinja uglavnom je to IgG. U goveda i ovaca prisutan je selektivan prijenos IgG1 iz seruma preko alveolarnog epitela mliječne žlijezde tijekom posljednjih nekoliko tjedana trudnoće, a time razina IgG1 u kolostrumu može doseći 40 do 70g/l, u usporedbi s oko 1.0 do 1.8 g/l u mlijeku i 13 g/l u serumu. Protutijela razreda IgG1 važna su u zaštiti protiv enteričnih infekcija sve dok traje dojenje.

Selektivni prijenos IgG iz majčine cirkulacije preko alveolarnog epitela mliječne žlijezde funkcija je Fc fragmenta molekule. Velike količine IgG prisutne u kolostrumu specijaliziranim se stanicama, prisutnima u gornjem dijelu tankog crijeva, unose i *prenose* u velike intracitoplazmatske vezikule kako bi dospjele u cirkulaciju mladunčeta u nerazgrađenom obliku. Male količine ostalih protutijela (IgM, IgA) prisutnih u kolostrumu ili mlijeku mogu se, kod nekih vrsta, također prenijeti putem crijeva, ali brzo nestaju iz cirkulacije mlade životinje. Razdoblje nakon rođenja tijekom kojeg se putem kolostruma protutijelo prenosi, (*„zatvaranje crijeva“*, eng. translocation cut-off time) kod većine je domaćih životinja precizno definirano i vrlo kratko (oko 48 sati) (Tablica 8.2).

U ptica je prisutan selektivni prijenos IgG iz majčine cirkulacije; u žumanjku kokošjeg jajeta razina IgG je 25 g/l u usporedbi sa 6 g/l u cirkulaciji majke. Kokoš nesilica godišnje proizvodi oko 100 g IgG koji ulazi u žumanjak, što je otprilike onoliko koliko proizvodi i za svoje potrebe. IgG ulazi u vitelin, a time i u cirkulaciju pilića od 12. dana inkubacije. Nešto IgG prenosi se u amnionsku tekućinu te ga pilić proguta. Prije nego li se izlegne, žumanjčana vrećica s preostalim imunoglobulinom majke u potpunosti se unosi u trbušnu šupljinu i sjedinjuje se sa stijenkom tankog crijeva pilića.

Tablica 8.3
Koncentracije razreda imunoglobulina IgG, IgA i IgM u kolostrumu i mlijeku u nekih vrsta sisavaca[α]

Koncentracija imunoglobulina (gram/litra)						
	Kolostrum			Mlijeko		
Vrsta	IgG	IgA	IgM	IgG	IgA	IgM
Govedo	36-77	4-5	3.2-4.9	1.0-1.8	0.2	0.04
Svinja	62	10	3.2	1.4	3.0	1.9
Konj	80	9	4	0.35	0.8	0.04

Pas	2.0	13.5	0.3	0.01	3.6	0.06
Čovjek	0.3	120	1.2	0.1	1.5	0.01

[α]Podvlaka označava glavne komponente.

Majčinska protutijela u krvotoku novorođenog sisavca ili tek izlegnutog pilića vrlo brzo se uništavaju kinetikom prvog reda. Poluvijek, koji traje ponešto dulje nego u odraslih životinja, iznosi oko 21 dan u krava i konja, 8 do 9 dana u pasa i mačaka i samo 2 dana u miševa. Naravno, novorođena životinja bit će zaštićena od zaraze bilo kojim virusom samo ako ženkin IgG sadrži specifična protutijela, a ako je početni titar tog virusa visok, zaštita može trajati mnogo dulje od poluvijeka IgG.

Iako su razine IgA prenesenog putem kolostruma u crijeva novorođene životinje znatno niže od razina IgG, ipak pomažu u zaštiti novorođenih životinja od enteričnih virusa protiv kojih je ženka razvila imunitet. Nadalje, postoje dokazi da nakon „zatvaranja crijeva“, imunoglobulini prisutni u običnom mlijeku, uglavnom IgA, ali i IgG i IgM, mogu nastaviti pružati određeni zaštitni imunitet protiv crijevnih infekcija. Često se novorođena životinja susreće s virusima dok je još uvijek djelomično zaštićena. Virus se u tim okolnostima u ograničenoj mjeri replicira, potičući imunosni odgovor bez izazivanja značajnijih oboljenja. Na taj način novorođena životinja stječe aktivni imunitet, a u isto je vrijeme djelomično zaštićena majčinskim imunitetom.

Zakazivanje prijenosa majčinskih protutijela

Neuspješan ili djelomično neuspješan prijenos majčinskih protutijela najčešći je poremećaj imunodeficijencije u domaćih životinja. Na primjer, između 10 i 40% mliječne teladi i do 20% ždrjebadi ne primi odgovarajuće razine majčinskih protutijela. Smrtnost tijekom neonatalnog razdoblja, posebice ona uzrokovana enteričnim i respiratornim bolestima, viša je nego u bilo kojem drugom razdoblju života, a usko je povezana s neuspješnim prijenosom protutijela. Biološki razlozi neuspješnog prijenosa su (1) prijevremeno rođenje slabih životinja, (2) odgađanje prvog podoja, (3) smrt ženke, (4) niska razina proizvodnje kolostruma, (5) niske razine protutijela u majčinskom serumu, a time i u kolostrumu, (6) loš majčinski instinkt, posebno u prvorotkinja, (7) preuranjena laktacija, (8) preveliki broj mladunčadi u leglu i (9) dominacija jačih jedinki nad slabijima. Među nabrojenim faktorima, najvažniji je količina dostupnog kolostruma i vrijeme između rođenja i prvog podoja. Važnu ulogu igra i nepravilna briga o životinjama koja se odnosi na nametanje neprirodnih uvjeta za porod i preuranjeno dojenje. Osigurati da svaka novorođena životinja dobije kolostrum veliki je izazov, posebice u velikim proizvodnim jedinicama. Imunizacija majke u svrhu zaštite

novorođenih životinja postala je važna strategija u veterinarskoj medicinskoj praksi (vidi Poglavlje 13).

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2.2. Analysis

The chosen chapter was extremely challenging to translate. The majority of the technical terms found in the text have their equivalents in the Croatian language. However some were either impossible or extremely hard to find. The reason is the lack of medical and veterinary texts written in the Croatian language. Veterinary science continues to develop and the number of texts in the English language continues to increase. On the other hand, there are still few Croatian textbooks and articles on this topic and thus, veterinarians continue to use the English terms.

During the translation process, it was important to convey the meaning in a clear, correct and comprehensible way while still keeping in mind the rules of the Croatian language. The translator needs to find a balance between conforming to the Croatian language and ensuring the comprehensibility of the translation. For example, the term *immunity* and *immune* are sometimes incorrectly translated as *imunitet* and *imunološki*. In the Croatian language, the correct translations would be *imunost* and *imunosni* because *imunološki* would refer to the field of immunology, which is *imunologija* in Croatian. Another example is the term *antibody* which has two possible translations in Croatian, *antitijelo* and *protutijelo.* In the veterinary texts, one can find both; however, it is important to consult either veterinarians or veterinary textbooks and texts in order to find out which one is more commonly used. Furthermore, it is important to stick to the chosen term and not use both interchangeably because it might confuse the reader and the translation might seem poorly done.

Another important aspect of translating these texts is the need to double-check each term and its correct translation. There are numerous terms which can be translated in more than one way. For example, in the case of the term *antigenic determinant,* the word *determinant* can be translated as *determinanta* as well as *odrednica.* This is why it was important to consult various literature on the topic of veterinary medicine and immunology.

All of the problems encountered during translation will be mentioned in the following analysis which is divided into four categories: style, syntax, grammar and vocabulary. It will also include the thought process and the methods of solving the problem.

2.2.1. Style

The style of this text is called expository and it is typical for scientific articles and books. It is concise, straightforward and clear. These types of texts must never be ambiguous because their aim is to convey knowledge and avoid confusion. The use of jargon is neither advisable nor acceptable.

Since it is a chapter from a textbook, it focuses on facts and it includes tables and figures, which describe and explain the topic even more thoroughly. Figurative language is not used and the chapter does not include the opinions of the authors. The only sentence in which one can notice an expression of opinion is the following one: "This phenomenon, irreverently called 'original antigenic sin,' is also seen in infections with enteroviruses, reoviruses, paramyxoviruses and togaviruses." The word *irreverently* means *without respect,* and was translated into Croatian as *pogrešno*. If it were translated literally *bez poštovanja,* it would sound clumsy and stylistically marked, thus not corresponding to the style of veterinary texts. Here, one could conclude that not only the authors of the book, but veterinarians as well, believe that such a name for a particular phenomenon is wrong and unacceptable.

The initial paragraphs and the one starting from the subtitle "Passive Immunity" are written more simply, while the rest are more complex and include detailed descriptions of the components of the immune response as well as the processes taking place. Neither figurative language nor decorative elements were used. The main goal of the chapter is to present facts and findings in a brief and clear way, without the use of vague adjectives and redundant phrases.

During the translation process, it was important to make the text as clear as possible while still keeping in mind that none of the important information should be left out. The translator should stick as closely to the original as possible, but from time to time, it is necessary to make some alterations such as sentence splitting. The emphasis was on the correct conveying of facts.

2.2.2. Syntax

The sentence structure in the chosen chapter is generally complex. Most of the sentences have at least one dependent clause, while some have even more. Additional information is provided by adding the brackets in order to indicate the name of a certain

process, complex or response. For example: “B lymphocytes respond (the humoral immune response) to an antigenic stimulus by producing and secreting *immunoglobulins* or *antibodies.* T lymphocytes respond (the cell-mediated immune response) by secreting cytokines […]”. Another example would be: “When T or B lymphocytes bind antigen they signal the cell to divide to form an expanded clone of cells (*clonal expansion*).” These sentences also show that the new, but important information, i.e., the names of components or processes, are always written in italics.

Additional information which the authors of the textbook found important, but did not want to write in the form of dependent clauses, in order not to confuse the reader and to keep the sentences as concise as possible, is written in brackets as well. For example: “In those species in which the maternal and fetal circulations are separated by relatively few (one to three) placental layers, antibody of the IgG (but not IgM) class […]”.

The sentences are generally long and contain numerous terms and compound words. For example, in the sentence: “When the particular clones of B cells bearing receptors complementary to any one of the several epitopes on an antigen bind that antigen, they respond after receiving the appropriate signals from helper T cells, by division and differentiation into antibody-secreting plasma cells.”, it is important to read carefully in order to understand which parts of the sentence refer to which term. The word *they* refers to *clones of B cells* and not *epitopes* or *antigen*. Another problem in this sentence are constructions such as *B cells bearing receptors* because in Croatian they cannot be written as concisely as in the English language. One of the first solutions that might come to translator’s mind is to use the word *koji,* i.e., *B stanice koje nose receptore koji su komplementarni.* However, it would not be a proper solution because the abundance of such constructions might sound clumsy and repetitive. Another construction which requires the use of the word *koji* is *antibody-secreting plasma cells.* It can be translated descriptively as *plazma stanice koje izlučuju protutijela.* The resulting translation is: “Kada specifični klonovi B-stanica, koji su nositelji receptora komplementarnih bilo kojem od nekoliko epitopa na antigenu, vežu taj antigen, oni, nakon primanja odgovarajućih signala od pomagačkih T-stanica, reagiraju dijeljenjem i diferencijacijom u plazma stanice koje izlučuju protutijela.“ The sentence consists of numerous dependent clauses. However, it was the only acceptable solution since it is important for the medical text to be clear and comprehensible.

A similar construction can be found in the sentence describing the role of Th2 cells which are typically: "(3) promoting the switch by B cells from IgG2 to IgG1 production in some species." Once again, it is important to do research in order to understand that B cells are the ones producing IgG1 and IgG2. Upon the first reading of the sentence, the translator could think that the emphasis is on the B cells promoting the switch from IgG2 to IgG1, when in fact Th2 cells are the ones promoting the switch of the production which is done by the B cells. Thus the translation is as follows: "(3) kod nekih vrsta životinja potiču prijelaz iz proizvodnje IgG2, koju vrše B-stanice, u proizvodnju IgG1."

Furthermore, there are sentences which are divided by semicolon. Such sentences are perfectly acceptable in the English language, while in Croatian it is important to replace a semicolon with a full stop or to connect the sentences with an independent clause. The example is the following: "The T cell antigen-specific receptor (TCR) is quite distinct; it is a two polypeptide heterodimer and although immunoglobulin like, it is encoded by an entirely different set of genes." In this case, it might be best to divide the sentence: "Antigen-specifični receptor na T-limfocitu (TCR) poprilično je jedinstven. Sačinjen je od dva polipeptidna heterodimera, a iako je nalik imunoglobulinu, kodiran je potpuno drugačijim skupom gena." The English construction *it is* is frequently used, but the literal translation sounds clumsy in the Croatian language. Thus, it is important to understand the sentence and then, according to its meaning, replace the construction with the one more common in Croatian. In this case, the construction was replaced by the word *sačinjen* because the sentence refers to the structure of the T cell antigen-specific receptor.

One of the main challenges was finding the proper translation of the two following subtitles: "Antigen Presentation by Cells Expressing MHC Class II: The Exogenous Pathway" and "Antigen Presentation by Cells Expressing MHC Class I: The Endogenous Pathway". These two subtitles are packed with important terms and information none of which should be omitted. It was important to do research and understand that MHC refers to *major histocompatibility complex* which is translated into Croatian as *glavni sustav tkivne podudarnosti;* however, its English acronym *MHC* is used in the Croatian language as well. Furthermore, class I and II can be abbreviated into MHC-I and MHC-II. It was also important to find Croatian texts on the topic in order to find out how the words *presentation* and *expressing* are translated into Croatian. Another problem was the preposition *by* since one of the first solutions was to translate it as *od strane.* However, this construction needs to be avoided, except in case of legal texts. The final solution is as follows: "Predočavanje antigena

putem stanica koje izražavaju MHC-II: egzogeni put“ and ”Predočavanje antigena putem stanica koje izražavaju MHC-I: endogeni put”. The resulting translation is short, it conveys the same meaning and none of the important terms and information was omitted.

In order to ensure clarity and correctness of the following sentence, the translator should, once again, have insight into all of the processes taking place during an immune response: “The cells may be restimulated periodically by the original antigenic peptide retained for long periods as peptide-MHC complexes on follicular dendritic cells in lymphoid follicles or by surrogate antigen in the form of either fortuitously cross-reactive antigens or anti-idiotypic antibodies.” This is a perfect example of complex syntactic structures which comprise a lot of important information. Finding the perfect translation for such sentences is often challenging because it is crucial to keep the translation clear and comprehensible, while still conveying the correct information. The translator needs to understand the process as well as find the correct translations for the terms *peptide-MHC complexes, surrogate antigen, cross-reactive antigens* etc. Although the sentence is long, it could not be divided. Thus, the translation is the following: “S vremena na vrijeme stanice mogu restimulirati prvobitni peptidni antigeni koji se na duže vrijeme zadržavaju u obliku kompleksa MHC-peptid na folikularnim dendritičnim stanicama u limfoidnim folikulama ili zamjenskim antigenima u obliku slučajnih križno-reaktivnih antigena ili antiidiotipskih protutijela.“

Sometimes translators need to opt for sentence splitting in order to ensure the clarity of the text. Such example can be found in the following sentence: „Immunoglobulin M (IgM) is a particularly avid class of antibody, being a pentameter of five IgG equivalents, with 10 Fab fragments and therefore 10 antigen-binding sites.“ In this case the translator can opt for splitting the sentence beacuse it is easier to read and comprehend two shorter sentences than one longer sentence. In case of splitting, it is always important to make sure that none of the crucial information is left out. Thus the translation of the sentence is the following: „Imunoglobulin M (IgM) je razred protutijela s visokim afinitetom. Radi se o pentameru koji se sastoji od pet IgG ekvivalenata, s 10 Fab fragmenata, a time i 10 mjesta za vezivanje antigena.“

2.2.3. Grammar

When it comes to grammar, the authors used mostly present simple and present perfect. Present simple was used to explain the already known or atemporal facts. For example: “Lymphocytes have antigen-specific receptors on their surfaces, which are the basis for immunologic specificity.” and “This chapter deals with the role of the immune response in recovery from viral infection and resistance to reinfection.” Present perfect was used to express that something that happened in the past, still influences the present. For example: “In response to the constant invasion by infectious agents, including viruses, vertebrates have evolved an elaborate set of defensive measures, called, collectively, the immune system.” or “Maternal immunization to protect newborn animals has become an important strategy in veterinary medical practice.” In this chapter, and in medical texts in general, the future tense is rarely used. One of the rare examples in this text is: “Of course, the newborn animal will be protected against infection with any particular virus only if […]”.

On the sentence level, the subject is mostly found at the beginning of the sentence, probably to give emphasis to that term and to simplify the text comprehension. This way the text is easier to follow and it is easier for the reader to recognize the important information in the text. For example: “Papain cleavage separates the molecules into two identical *Fab fragments* […]”. This sentence could have been written as: “The molecules are separated by papain cleavage into two identical *Fab fragments* […]”, but it would make the sentence confusing and harder to comprehend. This only shows how important it is for medical, or scientific texts in general, to be clear and precise. That is how the authors avoid ambiguity as well as mistakes.

Although the English language is famous for the use of passive voice, in this text, both the passive and active voice were used interchangeably: “Cytokines are low molecular weight hormone-like proteins […]. Many are produced by T lymphocytes (lymphokines) or monocytes/macrophages (monokines) […]”. Nowadays in the scientific texts active voice is more common than in the past. Active voice is normally used when emphasizing researchers and their contribution, while passive voice is predominantly used in the “Methods” part of scientific texts and it emphasizes the materials and equipment.

Another way of making the text as concise as possible is to use abbreviations. In this chapter the abbreviations are introduced systematically, i.e., the first time a certain term is introduced. After that, the authors use only the abbreviation and not the entire name of the cell

or complex. For example, the abbreviation for the *major histocompatibility complex (MHC)* was introduced on the page 129, and after that every time this complex was mentioned again, only its abbreviation was given. The same goes for *natural killer (NK) cells*, *T cell antigen-specific receptor (TCR), T helper lymphocytes (Th)* etc. In the Croatian language, these abbreviations remain the same although the full name of the cells and complexes is translated, which makes it easier for the translator to find the appropriate translation.

Another characteristic of the English texts is the use of capital letters in titles and subtitles. This chapter is no different and every noun, verb and adjective are capitalized. However, the capitalization is not really used in the Croatian language and thus only the first word in the title or subtitle can be capitalized.

The challenging part was the translation of the preposition *by* which in passive sentences indicates the main actor. These types of sentences can be translated using the words *putem, pomoću* or *posredstvom*. For example the preposition *by* in the sentence "[…] the positive selection of developing T cells in the thymus by "self" MHC molecules […]" was translated as "pozitivna selekcija T-stanica koje sazrijevanju u timusu posredstvom „vlastitih" MHC molekula", while the subtitle "Antigen Presentation by Cells Expressing MHC Class II: The Exogenous Pathway" was translated as "Predočavanje antigena putem stanica koje izražavaju MHC-II: egzogeni put".

2.2.4. Vocabulary

The entire chapter is abundant with terms which are mostly literary translated into Croatian. However, there are a few of them which are used in their English form. The majority of the terms were not hard to find because the immunologic processes of humans and animals are very similar or the same. Thus, the translator can use scientific articles, books, textbooks, vocabularies, and even notes and presentations from the field of human medicine. Most of the Croatian texts even have the English term written in the brackets. The only problem was the fact that one English term can have two to three slightly different translations, thus the translator needs to opt for one of them and use it thorought the text. In this case, it is advisable to do research in order to see which term is more frequently used in the veterinary texts.

2.2.4.1. Tricky translations

Alongside with the terms *immune* and *immunologic*, there was a number of others which had to be conformed to the Croatian language. Another similar example is the difference between *genetski* and *genski* in the Croatian language. While, *genski* refers to genes, i.e., "the basic physical and functional unit of heredity"[25], *genetski* refers to genetics, i.e., "study of heredity in general and of genes in particular."[26] These terms sound very similar and the translator can easily make a mistake and translate them incorrectly. The difference is visible in the following example: "[…] and the gradual emergence of mutations in a majority of these epitopes leads to the emergence of a novel strain (genetic/antigenic drift; see Chapter 4)", which was translated as: "[…] a postepena pojava mutacija kod većine navedenih epitopa dovodi do pojave novog soja (genetski/antigenski otklon; vidi Poglavlje 4)".

Another one was the term *antibody* which has two possible translations, that is, *antitijelo* and *protutijelo.* Both of them are correct and acceptable, however, *antitijelo* is deemed to be a loanword, while *protutijelo* is a term which conforms to the Croatian grammar. In the end, the term was translated as *protutijelo* because it is predominantly used in the veterinary medicine and it can be found in the *Veterinarski priručnik*.

2.2.4.2. Acronyms

Some of the easiest terms to translate were the ones which have acronyms because, even though each term has its own translation into English, the acronyms remain the same. This made searching for translations easier. For example, the term *natural killer cells* is translated as *prirodnoubilački limfocit, prirodnoubilačka stanica, prirođene stanice ubojice* or simply *stanice ubojice*, while its shortened term, *NK cell*, is translated as *NK stanica*. Another example is *major histocompatibility complex* and its acronym *MHC.* The full name of the term is translated as *glavni sustav tkivne podudarnosti*, while the acronym remains the same in the Croatian language. Some other examples are *H (heavy) chain* or *H (teški) lanac*, *Th (helper) lymphocytes* or *Th (pomagački) limfociti*, *TAP (transporter molecule)* or *TAP (prijenosne molekule)*, *TNF (čimbenik tumorske nekroze)*, *TGF (transformirajući čimbenik rasta)*, *CSF (faktor stimulacije kolonija)* etc.

[25] Retrieved from https://medlineplus.gov/genetics/understanding/basics/gene/ Accessed July 2021
[26] Retrieved from https://www.britannica.com/science/genetics Accessed July 2021

2.2.4.3. Synonymy

This part of analysis deals with numerous different ways of translating and writing a single term. This includes terms such as *natural killer cells*, whose possible translations were mentioned in the previous paragraphs. Another such term is *antigen-specific receptor* which in various literature is translated as *antigen-specifični receptori, receptori za antigen* or *receptori specifični za antigen*. Some of the other examples include *antigenic determinants*, which can be translated as *antigenske determinante* or *antigenske odrednice, immunologic specificity*, which can be translated as *imunološka posebnost* or *imunološka specifičnost, C terminus*, which can be translated as *C terminus* or *C-terminalni kraj*. In case of synonymy, the translator needs to do research in order to see which of these terms are predominantly used in veterinary medicine. In this text the priority was given to Croatian versions of these terms, *antigenske odrednice, imunološka posebnost* and *C-terminalni kraj* because they are accepted as official translations.

Another challenging term was *bursa of Fabricius* which refers to "a central lymphoid organ, required for development of the antigen-specific B cell repertoire."[27] In the Croatian language, there are three possible translations: *Fabricijeva bursa, Fabricijeva burza* and *Fabriciusova bursa.* The chosen one was *Fabriciusova bursa* because it is mentioned in the *Medicinski leksikon*. In cases of such terms, it is important for the translator to do research and find out which one of these is used more frequently and then stick to it.

When it comes to different ways of writing a single term, some of the best examples are the names of the cells, i.e., *T lymphocytes* and *NK cells* etc. These terms have three different ways of writing them, i.e., *T-limfocit, T limfocit* or *limfocit T* and *NK-stanice, NK stanice* or *stanice NK*. The correct way of writing these terms, according to the Croatian grammar rules, would be *limfocit T* and *stanica NK*. However, in this case they were translated as *T-limfocit* and *NK-stanica* because this form is more commonly used in veterinary medicine and this is how the terms are written in the *Veterinarski priručnik.*

[27] Retrieved from https://www.sciencedirect.com/topics/immunology-and-microbiology/bursa-of-fabricius Accessed July 2021

2.2.4.4. Terms without their equivalents in Croatian

One of the trickiest terms to translate were *"missing self-hypothesis", neutralization-escape mutants* and *knockout* mice. The only mention of the first term in the Croatian language is in the summary of a dissertation titled "Virusna regulacija aktivnosti NK-limfocita: uloga inhibicijskih LY49 limfocita" in which the term was left in its English form. Therefore, the sentence containing that term was translated as follows: "Temelj za njihovu selektivnost u odabiru virusom zaraženih stanica povezan je s podregulacijom sinteze i izražavanja MHC proteina razreda I („missing self" hipoteza), a to je rano obilježje mnogih virusom zaraženih stanica."

When it comes to the second term, *neutralization-escape mutants*, there were no mentions of it in the Croatian texts. However, in the veterinary medicine there is also a term *vaccine-escape mutants* and the Croatian equivalent is *vaccine escape mutanti*. Therefore, the term remained in its English form („Štoviše, reinfekcija u periodu slabljenja imuniteta pogoduje odabiru "neutralization-escape" mutanata, što rezultira pojavom novih sojeva virusa poput virusa gripe nastalih kao rezultat antigenskog otklona.")

The last term was *knockout mice* which in the Croatian research articles and various other medical webpages is used in its English form, i.e., *knockout* miš. The English equivalent is an internationally accepted term because it is used not only in Croatian, but also in Italian, French, Spanish and German veterinary texts as well. The exception is the Serbian language which uses the term *nokaut miš.* Leaving the term in its original English form until the field accepts an official translation is actually common practice. It would be unwise for any translator to make up his own translation without explaining what it refers to because it would lead to experts not knowing what it means.

2.2.4.5. Uncommon terms

There were a couple of terms which were difficult to came by in the English texts and extremely difficult to find in the Croatian ones. The first one is *translocation cut-off time* which refers to "the ability of the neonates to absorb Igs"[28]. This period usually lasts 48 hours, but in mice it can last up to 20 days. Since the majority of the Croatian terms in veterinary medicine ended up being literal translations, the first option included searching for *period*

[28] Retrieved from https://www.scribd.com/document/235582752/Veterinary-Immunology Accessed July 2021

prekida translokacije, vrijeme prestanka translokacije or simply *translokacija* in order to see what context could be found. Unfortunately, the term *translocation* has multiple usages and is used not only in immunology, but in genetics as well. However, another name for *translocation cut-off time* is *gut closure* and after searching for its literal meaning, *zatvaranje crijeva*, a scientific article including this term was found. Thus, the translator can opt for that term and put it in quotation marks since that it how it was indicated in the article as well.

The following term was *anchor residues* which "bind to specific pockets on the MHC I, resulting in some specificity of interactions with MHC"[29]. In other words, these residues "anchor" themselves on the class I molecules of the major histocompatibility complex (*glavni sustav tkivne podudarnosti* in Croatian). In the Croatian language, the term *anchoring* is literally translated as *sidrenje* or *usidrenje* while *residues* are translated as *ostatci.* This is why the best solution for translating the term was *usidreni ostatci* which again falls under the category of literal translations.

The term *LMP-containing proteasome complex* plays an important role in the viral protein degradation which afterwards bind to the cleft of the class I or II MHC molecules.[30] As such, there were no equivalents of this term in the Croatian language and the best option was to translate it literally as *proteosomski kompleks koji sadrži LMP.*

The last term is *antibody complement-mediated lysis* which refers to the cell degradation (for example, viral, bacterial or parasitic) through the complement system activated by antibodies (mostly IgM and certain subclasses of IgG). These antibodies trigger the complement activation which activates macrophages that destroy the foreign cells present in the body.[31] Another name for this lysis is antibody-dependent complement-mediated lysis or ADCML. Since the term *complement-mediated lysis* can be translated as *liza posredovana komplementom* or *liza pomoću komplementa,* the best option was to translate the term *antibody complement-mediated lysis* as *liza pomoću komplementa ovisnih o protutijelu.*

In case of these terms, it was important to add their English equivalents in the brackets. Since they are extremely difficult to find in their Croatian form, adding their name in English, makes it easier for veterinarians to understand the text and instantly know what the term refers to. One of the problems in the veterinary medicine in Croatia is that the majority

[29] Retrieved from https://www.andrew.cmu.edu/course/03-410/Lec04/lec04.html July 2021
[30] dr. sc. Tibor Andreanszky, dr. med. vet., private communication
[31] dr. sc. Tibor Andreanszky, dr. med. vet., private communication

of the literature they use during their education is in English. Thus, without the addition of the English equivalents, they might find the text incomprehensible because they have never heard of these terms in Croatian.

2.2.4.6. Everyday terms used in veterinary medicine

There are numerous terms used in everyday communication which in the medical vocabulary are specifically used to describe a certain part of the cell or a certain process.

The first term is *cascade* in the sentence "The resulting cascade of cell-cell interactions and cytokine secretion amplifies the immune response to match the scale of the virus infection […]". The word *cascade* is often associated with waterfalls. However, it can also mean "something arranged or occurring in a series or in a succession of stages so that each stage derives from or acts upon the product of the preceding".[32] This word can be a metaphor for a sequence and thus be translated as *niz* ("Rezultirajući niz međustaničnih reakcija i izlučivanje citokina pojačava imunosni odgovor s ciljem prilagodbe jačini virusne infekcije"). However, in the *Veterinarski priručnik* these series of events are actually literally translated as *kaskade.* Thus, the sentence "Because of the intricacy of the cytokine cascade, it is rarely possible to attribute a given biological event *in vivo* to a single cytokine" was translated as follows: "Zbog zamršenosti kaskade citokina, rijetko je moguće pripisati taj biološki proces *in vivo* jednom citokinu."

Another such term is *progeny* in the sentence "Each individual B lymphocyte and its progeny express a set of immunoglobulin genes that are specific for a single epitope." It is unusual for the offspring of lymphocytes to be called progeny. However, the term is common and it is literally translated in the Croatian language as *potomci*.

The next term is *marker* in the sentence "T helper cells carry a surface marker known as CD4." In medical vocabulary, the term is used with the meaning of "something that serves to identify, predict, or characterize".[33] The Croatian equivalent is either *marker* or *biljeg.* I opted for *biljeg* because it is more adapted to the Croatian language.

Limb in the sentence "Macrophages then also give expression to the efferent limb of the immune response […]" is yet another example of such a term. In this case the term refers

[32] Retrieved from https://www.merriam-webster.com/dictionary/cascade Accessed July 2021
[33] Retrieved from https://www.merriam-webster.com/dictionary/marker Accessed July 2021

to a certain part or element of the immune system. However, by using the word *limb* the authors emphasized its importance since without limbs, humans cannot function properly. When it comes to its translation, it is best to remain neutral and translate it as *element*.

The next term is *cleft* in the sentence "[…] but only if they are located in the peptide-binding cleft […]". This term is used in medicine as "a usually V-shaped indented formation: a hollow between ridges or protuberances"[34] or "a space or opening made by or as if by splitting"[35]. This term is used in medicine and it refers to various parts of the human body and can be translated as *pukotina* or *žlijeb*. The best option was *žlijeb* because *pukotina* is specifically used in neuroscience, that is, for the term *synaptic cleft* which is also called *synaptic gap*. In the case of *peptide-binding cleft*, there is no *gap*, which explains why *žlijeb* was a more appropriate option, and not *pukotina*.

Another term is *anchor* in the sentence "Peptide binding is determined by only two or three hydrophobic amino acids, called anchor residues […]". The terms *anchor* and *anchoring* refer to "a scaffold within the cell or its membranes, on which enzymes or other important molecules are suspended"[36] and are literally translated into Croatian as *sidrenje* and *usidreni*.

In the sentence "Specific amino acids that form pockets on the floor of the cleft of any particular MHC protein determine […]" there are two terms, *pocket* and *floor*. When it comes to the word *pocket*, in medical dictionary it generally refers to a cavity[37] and it can be literally translated as *džep* and it is the term which is mostly used in dentistry. However, the word *floor* cannot be literally translated as *pod* and the translator needs to understand that in this case, the term refers to the lowest part of the cleft, i.e., its bottom. Thus, the proper translation is *dno*.

The next term is *groove* in the sentence "The binding site, i.e., the *antibody-binding groove*, is located at the amino-terminal end of the molecule." The word groove is generally "a long narrow channel or depression"[38], while in the medical dictionary it is explained as "a narrow, elongated depression or furrow on any surface"[39]. It is a commonly used word in medicine and there are numerous terms featuring it such as pharyngeal groove, branchial

[34] Retrieved from https://www.merriam-webster.com/dictionary/cleft Accessed July 2021
[35] Ibid.
[36] Retrieved from https://medical-dictionary.thefreedictionary.com/anchoring Accessed July 2021
[37] Retrieved from https://medical-dictionary.thefreedictionary.com/pocket Accessed July 2021
[38] Retrieved from https://www.merriam-webster.com/dictionary/groove Accessed July 2021
[39] Retrieved from https://medical-dictionary.thefreedictionary.com/groove Accessed July 2021

groove or Harrison's groove.[40] The Croatian equivalent of this term is *žlijeb* and the translation is as follows: "Mjesto vezivanja, tj. *žlijeb za vezanje protutijela* nalazi se na amino-terminalnom kraju molekule."

Yet another such term is *naive* in the sentence "[…] infection with this construct can adoptively transfer complete protection to naive mice […]". While in everyday communication, someone who is naive is gullible, in the medical vocabulary, this term refers to "not previously subjected to experiments"[41] or "not having previously taken or received a particular drug"[42]. Thus, the proper translation is *netestirani miševi*.

The last such term is *laboratory artifact* in the sentence "One approach to understanding the mechanisms involved in recovery from viral infection that is not subject to laboratory artifact is simple clinical observation […]". *Artifact* is a term with various meanings in medicine such as "Anything, especially in a histologic specimen or a graphic record, which is caused by the technique used and does not reflect the original specimen or experiment"[43] or "A skin lesion produced or perpetuated by self-inflicted action, as in dermatitis artefacta"[44]. This term even has its separate meanings in cardiology, imaging and histology. That is why it was important to thoroughly read the text and understand from the context what the term refers to. In this case it refers to research since the paragraph explains certain clinical observations regarding congenital deficiency in T lymphocytes. Thus, the translation is "Jedan od pristupa razumijevanju mehanizama koji su uključeni u oporavak od virusne infekcije, a koji nije podložan laboratorijskom ispitivanju, jest jednostavno kliničko promatranje […]".

2.2.4.7. Verbs

The translation of verbs posed a problem and it was important to read numerous texts on the topic in order to find the appropriate translations.

Some of the most problematic verbs were *up-regulate* and *down-regulate*. According to the Merriam Webster dictionary, *upregulation* is "increase in a cellular response to a

[40] Retrieved from https://medical-dictionary.thefreedictionary.com/groove Accessed July 2021
[41] Retrieved from https://medical-dictionary.thefreedictionary.com/naive Accessed July 2021
[42] Ibid.
[43] Retrieved from https://medical-dictionary.thefreedictionary.com/artifact Accessed July 2021
[44] Ibid.

molecular stimulus due to increase in the number of receptors on the cell surface"[45], while *downregulation* refers to "reduction in a cellular response to a molecule (as insulin) due to a decrease in the number of receptors on the cell surface"[46]. In some notes on the human medicine which are available online, these verbs were translated literally as *nadregulirati* and *podregulirati*. However, in the end the chosen translation was *pozitivna* and *negativna regulacija* because it seemed as the more common option found in texts.

Another problematic verb was *revert* which normally means "to come or go back (as to a former condition, period, or subject)"[47], while in the medical field it is "to undergo reversion"[48], i.e., "an act or the process of returning (as to a former condition)"[49]. The first option was the verb *vraćati,* but my mentor suggested the phrase *regresiraju u stanje*. Thus, the translated sentence is the following: "Neke T i B-stanice regresiraju u stanje malenih dugovječnih limfocita odgovornih za *imunološku memoriju*."

One of the most common verbs found in this text was *present* which in medical vocabulary is usually found in the context of illnesses and with the meaning of „to manifest".[50] However, in this context it refers to certain peptides or cells being presented to lymphocytes. For example, „[…] they do this only when the foreign peptides are presented to them in association with membrane glycoproteins […]" or „The pathways used by cells to process and present antigenic peptides to Th and Tc cells are […]". After reading certain texts on immunology, the translator can conclude that this verb can be translated as *predstavljati, predočavati* or even *izražavati*, depending on the author and the text. In this chapter, *present* was mostly translated as *predočavati*, even though in the sentence „By serving as 'professional' antigen-presenting cells, these cells exercise […]", the term *presenting* was translated as *izražavanje* („Služeći kao „profesionalne" stanice za izražavanje antigena […]").

The next verb is *discharge*, found in the sentence „Close examination of T cell clones indicates that a single cell type can discharge both regulatory and effector functions and secrete a range of different lymphokines." This verb is generally used in the contexts of „to

[45] Retrieved from https://www.merriam-webster.com/medical/upregulation Accessed July 2021
[46] Retrieved from https://www.merriam-webster.com/medical/downregulation Accessed July 2021
[47] Retrieved from https://www.merriam-webster.com/dictionary/revert Accessed July 2021
[48] Ibid.
[49] Retrieved from https://www.merriam-webster.com/dictionary/reversion Accessed July 2021
[50] Retrieved from https://www.merriam-webster.com/dictionary/present Accessed July 2021

give outlet to or emit“[51] However, in this context it is not the literal translation *otpuštati*, but *vršiti* because it refers to the different functions these cells perform.

Subsume, found in the sentence „[…] the view now is that suppressor functions are subsumed by Th and Tc cells“ was also challenging. The term *subsume* means „to include or place within something larger or more comprehensive: encompass as a subordinate or component element”[52]. The proper translation would be *uključiti* or *obuhvaćati*, but in this case the best option seemed to be the noun *karakteristika*. Thus, instead of translating it along the lines of “[…] danas se smatra da Th i Tc stanice uključuju supresorske funkcije“, the final translation was „[…] te se danas smatra da su supresorske funkcije karakteristika Th i Tc stanica“ because it seemed as a more comprehensible option.

The next verb is *have* in the sentence „There is also evidence that both Tc and NK cells release lymphocyte-specific granules that have serine esterase activity (granzymes) […]“ In this case it was important to do proper research into Tc and NK cells in order to understand that the verb cannot be translated as *imati*, but as *biti odgovoran za* because granzymes are released by Tc cells and NK cells. Thus the proper translation is „Postoje i dokazi da i Tc i NK-stanice otpuštaju granule specifične za pojedine limfocite koje su odgovorne za serinsku esterazu (granzimi).“

Another interesting verb is *budding* in the sentence „Activation of complement via the alternative pathway appears to occur mainly after infections with enveloped viruses that mature by budding through the plasma membrane […]“ In this case, the second text chosen for the thesis included this verb and its translation was literal, i.e., *pupanje*. Furthermore, it was written in quotation marks which means that the verb is used in a figurative sense. The translation is the following: „Čini se da se aktivacija komplementa putem alternativnih puteva događa uglavnom nakon infekcija virusima u ovojnici koji sazrijevaju „pupanjem“ kroz staničnu membranu.“

The last verb is *prime* in the sentence „Following priming by antigen and clonal expansion of lymphocytes […]“. In medical vocabulary, *prime* generally means „to supply with an essential prerequisite (such as a hormone, nucleic acid, or antigen) for chemical or

[51] Retrieved from https://www.merriam-webster.com/dictionary/discharge Accessed July 2021
[52] Retrieved from https://www.merriam-webster.com/dictionary/subsume Accessed July 2021

biological activity."[53] However, the chosen translation was *prvi kontakt* because in immunology, priming refers to the initial encounter with an antigen.

2.2.4.8. Other problems

One of the first vocabulary challenges was the translation of the terms T and B cells and T and B lymphocytes. In human and veterinary medicine, both terms are used interchangeably. When it comes to the translated chapter, the more frequently used term is T or B cells, however T and B lymphocytes were used in the subtitle of the paragraph in which they were introduced. When it comes to translation, the translator can decide to follow the original text, meaning that in the parts of the text were the author opted for *T* or *B lymphocyte*, the translator can translate them as *T* or *B limfociti*, while in the parts where it is written *T* or *B cells* he can translate them as *T* or *B stanice.*

In the sentence "Immunoglobulin M (IgM) is a particulary avid class of antibody, being a pentameter of five IgG equivalents, with 10 Fab fragments and therefore 10 antigen-binding sites", a problematic term was the word *avid.* The translator's first thought might be that this word can be translated as *pohlepan*, even though it would be unusual for a medical text to describe immunoglobulins in such way. However, the proper translation is *visoki afinitet* because the term refers to avidity, i.e., "a characteristic of antibodies (such as antitoxins) that tends to enhance their rate or stability in binding with an antigen."[54] Thus the proper translation of the sentence is "Imunoglobulin M (IgM) je razred protutijela s visokim afinitetom. Radi se o pentameru koji se sastoji od pet IgG ekvivalenata, s 10 Fab fragmenata, a time i 10 mjesta za vezivanje antigena."

The term *management* in the sentence "Poor management also plays a major role by the imposition of unnatural conditions on parturition and early suckling." was also a problem because if the term were to be translated literally as *upravljanje*, the sentence would be unclear. Since this term actually refers to the care for animals, the best solution was translating it as *briga o životinjama* and thus the translation is as follows: "Važnu ulogu igra i nepravilna briga o životinjama koja se odnosi na nametanje neprirodnih uvjeta za porod i preuranjeno dojenje."

The last encountered issue was the word *undergraded* in the sentence "The very large amounts of IgG present in colostrum are ingested and *translocated* in large intracytoplasmic

[53] Retrieved from https://www.merriam-webster.com/dictionary/prime Accessed July 2021
[54] Retrieved from https://www.merriam-webster.com/dictionary/avidity Accessed July 2021

vesicles by specialized cells present in the upper part of small intestine to reach the circulation of the newborn in an undergraded form.” There was no mention of this term in dictionaries; however, it did appear in some contexts. It ended up being a typographical error. The correct term, *undegraded*, was found in the newer version of the book. Thus, it was translated as *nerazgrađen.*

To conclude, the chosen text on the immune response to viral inections was challenging due to a number of terms that do not have an established and accepted translation in the Croatian language. Another problem was also the lack of literature on the veterinary medicine. However, since the chosen text deals with immunology, which is very similar in humans and animals, the literature from the field of human medicine was of great help. Of great help were also the veterinarians from the Veterinary institute in Rijeka who explained the problematic terms and thus helped in understanding them and finding their appropriate translations. These terms were translated literally and their equivalents in the English language were written in brackets.

3. Second text: “Autoimunosne bolesti”

The chapter titled “Autoimunosne bolesti” is a part of the *Veterinarski priručnik*, written by more than a hundred authors from the Faculty of the Veterinary Medicine, the Croatian Veterinary Institute and the Ministry of Agriculture, and it consists of the general and clinical part. The general part of the book includes the production of animal products and biotechnology, ethology and the new philosophy of the veterinary public health. The clinical part of the book includes clinical toxicology, surgery, parasitic and infectious diseases, clinical immunology and pathology etc.[55]

The translated chapter is a part of Clinical immunology and it describes the most common autoimmune diseases. It is divided into three parts, immune mechanisms of autoimmunity, autoimmune diseases occurring after vaccination and organ-specific autoimmune diseases which is further divided into autoimmune skin diseases, autoimmune diseases of the locomotor system, autoimmune blood and hematopoietic tissue diseases, autoimmune diseases of the nervous system etc.

The first twenty pages of this chapter were translated and the analysis will be divided into style, syntax, grammar and vocabulary.

[55] Retrieved from https://www.medicinskanaklada.hr/veterinarski-priru%C4%8Dnik-2, trans. L. Štebih, Accessed July 2021

3.1. Translation

AUTOIMMUNE DISEASES

It is well known that the basic characteristics of immunity include a phenomenon called natural immune tolerance. It is a feature of the immune system of humans and animals which enables them to distinguish their antigens from other antigens that enter the body from the environment and not to react to them with an immune response. Such immune recognition of self-antigens and the ability of distinguishing them from the foreign ones is undoubtedly one of the key principles on which the preservation of the structure of each organism is based. However, this important feature of immune mechanisms can sometimes fail, thus triggering different degrees of immune responses against the chemical markers of cellular self-antigens. This phenomenon is called autoimmunity and the term refers to an immune reaction directed against the cells of one's tissue. Theoretically, a normal immune response with autoimmune characteristics can be triggered by and involve altered or latent autoantigens, or it can refer to an abnormal immune response to unaltered (normal) cellular antigens. Of the two aforementioned basic immunopathogenic mechanisms, the immune response to unchanged antigens present in the body is the more significant in practical terms and more frequent one. Sometimes autoimmunity is equated with a disease, however only the clinical manifestation of an immune response to one's cells should be called an autoimmune disease. The view that autoimmunity is an undesirable and harmful immune reaction for the body should be partially changed. There is growing irrefutable evidence that certain autoimmune reactions are indispensable for the normal maintenance of some of the physiological functions. Classic examples include immune recognition of histocompatibility self-antigens on the cell surface or recognition of self-immunoglobulins through anti-idiotypic reactions. However this chapter will focus primarily on pathological conditions caused by autoimmune processes, i.e., we will describe the most important autoimmune diseases found in animals.

When talking about the causes (triggers) of autoimmune reactions, it is generally agreed that they can vary and that they are often unknown. There is also an agreement that for certain autoimmune animal diseases predisposing factors, that may be related to sex, age, breed, genetic predisposition, certain infectious diseases or nutrition, exist.

The most important genes associated with susceptibility to autoimmune diseases in humans and animals are those involved in the major histocompatibility complex genes (MHC genes). Certain autoimmune diseases are associated with specific genes, while others are associated

with certain combinations of MHC molecules. In humans, certain combinations of MHC class II are strongly associated with some autoimmune diseases. Thus, for example, HLA-DR2 is associated with a predisposition for systemic lupus erythematosus and multiple sclerosis, while the combination of HLA-DR4 is associated with rheumatoid arthritis, pemphigus vulgaris, and type 1 diabetes.

A predisposition for autoimmune diseases exists among animals as well. It has been best researched in dogs and is related to animals that belong to certain breeds. It usually includes a smaller number of breeds within which dogs are inbred to a high degree, so there is minor polymorphism in the major histocompatibility complex genes. Predisposition for systemic lupus erythematosus has been found in dogs with DLA-12, while that for diabetes mellitus has been found in those with DLA-A3, A7, and A10.

As stated in the introductory part of this chapter, autoimmune diseases are clinical manifestations of conditions based on autoimmune processes. There is a vast number of such diseases and, from the clinical point of view, it is common to classify them according to the characteristics of immune mechanisms and the tissues and organs affected by them. Based on such an approach, autoimmune diseases are divided into organ-specific and systemic (or non-organ-specific), although such a division has certain shortcomings and is open to criticism. The fundamental objection stems from the fact that specific mechanisms of autoimmunity sometimes overlap and complement each other; thus, some patients may develop several autoimmune diseases affecting different organs or organ systems at once. However, regardless of this statement, the division of autoimmune diseases into organ-specific and systemic diseases is generally accepted, and in accordance with it, after presenting the basic immune mechanisms, we will present the clinically most important autoimmune diseases present in animals.

Generally, regardless of the characteristics of individual diseases in animals and their classification, it is certain that autoimmune diseases are best researched in dogs, other pets, and experimental animals that often serve as models for research of such diseases. Understandably, other animals fall ill as well, but for practical reasons, they have been well researched in these animals in particular. Due to frequent etiopathogenetic matches of such conditions in animals and humans, systematic research seeks to contribute to a better understanding of autoimmune diseases in humans.

Immune mechanisms of autoimmunity

Although autoimmune diseases in animals may be associated with a variety of effects and causes which favor their onset, those of immune nature are undoubtedly the most important ones. As with other immune responses, humoral or cellular mechanisms may be involved in autoimmune reactions. In some autoimmune diseases, only autoantibodies or sensitized T lymphocytes are involved. However, there are some autoimmune conditions in which both types of autoimmune reactions complement each other. Without elaborating on the theoretical knowledge about well-known immune mechanisms of autoimmune diseases, i.e., the loss of immune tolerance, we will briefly describe their basic mechanisms, i.e., the pathogenesis of autoimmunity.

Response to latent self-antigens

Under normal physiological circumstances, certain body antigens are inaccessible to the circulation and immune system, and as a result the circulating lymphocytes do not come into contact with them. Such latent antigens with features of autoantigens can be found in the testes, the anterior chamber of the eyeball, central nervous system, but also inside tissue cells, such as those of the liver. However, sometimes such antigens can be released and enter the circulation where they trigger an autoimmune reaction. For example, autoantibodies for liver membrane protein antigens can be found in dogs suffering from chronic liver inflammation. An immune reaction to latent antigens most often occurs after an injury to a particular organ; however, an infection and the resulting tissue damage can favor the release of otherwise unavailable body antigens. It is known that in tuberculosis, which is often accompanied by significant tissue damage, antibodies for a number of tissue antigens can be found in the serum of affected animals.

Autoimmune reactions to latent antigens are usually short-lived. Thus, due to their transience they are clinically less often manifested or observed. An autoimmune disease develops only in the case of a more permanent autoantigen stimulus.

Disorders of immunoregulatory mechanisms

Immune reactions that occur in the body are monitored repeatedly by mechanisms that affect different levels of immunity. An important additional feature of these control mechanisms is that they complement each other, as well as occasionally overlap. Their primary task is to control the onset, course, duration, intensity, and termination of each immune response. This otherwise specific and effective system of control can sometimes be disrupted and allow an

immune response to self-antigens to be triggered, which in turn causes a certain autoimmune disease. Immunoregulatory disorders can affect all levels of immune control, but they most commonly affect the control systems which control the activity of helper and suppressor T lymphocytes.

In some autoimmune diseases, a reduced number of suppressor T lymphocytes has been found, which in turn enables the increased activity of B lymphocytes and the formation of a significant number of autoantibodies. An example would be systemic lupus erythematosus, whose common characteristics are an increased activity of B lymphocytes, hyperglobulinemia, and the formation of antibodies that are directed against various antigens of one's organs and tissues. Such an autoimmune reaction will develop in systemic lupus erythematosus even in situations in which the number of suppressor T lymphocytes is within physiological limits, but their ability to suppress the immune response is reduced.

The onset of autoimmune diseases can sometimes be based on the failed regulatory role of helper T lymphocytes. Under normal circumstances, lymphocytes of this subpopulation do not stimulate the autoreactive B lymphocytes to form autoantibodies. This immunoregulatory role can be disrupted by various effects, and as a result helper T lymphocytes stimulate the proliferation of B lymphocytes and their secretion of autoantibodies responsible for a certain autoimmune disease.

It has been noted in both humans and animals that certain autoimmune diseases are associated with and more common in patients suffering from a lymphatic tissue tumor. Their etiopathogenesis shows significant occurrences of autoimmune diseases, which are a result of the breakdown or weakening of immunoregulatory control, while at the same time the mechanisms of immune tolerance are being disturbed. A classic example is myasthenia gravis which is often associated with malignant thymoma. It is an autoimmune disease that affects the neuromuscular junction and results in decreased muscle strength when the movement is repeated. People suffering from lymphatic tissue tumors have been found to have a much higher incidence of rheumatoid arthritis.

Immunoregulatory mechanisms may also be disrupted due to the inactivity of certain cytokines, most commonly interleukins 4 and 10 (IL-4 and IL-10) as well as the transforming growth factor-beta (TGF-β). In addition to a number of other effects, they are believed to prevent an excessive immune response.

Polyclonal activation of lymphocytes

It is common knowledge that antibody production directly depends on the cooperation of B lymphocytes with helper T lymphocytes which have previously been stimulated by the appropriate antigen. Similarly, B lymphocytes do not recognize autoantigens, but the immune response does not occur due to the absence of the necessary stimulation of helper T lymphocytes which are immunotolerant to the mentioned autoantigens. In some cases, the necessary involvement of helper T lymphocytes in the activation of B lymphocytes may be circumvented, while on rare occasions even T lymphocytes may be activated as well. This is common in infections caused by certain bacteria or viruses. Such nonspecific or polyclonal activation of B and T lymphocytes can be caused by the so-called superantigens, i.e., microbial proteins, often exotoxins, which are extremely strong mitogens and have the ability of lymphocyte transformation and directly activate T lymphocytes. While only 0.001% or less of the total T lymphocyte population is estimated to be involved in a normal immune response, superantigens are capable of activating tens of per cents of them. They are formed by certain species of bacteria such as *Staphylococcus aureus, Streptococcus pyogenes, Streptococcus dysgalactiae, Streptococcus equi* subsp. *equi, Yersinia pseudotuberculosis,* and *Mycoplasma arthritidis.* The same effect can be caused by some superantigens encoded by certain human and animal viruses. The best researched and well-known ones include rabies virus, herpesviruses (cytomegalovirus and Epstein-Barr virus), and retroviruses (feline immunodeficiency virus, human immunodeficiency virus and mouse mammary tumor virus). In a nonspecific, i.e., polyclonal way, they bind directly to the beta subunit of T-cell receptors, and extremely small amounts of superantigen are sufficient to induce rapid activation of this part of the lymphocyte population. Clinical manifestation includes fever, shock, and the death of the animal.

There are some indications that superantigens and immune responses induced by T lymphocytes may also be involved in autoimmune diseases, the evidence being the experimentally induced autoimmune encephalomyelitis in mice. The administration of the superantigen SEB (enterotoxin B bacteria *Staphylococcus aureus*) in mice recovering from autoimmune encephalomyelitis caused direct stimulation of the autoreactive peptide and rapid return of the encephalomyelitis symptoms.

From time to time, B lymphocytes are activated polyclonally as well, and their activation without the involvement of T lymphocytes can be stimulated by various substances. They are

often of microbial or parasitic origin, and the best-known ones are bacterial lipopolysaccharides, PPD or tuberculin, protein A, some mycoplasmas, parts of the virus, and proteolytic enzymes. Protein A, a 40-60 kDa component of the bacterial cell wall of *Staphylococcus aureus*, is particularly well researched. The action of protein A or other polyclonal activators of B lymphocytes can stimulate the formation of antibodies for autoantigens, with those of the IgG class being particularly relevant.

Despite the probability of polyclonal activation of B lymphocytes and the formation of autoantibodies, no activator can be considered as a decisive factor in the development of a particular autoimmune disease in animals. Therefore, it is assumed that, in the etiology of autoimmune diseases in animals, polyclonal activation of B lymphocytes is only of secondary importance.

Apoptosis and autoimmunity disorders

Apoptosis or programmed cell death is an extremely important mechanism by which old, worn out, damaged or abnormal cells are removed from the body. It also maintains the equilibrium which is essential for a balanced and coordinated cell renewal. It is triggered within various physiological processes or due to damage which renders the cells useless or dangerous to the organism. This suggests that cells undergoing apoptosis are morphologically and biochemically different from healthy cells, while the activation of programmed cell death mechanics can vary. Most importantly, cascades of caspase proteolytic enzymes belonging to a family of aspartate-specific cysteine proteases are being triggered by various mediators. These enzymes, which participate in apoptosis and serve as its agents, are found in the cytoplasm of the cell as proenzymes and can be divided into two groups. The first consists of initiator caspases that participate in the initial processes of apoptosis, but at the same time activate executioner caspases that perform proteolytic cleavage of numerous and diverse cellular proteins. Their activity is manifested by cell deformation, chromatin condensation, “budding” of parts of the cell wall, apoptotic body formation, and nuclear DNA fragmentation, which altogether lead to cell death. Cells affected by apoptosis are eventually rapidly phagocytosed by local phagocytes, thereby being permanently removed from the tissue. The briefly described mechanism is considered extremely important because it prevents the inflammatory response of the organism and other immune reactions to self-antigens released from cells. Macrophages and dendritic cells are primarily involved in the removal of apoptotic cells, while local tissue cells, such as epithelial cells, contribute to the

removal of dead cells. This feature significantly distinguishes programmed cell death from cell death caused by necrosis. In apoptosis, despite the dramatic biochemical changes, the cell's integrity is preserved and its cellular components remain within the cell, while in necrosis, cell degradation and the release of compounds with antigenic potential is regular and inevitable.

The process of programmed cell death can be divided into three stages. The induction or initial phase begins with external or internal stimuli triggering the mechanism of death receptors and regulatory proteins. The mid-phase of the apoptosis process is dominated by the enzymatic activity of caspases, while in the late phase, vital cellular structural proteins are cleaved and result in cell death.

In mammalian cells, two basic pathways lead to apoptosis. The extrinsic pathway commonly refers to programmed cell death induced by death receptors, while the main characteristic of the intrinsic pathway is its complete dependence on the metabolic state of the cell and signals in the mitochondria.

The extrinsic pathway of apoptosis is triggered by death receptors, which belong to the cell surface receptors for tumor necrosis factor. Carrying the death domains (DD), they reach the cytoplasm from the inside of the cell wall. The process of binding of the ligand to the corresponding death receptor results in receptor trimerization and the formation of a signaling complex which induces caspase activation and consequently leads to cell death.

The intrinsic pathway of programmed cell death is controlled by the BCL-2 family of proteins. The pathway is most often triggered by growth hormone deficiency, cell stress, or the effect of cytotoxic drugs such as anticancer chemotherapeutics. Such effects activate molecules that stimulate apoptosis or inactivate proteins from the BCL-2 family, which have anti-apoptotic effects. In this way, the mitochondrial permeability is changed and cytochrome c is released from it. In a complex known as the apoptosome, the cytochrome c activates caspase-9 which is responsible for the initiation of the executive caspase cascade. The result of their action is cell destruction and death.

Alongside its role in the regulation of the relationships between cells of other tissues, apoptosis is an extremely important regulatory mechanism in the control of immune system cells, especially in the control of lymphocyte populations. Apoptosis ensures the removal of activated lymphocytes formed during the immune response. Death of lymphocytes is carefully

monitored and usually has serious consequences in cases in which such monitoring is disrupted. Failed initiation of apoptosis in lymphocytes leads to the development of autoimmune processes which lead to autoimmune diseases. Some of these autoimmune processes are caused by failed apoptosis while in some of them such mechanisms are considered to be a part of the pathogenesis of the disease.

Disturbances in apoptosis can cause a lack of control over the duration and completion of the immune response and over activated lymphocytes. In other cases, triggered but disturbed apoptosis mechanisms may release autoantigens and make them available to immune mechanisms. Although disturbances in programmed cell death may trigger autoimmune mechanisms, other regulatory mechanisms must fail in order for a particular autoimmune disease to develop, and it is known that a genetic predisposition is required for their occurrence. The best known disease is hereditary deficiency of the Clq complement component which plays an important role in the removal of apoptotic cells.

There are several autoimmune diseases in which the participation of mechanisms of disturbed apoptosis is proven, but also some in which there is a reasonable ground for that claim. This primarily refers to systemic lupus erythematosus, autoimmune lymphoproliferative syndrome, multiple sclerosis, and rheumatoid arthritis. The results of certain research, which suggest the connection between these autoimmune diseases and disturbed apoptosis, primarily apply to these diseases in humans. However, animal studies have contributed to such findings as well.

Systemic lupus erythematosus, a chronic disease characterized by the presence of several autoantibodies, especially those directed against nuclear components, is characterized by pathological changes in various organs such as the skin, kidneys, and blood vessels. It is believed that in the development of this autoimmune disease, the cellular autoantigen source is apoptotic cells. Possible reasons for ineffective removal of apoptotic cells include inactive phagocytosis of macrophages and impaired activity of certain components of the complement system, especially CIq, C3, and C4. This was found in people suffering from systemic lupus erythematosus, as well as in laboratory mice of appropriate strains. In a mouse model, it was found that, due to ineffective mechanisms of the intrinsic pathway of programmed cell death, disrupted lymphocyte apoptosis can cause a disease which in these experimental animals resembles systemic lupus erythematosus.

Rheumatoid arthritis is another relevant autoimmune disease in humans and animals in which disrupted apoptosis is believed to play an important role in etiopathogenesis. The infiltration

of inflammatory cells causes severe damage to the synovial membrane and there is pronounced hyperplasia of synovial cells and secretion of cytokines which promote inflammation (IL-6, TNF-α). The hyperproliferation of helper CD4 + T lymphocytes, which can further promote the accumulation of autoreactive T lymphocytes, has been proven in experimental mice with rheumatoid arthritis.

Idiotypic cross-reactivity

There is evidence that cross-reactivity between idiotypes on antibodies of some viruses and their receptors which are bound to host cells, can trigger an autoimmune reaction due to the interference of anti-idiotypic antibodies. Although there are other insights into the possible role of viruses in the initiation of autoimmune processes, for now, they cannot be given primary significance in the etiology of autoimmune diseases in animals.

Autoimmune diseases occurring after vaccination

Just like in human medicine, there is growing evidence in veterinary medicine that certain autoimmune diseases may be associated with active immunization and the administration of certain vaccines. It has been known for forty years that vaccination can trigger certain autoimmune diseases in humans. Although they can relatively rarely be objectively proven to be the direct consequence of vaccination, it is believed that they usually occur in individuals with a genetic predisposition to autoimmune diseases. The most widespread and documented mass outbreak is that of Guillan-Barré syndrome in humans vaccinated against influenza in the United States in the mid-1970s, with a vaccine made from the string of virus of swine influenza A/New Jersey/76, subtype H1N1. This disease is accompanied by paresis and even paralysis which is the result of inflammatory changes of the peripheral nerves triggered by autoimmune mechanisms.

It was once believed that such side effects of the vaccination would primarily emerge as a side effect of viral vaccines such as those against influenza, rabies, mumps, rubella, polio, and hepatitis B, but the vaccines containing bacterial antigens pose a risk as well. This particularly applies to tuberculosis (BCG) and tetanus (toxoid) vaccines.

Recently, there have been increasing reports of autoimmune diseases linked to animal vaccination. This is especially true for dogs, which are, of all the domestic animals, most commonly vaccinated and have the most varied assortment of vaccines available to them. It can be argued that there is a growing awareness that many vaccinations of, for example, dogs

are unnecessary and that they might be the triggers of various side effects, among which those with an autoimmune basis make up only a small part. In this case, the responsibility falls on various polyvalent vaccines, which sometimes contain antigens of five or more pathogens of various canine infectious diseases, or on vaccines that contain more potent adjuvants. There is a particular risk of developing such adverse reactions with live modified virus vaccines. Vaccination with such vaccines can cause the formation of several different autoantibodies which can develop shortly after vaccination, as well as after a few months. Usually, their titer decreases rapidly, and it is not known whether they can significantly damage target tissues and cause clinically pronounced signs of disease. One of the examples are thyroglobulin antibodies that appear after rabies vaccination. It is not known whether they can significantly damage the thyroid gland and cause autoimmune thyroiditis, but serum levels of these antibodies can be high.

The best researched and described autoimmune disease which is the result of dog vaccinations is autoimmune hemolytic anemia. In a systematic study, the disease was proven in about sixty dogs, and in the majority of cases, it was preceded by regular annual vaccinations. The vaccination was carried out approximately one month before the onset of autoimmune hemolytic anemia, and the types of vaccines were different. Given that autoimmune hemolytic anemia is a very severe autoimmune disease with a high mortality rate, this side effect is considered to be a serious consequence of the vaccination of dogs.

In addition to dogs, some vaccine side effects, which are based on autoimmune mechanisms, have recently been described in cats. In various studies focusing on chronic kidney diseases, which are very common in cats, kidney damage has been proven to be of autoimmune etiology. The changes are usually so pronounced that they cause the failure of both kidneys and can be considered to be the direct cause of the animal's death. The development of these changes is associated with the administration of viral vaccines, primarily cell-culture-based ones which are made from feline kidney tissue. Numerous vaccine strains of the virus from which cat vaccines are produced, are cultivated using such cell cultures. In the so-called "viral harvest" it is impossible to avoid the presence of proteins derived from kidney cells which then become one of the vaccine ingredients. Understandably, cats immunized with such vaccines will, in addition to the presence of viral antigens, also respond to renal cell antigens, while the created antibodies will damage the kidney cells of vaccinated cats.

Autoimmune reactions that occur after vaccination do not always have to be adverse. To the contrary, recent procedures that reduce the fertility of animals vaccinated with the so-called anti-fertility vaccines, have been based on autoimmune, but also some other mechanisms. These vaccines most often contain heterologous hormonal antigens that stimulate the formation of autoantibodies for their hormones, which during an autoimmune reaction disrupt the production of sex hormones in the vaccinated animal or change its sexual behavior. The result is immunocastration of male pigs, dogs, or foxes. In fattening pigs, such procedure prevents the undesirable odor of the meat of slaughtered uncastrated male animals, while in dogs and foxes, it controls the size of the population and prevents uncontrolled and undesirable reproduction. Pigs and dogs can be actively immunized with a gonadotropin-releasing hormone (GnRH) vaccine, the inactivation of which disrupts a crucial part of hormonal control of the sexual cycle. Dogs of both sexes can also be immunized with a luteinizing hormone of another biological species (sheep or bovine), and the resulting autoantibodies will disrupt physiological sexual functions in both female and male animals. In male animals, the gonads atrophy, while in females the sexual cycle is disturbed. In both cases, the consequence is infertility.

Organ-specific autoimmune diseases

The name of this group of autoimmune diseases, which will be discussed in this chapter, clearly indicates that they primarily affect certain organs and organ systems. We note that the order of their presentation is not determined by the importance or frequency of a particular disease, but is in accordance with the organs or organ systems in which autoimmune damage occurs.

Autoimmune skin diseases

This important group of autoimmune diseases is most often characterized by the appearance of blisters (vesicles and bullae) on the skin of the diseased animals. This refers to the group of pemphigus and pemphigus-like diseases, while in other types, the main characteristics are dermatites of varying severity, ulcerative and crustal changes on the skin, or hair loss caused by autoimmune processes.

PEMPHIGUS DISEASES

Pemphigus is not a unique autoimmune disease, but a clinical term referring to several similar diseases which have an autoimmune basis and are characterized by the appearance of blisters

(vesicles and bullae) on the skin and mucous membranes. Pemphigus can also be called a pemphigus complex because it includes: (1) pemphigus vulgaris, (2) pemphigus foliaceus, (3) pemphigus erythematosus, and (4) pemphigus vegetans. Although the incidence of individual pemphigus in domestic animals may vary, they are generally considered to be rare autoimmune diseases, some of which are known to occur in dogs, cats, horses, and goats. As is the case with most other autoimmune diseases, pemphigus has been most systematically studied in dogs, one of the main reasons being that all of its forms occur in dogs. However, the best studied type is pemphigus vulgaris (although it is not the most common one in dogs), and it is for this reason that, within the entire pemphigus complex, the greatest attention is paid to that "model".

TABLE 12-1. PREDISPOSITION OF INDIVIDUAL DOG BREEDS TO THE MOST IMPORTANT ORGAN-SPECIFIC AND SYSTEMIC AUTOIMMUNE DISEASES

BREEDS	LT	DMI	ALP	MAS	UDS	AIHA	AITP	MG	SLE	DEL	DM
Great Dane	+										
Borzoi	+										
Dobermann	+										
Golden Retriever	+				+			+			
Dachshund	+							+			
Cocker Spaniel	+					+	+				
Miniature Schnauzer	+										
Irish Setter	+				+	+			+		
Beagle	+								+		
Old English Sheepdog	+				+	+	+				
Samoyed		+			+	+					
German Shepherd	+		+	+				+	+	+	
Boxer				+							
Bernese Mountain Dog				+							
Siberian Husky					+					+	
St. Bernard					+						
Australian Shepherd					+						
Sheltie					+				+	+	+
Akita Inu					+		+				
Miniature Dachshund						+					
Scottish Terrier						+	+				
Vizsla						+					
Poodle							+		+		
Shorthaired Pointer							+				
Rough Collie			+						+	+	+

LT = lymphocytic thyroiditis
DMI = insulin-dependent diabetes mellitus
ALP = atrophic lymphocytic pancreatitis
MAS = steroid responsive meningitis-arteritis
UDS = uveodermatologic syndrome
AIHA = autoimmune hemolytic anemia
AITP = autoimmune thrombocytopenia
MG = myasthenia gravis
SLE = systemic lupus erythematosus
DEL = discoid lupus erythematosus
DM = dermatomyositis

In dogs, pemphigus vulgaris usually occurs in middle-aged animals (between five and six years old), regardless of gender or breed. The disease is manifested by the appearance of characteristic vesicles on the skin and mucous membranes, which are filled with clear fluid. The vesicles subsequently rupture, leaving shallow damage or even ulcers. The changes are especially common at the transition zone between the skin and the mucosa (lips, eyelids, prepuce, anus), as well as on the tongue and the oral mucosa. Local secondary bacterial infections, which can turn into septicemia and influence the clinical picture and the general condition of the patient, are common in the chronic course of the disease. During the examination, when running the fingertip over the skin of a sick dog, the Nikolsky's sign, which manifests in surface layer separating from the basal layer on the larger area of the skin, can be noticed.

The described events are the result of autoimmune processes that begin with the formation of autoantibodies (mainly IgG) for cell surface antigens on keratocytes and/or intercellular substance antigens in the skin or mucous membranes. The antigens responsible for the onset of pemphigus have not yet been determined, but it is believed that the cell surface glycoprotein plays the main role. The following immunopathogenic events include the resulting autoantibodies reaching the epidermis and binding to the corresponding antigen on keratocytes. This stimulates the release of the plasminogen activator, which converts plasminogen to plasmin. The result is acantholysis, i.e., the loss of intercellular cohesion, which enables the formation of characteristic blisters. It was once thought that the complement plays an important role in the pathogenesis of pemphigus as well, but the results of experiments conducted in *in vitro* conditions have disputed this claim. Therefore, it can be argued that the role of complement in the development of pemphigus is still dubious.

The main characteristic of pemphigus vulgaris, which can be histologically proven, is that acantholysis and separation of the epidermis occur above the basal layer cells, thus a row of

that cell layer remains at the bottom of the damaged skin surface. In addition to histological testing, pemphigus vulgaris can also be diagnosed by different immunological procedures. Direct immunofluorescence, which detects the deposits of immunoglobulins in the intercellular spaces of the epidermis, is very appropriate, while indirect immunofluorescence is of limited diagnostic significance in animals because few dogs with pemphigus have a significant titer of specific serum autoantibodies.

Accurate diagnosis and differentiation of pemphigus in dogs are particularly important for the prognosis. For animals that have pemphigus vulgaris, the prognosis is mainly poor, while in the case of other forms of pemphigus it is generally more favorable. Pemphigus foliaceus, which in dogs is more common than pemphigus vulgaris, is a milder disease, and for differential and diagnostic purposes it can be noted that this autoimmune disease is also characterized by acantholysis. However, blisters appear just below the stratum corneum of the epidermis. Furthermore, the changes very rarely affect the mucous membranes, while the changes on the skin are usually extensive. They include hair loss and are more common on the scalp, ears, and muzzle. Otherwise, the results obtained by direct immunofluorescence are the same as in pemphigus vulgaris.

Pemphigus erythematosus resembles the milder form of pemphigus foliaceus and usually affects the skin of the face and neck. The symptoms of the disease are exacerbated by sunlight and, based on its immune characteristics, pemphigus erythematosus resembles systemic lupus erythematosus and pemphigus foliaceus. Within the entire group of pemphigus, so far pemphigus vegetans has been the least common. In dogs, clinically, immunologically and histologically it resembles pemphigus vulgaris.

Regardless of the pemphigus type, animals are primarily treated with glucocorticoids, which most often have to be combined with antibiotics. At the beginning of the treatment the doses of glucocorticoids are usually high, and after the alleviation of the symptoms, the dose of the appropriate preparation is reduced. Treatment is long-lasting, i.e., it lasts for weeks or even months, and side effects of the immunosuppressive effect of glucocorticoids may occur. Due to this possibility, the animals must be under constant supervision. The side effects of the treatment of the underlying disease may vary and can sometimes be very severe (infections, degeneration of vital organs, bleeding, etc.). Other preparations (e.g. gold salts) may be used in addition to glucocorticoids, but their effect is generally weaker.

As already mentioned, certain types of pemphigus have also been reported in other domestic animals. In cats, all types are present except for pemphigus vegetans, with the pemphigus foliaceus being the most common one. Treatment of cats suffering from pemphigus with high doses of glucocorticoids is not particularly successful and is effective in only about sixty percent of cases. Sometimes a very favorable therapeutic effect can be achieved by using preparations containing gold salts. In horses, pemphigus foliaceus is the most common autoimmune disease in general, and this form of pemphigus has also been reported in goats.

BULLOUS PEMPHIGOID

This is an autoimmune disease that is characterized by changes in the skin and by the appearance of vesicular protrusions of the epidermis, i.e., the appearance of bullae or vesicles. Based on the clinical signs, bullous pemphigoid is very similar to pemphigus vulgaris, but differs from it immunopathogenetically and pathohistologically.

The pathogenesis of bullous pemphigoid is also based on the action of autoantibodies, predominantly those of the IgG class; however, they are directed towards the protein constituents of the basement membrane located at the junction of the epidermis and corium. Binding of autoantibodies to type XVII collagen and to the corresponding antigens of the basement membrane activates the complement system, developing, in that area, a strong inflammatory reaction with the infiltration of monocytes and eosinophilic leukocytes as well as fibrin deposition. The consequence of these immunopathogenic events is the formation of blisters, which are always located below the epidermis. The popping of these blisters causes damage and significant ulcers.

Among domestic animals, bullous pemphigoid usually affects dogs, but those belonging to the Collie, Doberman and Shetland Shepherd breeds are more prone to it. There are only isolated reports of this disease in cats, pigs and horses. In dogs, the disease usually affects parts of the skin on the ears, head, neck, armpits and abdomen. The appearance of vesicles or bullae is also common on the oral mucosa, while the general condition of the animal depends on the extent of the changes, their intensity, and secondary bacterial infections.

Bullous pemphigoid can be diagnosed not only by histological examination but also by direct immunofluorescence, which is used to detect the deposition of immunoglobulins and the presence of the complement alongside the basement membrane. IgG predominates in the altered tissue, while the presence of IgA and IgM is markedly lower.

The methods of treatment of animals suffering from bullous pemphigoid are the same as those that are applied in the treatment of pemphigus. The drugs of choice are once again glucocorticoid preparations, while antimicrobial treatment is usually indispensable due to the presence of secondary bacterial infections. In the case of mild and localized changes, it is possible to achieve satisfactory treatment results with low doses of glucocorticoids, although the use of these drugs is always accompanied by the risk of side effects. For patients with more severe forms of bullous pemphigoid, the prognosis of the disease is generally unfavorable.

LINEAR IgA BULLOUS DERMATOSIS

Linear IgA bullous dermatosis, also known as linear IgA dermatosis, belongs to a group of autoimmune diseases of the skin or mucous membranes which are clinically detected by the appearance of subepidermal blisters. It is a rare disease in humans, while among animals a very similar disease has been proven and described in dogs. Unlike bullous pemphigoid, in which autoantibodies recognize the transmembrane collagen type XVII (BPAG2 protein), in linear IgA bullous dermatosis, autoantibodies of this class are directed against LAD-1 antigen, which is an extracellular form of type XVII collagen. It is characterized by the linear IgA deposit in the area of the basement membrane, although autoantibodies of immunoglobulin G class can also be deposited at that site.

Linear IgA bullous dermatosis was objectively demonstrated in adult dogs in only a few cases, and was clinically manifested by erosive, ulcerative, and crustal changes on the skin of the face and legs, and on the oral mucosa. Cracks in the basement membrane without inflammation and with moderate infiltration of neutrophilic leukocytes were also found. The deposit of immunoglobulins (IgA and IgG) in the basement membrane zone and circulating antibodies for the soluble LAD-1 protein have also been proven.

EPIDERMOLYSIS BULLOSA ACQUISITA

The most important immune characteristics of this rare autoimmune skin disease are the linear deposits of IgG and IgA and certain components of the complement system in the basement membrane area. They are specific for the type VII collagen antigen that forms the fibers binding the dermis to the epidermis. Circulating antibodies deposited in the tissue can be detected by various immunological methods. Suitable methods for their detection include

individual immune-enzymatic methods and immunoblotting, while the specific sites of their deposition can be accurately determined by immunoelectron microscopy.

Except in humans, epidermolysis bullosa acquisita has so far been found under natural circumstances only in dogs. Under experimental conditions, patient antibodies containing specific antibodies were transferred to adult immunocompetent mice.

Under natural circumstances, epidermolysis bullosa acquisita in dogs is characterized by the appearance of numerous blisters and ulcers on the skin and mucous membranes with pronounced urticaria. Necrosis and extensive bacterial infections occur in the later stage of the disease. Bacterial infections are the main threat in immunosuppressive treatment, which can generally have a beneficial effect.

ALOPECIA AREATA

Alopecia areata or lymphocytic folliculitis is an autoimmune skin disease that has so far been described in humans and several different animal species. Among animals, it is most often found in certain breeds of dogs, primarily in: Dachshund, Doberman, German Shepherd, Hungarian Vizsla, Miniature Poodle. However, crossbreed dogs are no exception. Except in dogs, mostly individual cases have been described in Siamese cats, Holstein cattle, horses, several species of primates, and individual strains of laboratory mice and rats. The disease is characterized by the appearance of larger or smaller, mostly regular, round or oval bald patches, which usually have sharply demarcated edges and can be found on different parts of the body. The skin of the hairless area is not inflamed or the inflammation is slight. Generalized cases in which the whole body of the animal is affected are extremely rare.

Autoimmune processes are directed towards cells and keratin in hair follicles, and in addition to immunoglobulins G and M which are specific for these parts and components of the skin, infiltration of T lymphocytes with CD4 and CD8 markers has been proven in dogs. The C3 complement component is believed to be involved in the pathogenesis as well.

Treatment of animals suffering from alopecia areata is usually more favorable if the affected area is smaller and if the treatment starts soon after the onset of the disease. The glucocorticoid treatment had the best therapeutic effects in dogs, primates, horses, mice, and rats, although the disease may sometimes return after the cessation of the treatment.

In experiments performed on mice, the beneficial efficacy of mechloretamine, which inhibits the effect of tumor necrosis factor, interleukin 12 and interferon-gamma, has also been demonstrated.

Autoimmune diseases of the locomotor system

Autoimmune diseases of the locomotor system in animals have so far been found in several species of domestic and wild animals, but are of the greatest importance in pets, especially dogs. Although these diseases rarely occur, they can be very severe and unpleasant for the affected animals, but also demanding for their owners.

MYASTHENIA GRAVIS

Myasthenia gravis is a disease characterized by neuromuscular disorders, which is clinically manifested by marked muscle weakness. It is a weakness of individual voluntary muscles or muscle groups, and occurs due to impaired neuromuscular transmission. Among domestic animals, myasthenia gravis has been described in dogs and cats, but it must be noted that the disease is best researched in humans, who can also develop it. In cats, myasthenia gravis is actually rarely found, while the disease is more common in dogs and humans and occurs in two forms. See p. 2373.

One form of myasthenia gravis is hereditary and present in some breeds of terriers and spaniels, primarily in puppies. The disease is inherited through the autosomal recessive pattern and does not have a pronounced immune basis. This congenital form of myasthenia gravis is based on the destruction of acetylcholine receptors and the prevention of neuromuscular stimulation transmission.

The acquired myasthenia gravis has an autoimmune basis, which occurs as a result of the action of autoantibodies on the surface acetylcholine receptors on the muscle cells. Specific anti-receptor antibodies (IgG) bind to the acetylcholine receptor, blocking it and thus preventing acetylcholine activation. The loss of acetylcholine receptors is responsible for reduced motor activity, which is manifested by the absence of muscle contractions.

In addition to autoantibodies, the complement, which can be proven at the site of immunopathologic events in the neuromuscular system, participates in the pathogenesis of myasthenia gravis as well. The belief that thymic abnormalities and disorders associated with it may also be involved in the development of myasthenia gravis additionally contributes to

the complexity of its immunopathogenesis. The most important disorders are thought to be at the level of T lymphocyte differentiation, particularly of helper and suppressor lymphocytes. It is further assumed that the abnormality of the helper T lymphocytes allows the production of anti-receptor antibodies, and the inactivity of suppressor lymphocytes and the lack of suppressor factors they secrete allow for the loss of immune tolerance to protein acetylcholine receptors. The consequence of such a disorder is the formation of antibodies for that self-antigen.

This form of myasthenia gravis, which has autoimmune characteristics, usually affects dogs belonging to the so-called large breeds (e.g., German Shepherds), although breed predisposition to the disease has not been proven. In animals, the signs of the disease develop gradually, and a very noticeable symptom is the weakness of the voluntary muscles. Their weakness is intensified by repetitive movements or by prolonged muscular activity. Rest or interruption of muscle work improves the condition, but this usually does not apply to the groups of permanently active muscles. This includes the muscles of the head and neck. Thus, dogs suffering from myasthenia gravis can develop the following symptoms: uncontrollable drooping of the eyelids, difficulties in chewing food and swallowing it, as well as other characteristic signs.

The characteristic clinical picture represents a simple and reliable diagnosis of the disease. However, myasthenia gravis can also be diagnosed by various pharmacological, electromyographic and immunological procedures. A test, which involves injecting the dog with short-acting anticholinesterase drug, is very reliable for diagnostic purposes. In an animal suffering from myasthenia gravis, signs of marked improvement usually appear within a minute of administration. The effect of anticholinesterase includes blocking the enzyme cholinesterase and its cleavage of acetylcholine. This allows for the accumulation of acetylcholine in quantities sufficient to stimulate the remaining acetylcholine receptors in the neuromuscular junction, so that muscle contractions take place unhindered.

Serological procedures are rarely used to diagnose myasthenia gravis, although they can detect the anti-receptor antibodies. They have been found in about ninety percent of the examined animals by performing a suitable radioimmunoassay test (RIA) or some of the tests using staphylococcal protein A (protein A of the *Staphylococcus aureus* type). Indirect immunofluorescence is also of certain diagnostic value.

Treatment of dogs suffering from myasthenia gravis is preferably carried out with long-acting anticholinesterase preparations containing edrophonium chloride. Such treatment can be supplemented by concomitant administration of glucocorticoids, but the treatment success can vary. In some animals only transient improvement is achieved, while others show notable improvement. The outcome of the disease particularly depends on timely treatment as well as on the side effects that develop alongside the underlying disease. Nevertheless, the outcome of the disease is most often favorable.

AUTOIMMUNE POLYMYOSITIS

Among the autoimmune diseases of the locomotor system in dogs, the most common is a group of muscular diseases which can be collectively called autoimmune polymyositis. Although they can be classified differently (e.g., atrophic myositis, autoimmune masticatory muscle myopathy etc.), all these diseases have common characteristics of idiopathic autoimmune changes to the muscle tissue and can be effectively treated using glucocorticoids. Additionally, they share more similarities than differences, so it is advisable and justified to call them by one name. Regardless of the symptoms and their localization, it has been observed that autoimmune polymyositis is more common in dogs of large breeds.

The most recognizable clinical signs are usually associated with changes in the masticatory muscles which may be painful, swollen, or atrophic. This is most often associated with inability or difficulty in opening the mouth. Trismus can be so severe that it persists even during general anesthesia. Changes to the muscles of the trachea and pharynx can be so pronounced as to make it difficult for the affected dogs to produce sounds. Since autoimmune polymyositis affects different muscle groups, the symptoms can be different. In some dogs, difficulties when walking, restrained gait, stiff neck or general muscle weakness are noticeable.

The diagnosis of autoimmune polymyositis can be confirmed by the finding of high levels of serum keratin phosphokinase, by examining the biopsies of affected muscles or autoantibodies specific for individual components of muscle tissue. Histological examination usually reveals necrotic, degenerative and inflammatory changes with signs of fibrosis. Diseased tissue can be infiltrated by lymphocytes and plasma cells, and sometimes by eosinophilic leukocytes, although histological findings can vary widely.

Autoimmune blood and hematopoietic tissue diseases

Autoimmune hemolytic anemia and autoimmune thrombocytopenia are the best researched and most common autoimmune blood and hematopoietic tissue diseases among animals, especially in pets.

AUTOIMMUNE HEMOLYTIC ANEMIA

Autoimmune hemolytic anemia is the most common acute autoimmune disease known in dogs, cats, horses, and cattle, and its main characteristic is that hemolysis disorders are based on autoantibodies for host erythrocytes. Due to the involvement of different immune mechanisms, autoimmune hemolytic anemia is usually divided into several types, and one of their important additional characteristics is the absence or presence of the complement in the destruction of erythrocytes. Additionally, in some types of autoimmune hemolytic anemia, the differences are more pronounced with respect to the place in the body where hemolysis occurs. In some it is within the blood vessels, while other types of autoimmune hemolytic anemia are marked by decaying erythrocytes outside the bloodstream. Since autoimmune hemolytic anemia has been most systematically studied in dogs, we present this autoimmune disease primarily on the basis of knowledge gained from this animal species, while the characteristics of this disease in other domestic animals will be presented after that description.

In dogs, autoimmune hemolytic anemia usually occurs between the ages of two and eight, and whether there is a breed predisposition to the disease is not entirely clear. Although dogs of all breeds can develop the disease, Old English Sheepdogs, Poodles, Cocker Spaniels, Irish Setters and German Shepherds are the most susceptible. It is interesting that the disease is three to four times more common in bitches than in male animals, and it is believed that the disease has a genetic basis.

Not all factors involved in the pathogenesis of autoimmune hemolytic anemia are known. One of the interpretations claims that anti-erythrocyte antibodies are formed due to biochemical changes and thus alter erythrocyte antigenicity. It is hypothesized that such changes could be induced by some drugs, effects of other chemical compounds, or individual microbes.

There is more information about the effect of the resulting autoantibodies and about the fate of the host erythrocytes. The ways of their destruction may vary and occur due to intravascular agglutination, intravascular hemolysis or due to extravascular hemolysis. The

additional data on the characteristics of the types of autoimmune hemolytic anemia in dogs (types I to V) are given in Table 12-2.

Based on the data shown in Table 12-2, the similarities between the types I and IV, and types II and V of autoimmune hemolytic anemia are noticeable. Types I and IV are characterized by intravascular agglutination, followed by the phagocytosis of agglutinated erythrocytes in the spleen and liver, respectively. An important difference between these types is that in type IV the complement system is also activated. Types II and V of autoimmune hemolytic anemia are even more similar. The peculiarity of type V is that this form of autoimmune hemolytic anemia is characterized by the involvement of the so-called "cold" antibodies, which are especially active at low temperatures and their activity is determined at 4°C. Autoantibodies participating in type IV also belong to the "cold" antibodies (Table 12-2).

The properties of autoantibodies also affect the clinical picture of the disease, thus the types of autoimmune hemolytic anemia with "cold" antibodies are characterized by a particular sensitivity of dogs to the cold. In such animals, in cold weather, erythrocytes can agglutinate in the capillaries of the legs and at the ends of the ears and tail, resulting in the development of blood stasis, which can contribute to tissue necrosis.

TABLE 12-2. FEATURES OF CERTAIN TYPES OF AUTOIMMUNE HEMOLYTIC ANEMIA IN DOGS

AIHA TYPE	IMMUNOGLOBULIN CLASS	IMMUNOGLOBULIN EFFECT	COMPLEMENT PARTICIPATION	OPTIMAL TEMPERATURE	PLACE OF ERYTHROCITE REMOVAL	CLINICAL MANIFESTATION
I	IgG, IgM	agglutination	-	37 ° C	spleen	intravascular agglutination
II	IgM	hemolysis	+	37 ° C	liver	intravascular hemolysis
III	IgG	incomplete	+	37 ° C	spleen	anemia
IV	IgM	agglutination	+	4 °C	liver	cyanosis of the legs
V	IgM	incomplete	+	4 °C	liver	anemia

Severe anemia is a common sign of the disease, and in typical cases it is macrocytic anemia with spherocytosis. The other most common symptoms are directly related to anemia, which makes animals melancholic, weak, and hinders their engagement in physical activity. Their visible mucous membranes are pale, sometimes with signs of jaundice; signs of lymphadenopathy and hepatosplenomegaly may be pronounced as well. The liver and spleen

are particularly enlarged in dogs in which erythrocytes are destroyed outside the bloodstream. Although autoimmune hemolytic anemia is a stand-alone autoimmune disease, in approximately one-third of affected animals it occurs together with other autoimmune diseases of autoimmune thrombocytopenia or systemic lupus erythematosus, which means that the additional clinical signs are present as well. The results of laboratory tests also depend on the combination of several autoimmune diseases. The main criteria for diagnosing autoimmune hemolytic anemia are based on characteristic hematological and biochemical findings, while the diagnostically most significant one is the direct antiglobulin test (Coombs test). Other immunological methods may be used as well, such as the indirect antiglobulin test or the rapid slide agglutination test, but types II, III, and V of autoimmune hemolytic anemia are still most reliably diagnosed using a direct Coombs antiglobulin test.

Different therapeutic procedures can be undertaken in the treatment of dogs suffering from autoimmune hemolytic anemia. However, the best treatment results are usually achieved with high doses of glucocorticoids. They do not prevent the formation of anti-erythrocyte antibodies, but prevent the phagocytosis of erythrocytes to which they are bound. Such an effect of glucocorticoids is best expressed against erythrocytes opsonized with IgG (in type III AIHA), and it can generally be argued that the success of treatment depends on the type of the disease.

The prognosis also depends on the type of autoimmune hemolytic anemia in dogs. Types II, III and V are generally considered to be prognostically more favorable than types I and IV.

Autoimmune hemolytic anemia in other domestic animals occurs less frequently. It has been reported in cats, cattle, and horses, but due to a limited number of descriptions, more detailed characteristics of this autoimmune disease in these animal species cannot yet be listed. Just like in dogs, anemia is the most obvious and important symptom. The disease in cats, cattle and horses is also reliably diagnosed on the basis of a positive result of a direct antiglobulin test, while the treatment is carried out with the help of glucocorticoid preparations. In cats suffering from autoimmune hemolytic anemia, it is advisable to supplement such treatment with a tetracycline antibiotic to prevent the outbreak of a latent infection caused by the microbial species, *Mycoplasma haemofelis*. It was formerly classified as rickettsia and known as *Haemobartonella felis*, after which the disease was also called haemobartonellosis.

AUTOIMMUNE THROMBOCYTOPENIA

Primary autoimmune thrombocytopenia, in the older literature known as autoimmune thrombocytopenic purpura, is an autoimmune disease of unexplained etiology characterized by platelet (thrombocytes) autoantibodies in the bloodstream and megakaryocyte autoantibodies in the bone marrow. The disease is clinically manifested by the appearance of petechial and spotted bleeding (purpura) in the skin and mucous and serous membranes. Bleeding into a body cavity or from an orifice can occur as well. Among domestic animals, autoimmune thrombocytopenia is the best known and most common in dogs, while in cats and horses it occurs less frequently.

In dogs, the autoimmune thrombocytopenia most commonly affects Poodles, Old English Sheepdogs and Cocker Spaniels, while the age of the affected animals may vary. The age usually ranges from one to twelve. However, the disease is still most common in five-year-old and six-year-old animals. It is also known that the females develop the disease twice as often as the males. Autoimmune thrombocytopenia may occur as a stand-alone disease or may be associated with another autoimmune disease such as systemic lupus erythematosus, autoimmune hemolytic anemia, or rheumatoid arthritis.

Although the pathogenesis of the disease is unclear, it is known that the affected dogs have platelet autoantibodies and autoantibodies specific for megakaryocytes in the bone marrow. Roughly eighty percent of animals with autoimmune thrombocytopenia have been shown to have antiplatelet antibodies belonging to the IgG class. They are not able to activate the complement system, but opsonize the platelets by allowing them to phagocytose. The most intense thrombocyte phagocytosis occurs in the spleen and partly in the liver, and the result is the development of disease-specific thrombocytopenia. It can be so severe that the platelet count is less than 20×10^{9}/L of blood, and the bleeding time is markedly prolonged. Due to the antigenic similarity of platelets and their precursors, i.e., megakaryocytes, the resulting antiplatelet antibodies also react with megakaryocytes, thus disrupting thrombocytopoiesis. However, this is not the primary cause of thrombocytopenia.

The clinical signs of autoimmune thrombocytopenia and their severity are directly related to the degree of thrombocytopenia and coagulopathy. Symptoms of the disease are petechial bleeding in the skin, gums, conjunctivae and other mucous membranes. After palpation or the usual examination of the patient, ecchymoses may occur at the site of contact. More extensive bleeding is less common, but can be so severe that it can endanger the animal's life. In dogs, bleeding into the gastrointestinal tract can sometimes be so severe that the animal dies from it.

There are well-founded theories that in cats, the autoimmune thrombocytopenia develops during chronic infection with feline leukemia virus.

Laboratory diagnosis of autoimmune thrombocytopenia can be based on various hematological examinations and immunological tests which are usually used to check platelet counts, coagulopathy and other signs. However, the most commonly used laboratory procedures for diagnosing autoimmune thrombocytopenia include the determination of platelet phospholipids called platelet factor 3 and the application of the direct immunofluorescence procedure.

The demonstration of platelet factor 3 actually refers to the detection of the presence of antiplatelet antibodies in the patient's blood serum and their effect on platelets in the blood plasma of a healthy dog. In animals suffering from autoimmune thrombocytopenia, antiplatelet antibodies bind to the normal platelets and damage them by releasing the aforementioned factor, which then induces blood plasma clotting. Since this procedure can sometimes yield rather unreliable results, bone marrow examination using the direct immunofluorescence method is considered to be a safer diagnostic method. This test detects megakaryocyte-bound antiplatelet antibodies in the aspirated sample of the patient's bone marrow.

The success of treatment and the prognosis often depend on timely diagnosis and persistent and long-term treatment. Proper selection, appropriate doses of selected drugs and duration of the treatment are often crucial because even with timely treatment which lasts for a short period of time, the recurrence of symptoms of autoimmune thrombocytopenia is possible. Affected animals usually respond positively to glucocorticoid therapy. High doses of such formulations, such as prednisolone, primarily reduce the phagocytic activity of macrophages and the binding of antiplatelet antibodies to the platelets. It also reduces the level of autoantibodies in the blood, and at the same time increases the strength of the capillaries, thus preventing them from bursting. The desired immunosuppressive effect can be achieved by other formulations such as cyclophosphamide, vincristine sulfate, or azathioprine. Concomitant use one of these drugs and the corresponding glucocorticoid is also possible. It is even recommended if a significant increase in the number of platelets is not found 7-10 days after the start of glucocorticoid monotherapy. In dogs that develop an acute form of autoimmune thrombocytopenia accompanied by profuse bleeding, the condition can be improved by blood transfusion, while in chronically ill animals with persistent signs of

autoimmune thrombocytopenia or in those with occasional outbreaks, splenectomy may be the recommended and appropriate treatment option.

3.2. Analysis

This chapter was easier to translate as it did not feature as many specific medical terms as the previous one. The easiest part of the translation was finding the names of the diseases since they are mostly literal translations from English. Although there are numerous books and articles in the English language on the topic of veterinary science, there were still some difficulties which will be mentioned in the analysis. Regardless of the text being easier to understand, it is still intended only for the students or medical professionals from the field of veterinary medicine.

Since both texts are from the field of immunology, there were some terms which were used in both texts. These include the names of the cells such as interleukins, cytokines and suppressor and helper lymphocytes. However, there were also some more complex terms which were harder to translate. The first one is *titer* which is translated into Croatian as *titar* and refers to "the standard of strength of a volumetric test solution"[56]. Some of the others include *major histocompatibility complex*, translated as *sustav tkivne podudarnosti* and *budding,* mentioned in the analysis of the first text, which is literally translated as *pupanje*. The last one was *cross reactivity,* translated as *križne reakcije*, which refers to "the ability of an antibody to bind with more than one antigen or of an antigen to bind with more than one antibody."[57]

3.2.1. Style

As opposed to the previous text in which the style was strictly expository, i.e., precise, clear and straightforward, the text at hand had some unnecessary phrases. However, there were still no ambiguities and the majority of the sentences were easy to understand.

Even though this chapter is from a textbook, meaning that the text should be providing only factual information, there were parts in which the authors presented some assumptions. The examples are the following: "nijednom se aktivatoru ne može sa sigurnošću pridati odlučujuća uloga pri nastanku određene autoimunosne bolesti" and "Zbog toga se pretpostavlja da poliklonsko aktiviranje […]".

[56] Retrieved from https://medical-dictionary.thefreedictionary.com/titer Accessed July 2021
[57] Retrieved from https://medical-dictionary.thefreedictionary.com/cross+reactivity Accessed July 2021

As opposed to the previous text which was written in third person singular, this chapter includes some sentences which were written in second person plural. For example, "[…] dok ćemo osobitosti te bolesti u drugih domaćih životinja iznijeti nakon toga opisa." However, this does not mean that the chapter is purposefully written in an informal way. The usage of second person plural is common in science and it is used to avoid the use of first person singular. It is also worth mentioning that multiple authors wrote this book which can be confirmed by the use of synonyms for one word. For example, for the term *vaccine* the authors predominantly used the term *cjepivo*. However, the Serbian equivalent *vakcina* is mentioned as well.

This text also featured some redundancies and certain alterations to the text were needed in order to avoid repetitions and simplify the sentences without losing any important information. One of the examples can be found in the sentence "Kod pasa pemfigus vulgaris obično nastaje kod životinja srednje dobi (između pet i šest godina), neovisno o spolu ili pasminskoj pripadnosti." The issue was with the term *pasminska pripadnost* because it is redundant. Furthermore, such a construction would not work in the English sentence and translating it as *dogs belonging to a certain breed* would be too complicated. Therefore, it was translated simply as *breed* because it has the same meaning as the phrase *pasminska pripadnost*.

Another example can be found in the Croatian subtitle "Imunosni mehanizmi nastanka autoimunosti". If the translator were to translate it literally it would sound clumsy. Furthermore, it is always best to keep the titles and subtitles as short as possible without losing any important information. Therefore, it was translated as "Immune mechanism of autoimmunity".

The last stylistic characteristic worth mentioning is the use of empty phrases, some of which were already mentioned. Alongside with that, there were some unusual word choices such as "dramatične biokemijske promjene u stanici" or "brižno nadzirana smrt limfocita" instead of "pomno nadzirana smrt limfocita".

3.2.2. Syntax

The sentences are not as long as in the case of the previous text. However, there were some which sounded clumsy in Croatian and thus posed a problem during the translation into

English. For example, one of the problematic sentences was the following one: “Naprotiv, u novije se vrijeme na autoimunosnim, ali i nekim drugim mehanizmima, osnivaju postupci kojima se smanjuje plodnost životinja cijepljenim tzv. antifertilitetnim cjepivima.” The problem in this sentence is the use of the verb *osnivati* which in English would be translated as *establish.* Due to the author’s choice of the verb and the preposition ‘na’, it seems as if procedures are literally ‘established’ or ‘founded’ on autoimmune and some other mechanisms. The correct choice of verb would be *bazirati,* meaning that these procedures are based on autoimmune and other mechanisms. Thus, the correct translation would be “To the contrary, recent procedures that reduce the fertility of animals vaccinated with the so-called anti-fertility vaccines, have been based on autoimmune, but also some other mechanisms.”

There were also some sentences in which the clauses were not very well connected and as a result they sounded clumsy. For example, the following one: “Naziv te skupine autoimunosnih bolesti jasno upućuje da je riječ o bolestima koje ponajprije zahvaćaju pojedine organe i organske sustave i njih obrađujemo u ovom poglavlju.” The sentence might have been better if the last part “i njih obrađujemo u ovom poglavlju” was incorporated into the first part of the sentence or it might even be omitted since it does not give any important information nor is it necessary for the understanding of the chapter. It is clear from the title and the aforementioned sentence that organ-specific autoimmune disease will be the topic of that part of the chapter. When it comes to the translation of that sentence, the last part of the sentence was kept and inserted after the term *autoimmune diseases*. Thus the translation is the following: “The name of this group of autoimmune diseases, which will be discussed in this chapter, clearly indicates that they primarily affect certain organs and organ systems.”

Another clumsy sentence was the following one: “To osobito vrijedi za pse koji se od svih domaćih životinja najčešće cijepe i za njih postoje vrlo različita cjepiva.” This is another sentence in which the last part is not well connected with the rest. It would be much better if the last part were “i za koje postoje vrlo različita cjepiva” because it is easier to understand to what the sentence refers. Naturally, translators sometimes have to ‘correct’ such sentences in the target language. Thus, the translation is the following: “This is especially true for dogs, which are, of all the domestic animals, most commonly vaccinated and have the most varied assortment of vaccines available to them.”

Another issue in some parts of the text was the order of the dependent clauses. For example, the sentence “Razlog je tome što su rijetki psi s pemfigusom koji imaju znatan titar

specifičnih serumskih autoprotutijela" sounds clumsy and the best option was to unify it with the previous sentence, i.e., "Vrlo je prikladna izravna imunofluorescencija, kojom se dokazuje taloženje imunoglobulina u međustaničnim prostorima epidermis, dok je neizravna imunofluorescencija u životinja ograničenoga dijagnostičkog značenja". This made both sentences clearer and easier to understand. The translation is as follows: "Direct immunofluorescence, which detects the deposits of immunoglobulins in the intercellular spaces of the epidermis, is very appropriate, while indirect immunofluorescence is of limited diagnostic significance in animals because few dogs with pemphigus have a significant titer of specific serum autoantibodies." Even though the resulting sentence is much longer, it unifies both terms and it is clear what certain dependent clauses refer to.

Another example of problematic word order is in the sentence "Pemfigus vegetans je dosad najrjeđe ustanovljen unutar cijelog kompleksa, a u pasa klinički, imunološki i histološki najviše nalikuje na pemphigus vulgaris." In this case, the sentence was divided and the resulting translation is: "Within the entire group of pemphigus, so far pemphigus vegetans has been the least common. In dogs, clinically, immunologically and histologically it resembles pemphigus vulgaris." Thus both sentences are more clear, comprehensible and easier to read.

The first part of the following sentence "Pripravcima s glukokortikoidima postižu se najbolji terapijski učinci u pasa, primate, konja, miševa i štakora premda se bolest katkad može vratiti nakon prestanka liječenja" is problematic because it sounds clumsy. One of the options was to change the word order in the sentence. The chosen translation is the following: "The glucocorticoid treatment had the best therapeutic effects in dogs, primates, horses, mice, and rats, although the disease may sometimes return after the cessation of the treatment."

The sentence "Određenoga je dijagnostičkog značenja i neizravna imunofluorescencija" is unclear because it is not specified whether the indirect immunofluorescence is of great value or not. At first it was translated as "Indirect immunofluorescence is another valuable diagnostic technique", however the best solution was keeping it close to the original because in medicine one should never make their own assumptions because they might be incorrect.

Another problem encountered during the translation was the occasional use of empty phrases. For example, the first part of the sentence "Istraživanja na osnovi kojih su ostvareni rezultati koji upućuju na […]" is redundant and goes against one of the basic rules of writing scientific texts, i.e., conciseness. The sentence could have been written as "Rezultati

istraživanja koji upućuju na […]", as it would be much simpler and more comprehensible. Following that thought, the sentence was translated as: "The results of certain research, which suggest […]".

Another sentence which falls into the category of empty sentences is the following one: "Ipak, može se izreći općenita tvrdnja da je ishod bolesti najčešće povoljan." The first part of the sentence seems too informal for this type of text and could have been omitted and translated as: "Nevertheless, the outcome of the disease is most often favorable."

Furthermore, just like in the previous text, the additional information is given in brackets in order to not confuse the reader and to make the text more comprehensible. For example, "Od tog oblika miastenije gravis, koji ima autoimunosna obilježja, obično obole psi koji pripadaju tzv. velikim pasminama (primjerice njemački ovčari), iako pasminska sklonost bolesti nije sasvim sigurno dokazana."

3.2.3. Grammar

When it comes to grammar, the tenses used in the text are present and past. Present is predominantly used for presenting the facts and explaining the details of each disease. Past is used rarely, but when it is, it is used for the past findings and hypothesis ("Jedno se vrijeme vjerovalo da su takve nuspojave cijepljenja ponajprije vezane uz virusna cjepiva poput onih protiv influence, bjesnoće, zaušnjaka […]"). When it comes to translation, the predominantly used tense was present because the facts and findings mentioned in the chaper are still relevant.

Some of the sentences in this text had typographical errors and it is always the best to check them to confirm that they truly are errors, and not actual words. For example, one of them was *radovita* in the sentence "primjer je sistemski eritematozni lupus čija je radovita značajka pojačana aktivnost B-limfocita, hiperglobulinemija […]". In this case, the correct word was *redovita*.

3.2.4. Vocabulary

Compared to the previous chapter, the vocabulary in this one was simpler and there were fewer specific terms. The majority of them were fairly easy to find. However, a great

number of English texts on veterinary medicine does not automatically mean that all of them are reliable. Thus, it was important to consider which ones could be trusted and which ones could not. The main issue is that the majority of incorrect terms, mostly direct translations from Croatian, can be found in some literature or on certain websites. However, it is important to understand which ones are direct translations from other languages and which ones were originally written in English. It is also crucial to do a thorough research on the topic and in case of terms with multiple translations available, the best option is to use the most commonly used term.

3.2.4.1. Basic medical vocabulary

There are some frequently used medical terms which appear in the majority of medical texts such as test results, medical reports, instructions for the use of medicines etc. Sometimes these terms can be easier to recognize in the English texts than in the Croatian ones. The typical medical vocabulary found in the chaper "Autoimunosne bolesti" will be examined in this part of the analysis.

The most common term found in the text is the adjective *znakovito*. The first mention is in the sentence "U njihovoj je etiopatogenezi znakovito da nastaju zbog sloma ili slabljenja imunoregulacijskog nadzora pa su istodobno poremećeni i mehanizmi imunotolerancije." In this case, it refers to the importance of these symptoms. The chosen translation is as follows: "Their etiopathogenesis shows significant occurrences of autoimmune diseases, which are a result of the breakdown or weakening of immunoregulatory control, while at the same time the mechanisms of immune tolerance are being disturbed." In this case the adjective is translated as *significant*, but it was also important to specify that there are significant occurences of autoimmune diseases, otherwise the reader might not know what it refers to. In the following sentence featuring this adjective, "Bolest se očituje pojavom znakovitih vezikula na koži i sluznicama ispunjenim bistrom tekućinom", the term *znakovit* refers to specific symptoms of the disease and was translated as "The disease is manifested by the appearance of characteristic vesicles on the skin and mucous membranes, which are filled with clear fluid." The last sentence is "Najintenzivnija fagocitoza trombocita zbiva se u slezeni, djelomice i u jetrima, a na taj se način razvije za bolest znakovita trombocitopenija" and the term once again refers to one of the symptoms being characteristic for the disease. It was translated as "[…] and the result is the development of disease-specific

thrombocytopenia." In this case the term was not translated as *characteristic* because by using the word *specific* the sentence can be shortened, thus making it more comprehensible.

The next interesting term is *istodobna upotreba* in the sentence "Moguća je također istodobna upotreba pojedinog od navedenih lijekova i odgovarajućeg glukokortikoida." The term *istodobna upotreba* or *primjena* is a medical term most often found in the instructions for the use of a certain drug. Its English equivalent is *concomitant use* and it is one of those specialized terms the translator might at first be unaware of.

An interesting way of saying in Croatian that a certain part of body is inflamed is by using the expression *upalno promijenjeno područje*, instead of saying that there is an inflammation in a certain part of the body. The expression used in the English language is much simpler and it is *the inflamed area.* Thus, the sentence "Koža bezdlačnog područja nije upalno promijenjena ili je upala tek neznatna" can be translated as "The skin of the hairless area is not inflamed or the inflammation is slight".

Some other terms mentioned in the chapter are *prognoza bolesti* (*prognosis of the disease*), *naglašena* hiperplazija (*pronounced* hyperplasia), *uputno je* (*it is advisable*), *neznatna* upala (*slight* inflammation).

3.2.4.2. Acronyms

While the acronyms can pose a challenge during translation, in this case, they helped in finding the proper names of the diseases. All of the abbreviations mentioned within the text are used in their English forms and thus there was no need for thorough research into the meaning of each of them. When it comes to the acronyms listed in Table 12-1., they only helped in finding the correct English equivalents of the diseases. However, there was still some confusion regarding the acronym DMI and its Croatian equivalent *dijabetes melitus ovisan o inzulinu*. The English term for this disease is *insulin-dependent diabetes mellitus*, which was confusing because in that case the acronym should be IDDM or IDM and not DMI. However, after doing research, one can learn that *I* in the acronym is not a letter, but the number one because insulin-dependent diabetes mellitus is also called Type 1 diabetes mellitus.

Other acronyms mentioned in the text were used to give some additional information to veterinary students or professionals. For example, in the sentence "[…] a prikladan je i dijagnostički postupak radioimunski test (RIA) ili neki od testova pri kojima se upotrebljava […]", the English acronym RIA is specified in the brackets because the English name for this test is *radioimmunoassay*.

3.2.4.3. Synonymy

Synonymy in medical texts can be confusing because the translator might have never heard of a certain synonym, which in turn can lead to literal translations. One of the best examples can be found in this chapter in which *nuspojave, popratne pojave* and *neželjene posljedice* can be translated into English as *side effects*. However, in some cases, depending on the context, *nuspojava* has to be translated as *adverse drug reaction*[58] because in the English language *adverse reaction* refers to "unintended pharmacologic effects that occur when a medication is administered correctly"[59], while *side effect* "is a secondary unwanted effect that occurs due to drug therapy."[60]

As already mentioned in the introduction to this thesis, the translators need to know who their audience is, i.e., who will be reading the translated text, and have to conform it to the needs of that audience. In this case, the problematic terms were two Croatian ones, that is, *kronična upala jetara* in the sentence "Primjerice, pri kroničnoj upali jetara u pasa mogu se ustanoviti autoprotutijela za proteinske antigene jetrene membrane" and *krvarenje* in the sentence "Opsežnija krvarenja su rjeđa, ali mogu biti toliko jaka da čak ugroze i život životinje". The Croatian synonym for *kronična upala jetara* is *hepatitis*, while in English it is also *hepatitis* or *chronic liver inflammation.* The best option was translating it literally since it was the author who decided not to use the term *hepatitis*, but *kronična upala jetara*. When it comes to the second term, it was translated as *bleeding* since the author did not opt for the term *hemoragija*. However, if this were a more formal text, this term could have been translated as hemorrhage.

Yet another translation challenge can be found in the sentence "Teorijski gledano, normalnu imunosnu reakciju s autoimunosnim obilježjima mogu pokrenuti i u nju biti

[58] Retrieved from http://struna.ihjj.hr/naziv/nuspojava-lijeka/35597/#naziv Accessed August 2021
[59] Retrieved from https://www.pharmacytimes.com/view/adverse-event-not-the-same-as-side-effect Accessed August 2021
[60] Ibid.

uključeni izmijenjeni ili prikriveni autoantigeni ili je riječ o nenormalnoj imunosnoj reakciji […]", more precisely, it was the term *prikriveni autoantigeni*. Firstly, it was important to know what *autoantigen* is and how it is translated into English. The English equivalent was simple to find because it is the same as in Croatian, *autoantigen*. Its definition is: "an antigen that is a normal bodily constituent and against which the immune system produces autoantibodies"[61] and it is also called *self-antigen,* which is actually a more frequently used term. Following that, it was important to find out the proper translation for the adjective *prikriveni.* The well known translations such as *disguised, covered, concealed* were not an option. This is where the translator needs to do a thorough research in order to find that a synonym for *prikriveni* is *latentni*. After finding the synonym, it was easy to translate the term *prikriveni autoantigen* as *latent self-antigen.*

Other synonymous words were not from the medical field, but were problematic due to the writing style of the author of the text. For example, in the sentence "Od toga oblika miastenije gravis, koji ima autoimunosna obilježja, obično obole psi koji pripadaju tzv. velikim pasminama (primjerice njemački ovčari), iako pasminska sklonost bolesti nije sasvim sigurno dokazana", the noun *sklonost* was slightly problematic because it can be translated as *propensity, tendency* or *preference.* However, none of these words would fit the context. In medicine, it is often said that certain breeds have predispositions, i.e., "the state of being likely to behave in a particular way or to suffer from a particular disease"[62], for certain diseases and that term seemed to be the best option in the given context.

3.2.4.4. Uncommon terms

The first uncommon term is *žetva virusa* in the sentence "Pri tzv. žetvi virusa ne može se izbjeći prisutnost bjelančevina koje potječu od bubrežnih stanica i one postaju sadržajem cjepiva". Since this term is not common, finding its definition was somewhat challenging. There were some mentions of the term, but none of the Croatian webpages gave its full and clear definition. The best that could be found was that after the virus multiplies, it is literally harvested and it becomes one of the ingridients of the vaccines.[63] Since numerous Croatian medical terms are often literal translations of their English counterparts, the best option was to search *viral harvest.* This ended up being the correct translation and thus the sentence was

[61] Retrieved from https://www.merriam-webster.com/medical/autoantigen Accessed August 2021
[62] Retrieved from https://dictionary.cambridge.org/dictionary/english/predisposition Accessed August 2021
[63] Retrieved from https://imunizacija.hr/boje-su-u-nama-doslovno/ , trans. L. Štebih, Accessed August 2021

translated as “In the so-called “viral harvest” it is impossible to avoid the presence of proteins derived from kidney cells which then become one of the vaccine ingredients.”

The next problematic term was *linearno odlaganje IgA* found in the subtitle “Bulozna dermatoza s linearnim odlaganjem IgA” and in the sentence “Bulozna dermatoza s linearnim odlaganjem IgA, poznata I pod imenom linearna IgA dermatoza, pripada skupini autoimunosnih bolesti kože […]”. Once again, the translator can opt for trying to find the literal translation of this disease, which would be *bullous dermatosis with linear deposition of IgA.* This would actually be an acceptable translation since one of the disease’s characteristics is linear deposition. However, its correct name is *linear IgA bullous dermatosis* or *linear IgA dermatosis.* Thus, the sentence was translated as follows: “Linear IgA bullous dermatosis, also known as linear IgA dermatosis, belongs to a group of autoimmune diseases […]”.

However, the most challenging translation in this entire chapter was *aglutinacija na predmetnici* in the sentence “Mogu se primijeniti i drugi imunološki postupci, poput neizravnoga antiglobulinskoga testa ili aglutinacija na predmetnici, ali se tipovi II, III i V autoimunosne hemolitičke anemije ipak najpouzdanije dijagnosticiraju s pomoću izravnoga Coombsova antiglobulinskoga testa”. Since literal translation of the previous two terms yielded results and helped in finding the appropriate English equivalent, the same technique was used for this term as well. The translation of *aglutinacija* is simply *agglutination*, however, finding the proper translation of the noun *predmetnica* was a challenge. Some of the offered translations for this term were *case, subject* and *subject matter*. Bujas’s Croatian-English dictionary does not have this term listed and *Hrvatski jezični portal* does not provide its definition. From the contexts found online, *predmetnica* also means *natuknica*, but that would not fit in this context. Following that, certain texts from the field of veterinary medicine were found, however, none of them offered a solution. Finally, on the webpage of the Croatian Veterinary Institute, in an article on transfusion, *aglutinacija na predmetnici* and its translation, *rapid slide test*, were included. This only proves that adding the English equivalents of certain medical terms can help not only the veterinary professionals who might not be familiar with the Croatian term, but also the translators who might have difficulties with translating certain terms.

3.2.4.5. Verbs

When it comes to verbs in this chapter, they were not as challenging to translate. However, there were some uncertainties during the translation process, but they were mostly related to the author's choice of verbs.

The first such example is the verb *prevesti* in the sentence "Na taj način potakne se oslobađanje aktivatora plazminogena, koji prevede plazminogen u plazmin". It is obvious that the author did not mean that the plasminogen activator literally "translates" plasminogen into plasmin. The meaning conveyed by this sentence is that plasminogen is *pretvoren* into plasmin. Thus, the possible translations are *convert, turn* and *transform.* In the end, the verb of choice was *convert* and the translation is as follows: "This stimulates the release of the plasminogen activator, which converts plasminogen to plasmin."

The next problematic verb was *dokazati* in the sentence "Bulozni pemfigoid se osim histološkom pretragom može dijagnosticirati i izravnom imunofluorescencijom, kojom se dokazuju taloženje imunoglobulina i prisutnost komplementa uzduž temeljne membrane." It would be incorrect to translate this verb as *prove* because it does not fit the context. Some other options such as *evidence, demonstrate, show, verify* would not be the right choices either and the translator needs to look into the definition of the direct immunofluorescence in order to find out that it is "a technique used in the laboratory to diagnose diseases of the skin, kidney, and other organ systems."[64] This leads to conclusion that this technique is used to *detect* immunoglobulins and thus the correct translation is "Bullous pemphigoid can be diagnosed not only by histological examination but also by direct immunofluorescence, which is used to detect the deposition of immunoglobulins and the presence of the complement alongside the basement membrane."

The next verb is *zakočiti* in the sentence "Specifična antireceptorska protutijela (IgG) vežu se na acetilkolinski receptor, zakoče ga i tako onemoguće acetilkolinsko aktiviranje." As seen from the context, this verb cannot be translated as *break, prevent, secure* or *scotch.* A thorough research of antireceptor antibodies led to translating this verb as *block,* which means that the translation is as follows: "Specific anti-receptor antibodies (IgG) bind to the acetylcholine receptor, blocking it and thus preventing acetylcholine activation."

[64] Retrieved from https://dermnetnz.org/topics/direct-immunofluorescence/ Accessed August 2021

The translation of the verb *pomišljati* in the sentence "Zanimljivo je da je u kuja tri do četiri puta učestalija nego u muških životinja, a pomišlja se da bolest ima genetsku osnovu" was not challenging, but it was important to understand that its English equivalents, *think* and *mean*, would not be a suitable option. The translator needs to realize that the problem lies in the author's choice of the verb. A better sounding choice would be *smatrati* or *vjerovati*. The sentence was translated as "It is interesting that the disease is three to four times more common in bitches than in male animals, and it is believed that the disease has a genetic basis."

3.2.4.6. Other problems

This part of the analysis will include all of the terms which could not be included into any of the previous categories.

The first issue was the term *srodni psi* in the sentence "Riječ je obično o malobrojnim pasminama unutar kojih su psi srodni pa je među njima neznatan polimorfizam gena sustava tkivne podudarnosti." According to the *Hrvatski jezični portal*, the adjective *srodan* has two meanings "koji je istoga roda ili podrijetla, krvnim srodstvom povezan"[65] (transl. of the same kind or origin, related by blood) or "koji je blizak po nekim osobinama ili svojstvima"[66] (transl. which is similar in certain features or properties). In the first version of the translation, this term was translated as *related* since one of the main ideas was that these dogs might be blood related or few different dog breeds were somehow genetically related. However, the correct translation ended up being *inbred to a high degree* because inbreeding can lead to polymorphism and it refers to pugs, boxers, dachshund, bulldogs and other dogs which have numerous health problems due to inbreeding.

The next term worth mentioning is *tolerantnost* in the sentence "Jednako se tako zna da B-limfociti nisu tolerantni prema autoantigenima, ali imunosna reakcija izostane zbog izostanka nužnog podražaja pomoćničkih T-limfocita koji su prema istim autoantigenima imunotolerantni." This is one of the sentences which demonstrates the importance of researching the topic. Although the translation of the adjective *imunotolerantan* is *immunotolerant,* the translation of *nisu tolerantni prema autoantigenima* cannot be *they are*

[65] Retrieved from https://hjp.znanje.hr/index.php?show=search_by_id&id=d1xvWxY%3D&keyword=srodan Accessed August 2021
[66] Ibid.

not tolerant towards autoantigens, since it does not refer to the same thing. In this case tolerance refers to immunological tolerance, i.e., nonreactivity to certain antigen. More precisely, the B lymphocytes "not being tolerant" to self-antigens means that they do not recognize them. Thus, the correct translation of the sentence is "Similarly, B lymphocytes do not recognize autoantigens, but the immune response does not occur due to the absence of the necessary stimulation of helper T lymphocytes which are immunotolerant to the mentioned autoantigens."

The term *spojevi antigenskog potencijala,* found in the sentence "[…] dok je pri nekrozi raspadanje stanice i oslobađanje spojeva antigenskog potencijala redovito i neizbježno", was another issue encountered during the translation. At first, an inexperienced translator might think that there is such a thing as compounds which are called "antigenic potential". However, the meaning behind this is that these are actually compounds with antigenic potential and not "compounds of antigenic potential" or "antigenic potential compounds".

The next issue was the translation of the term *temeljna membrana* in the sentence "Bulozni pemfigoid se osim histološkom pretragom može dijagnosticirati i izravnom imunofluorescencijom, kojom se dokazuju taloženje imunoglobulina i prisutnost komplementa uzduž temeljne membrane." Finding a definition of this term was unusually challenging because the texts it was appearing in were mostly from the field of architecture and building or were webpages in Romanian and Slovenian which were automatically translated into Croatian. However, the literal translation of this term, i.e., *base membrane* yielded results once again. Upon searching "base membrane bullous pemphigoid", the translator can find out that the proper translation for *temeljna membrana* is *basement membrane*.

Krvotvorno tkivo in the sentence "Među životinjama, osobito kućnim, od autoimunosnih bolesti krvi i krvotvornih tkiva najbolje su istražene i najučestalije autoimunosna hemolitička anemija i autoimunosna trombocitopenija" was yet another challenging term. It was necessary to do research in order to find out that *krvotvorno tkivo* is "koštana srž koja ispunjuje šupljine spužvastoga koštanog tkiva u kojemu se stvaraju i diferenciraju krvne stanice"[67] (transl. bone marrow that fills the cavities of spongy bone tissue in which blood cells are formed and differentiated) and it is also called *aktivna koštana srž*

[67] Retrieved from http://struna.ihjj.hr/naziv/crvena-kostana-srz/16121/ Accessed August 2021

and *hematopoetsko tkivo*. Thus, it was easy to conclude that the accepted translations are *red bone marrow* or *hematopoietic tissue*. It is up to the translator to opt for one of these translations and stick to it throught the entire chapter. In this case the chosen term was *hematopoietic tissue* because the author of the original opted for calling it *krvotvorno tkivo* and not *aktivna koštana srž*.

The next problematic term was the adjective *nujan* in the sentence "Ostali najčešći simptomi u izravnoj su vezi s anemijom, pa su životinje nujne, slabe i teško podnose napore." According to the *Hrvatski jezični portal,* the word *nujan* means "sjetan, melankoličan"[68] (transl. sad, melancholic). Another problem in this sentence was the last part "teško podnose napore" which could not be literally translated because it would not connect well with the rest of the sentence. It was important to understand the basic meaning behind it, that is, that *napor* can refer to physical activity and the animal's impossibility to engage in it. Thus, the proper translation of the sentence was "The other most common symptoms are directly related to anemia, which makes animals melancholic, weak, and hinders their engagement in physical activity."

The next issue was the term *provodljivost* in the sentence "Riječ je o slabosti pojedinačnih voljnih mišića ili mišićnih skupina, a nastaje zbog poremećene neuromuskularne provodljivosti." While in other non-medical contexts, *provodljivost* can be translated as *conductivity, conduction* or even *permeability,* depending on the field, in this case none of these options fit the context. While *neuromuscular conductivity* exists and it is used in some medical contexts, since this sentence refers to muscle activity, the correct translation is *neuromuscular transmission,* i.e., "a process that permits the central nervous system to control the movement of muscles in the body."[69]

Yet another challenging term was *slom* in the sentence "U njihovoj je etiopatogenezi znakovito da nastaju zbog sloma ili slabljenja imunoregulacijskog nadzora pa su istodobno poremećeni mehanizmi imunotolerancije." There are numerous possible translation of this noun and it was important to take into account the context. After finding the correct translation for the term *imunoregulacijski nadzor*, which cannot be translated as *immunoregulatory surveillance* or *immunoregulatory monitoring*, but *immunoregulatory*

[68] Retrieved from https://hjp.znanje.hr/index.php?show=search_by_id&id=eFxlXhA%3D&keyword=nujan Accessed August 2021
[69] Retrieved from https://www.sciencedirect.com/topics/neuroscience/neuromuscular-transmission Accessed August 2021

control, it was fairly easy to find out that the term used for expressing "a failure to function"[70] is *breakdown*. Thus, the correct translation of the sentence is as follows: "Their etiopathogenesis shows significant occurrences of autoimmune diseases, which are a result of the breakdown or weakening of immunoregulatory control, while at the same time the mechanisms of immune tolerance are being disturbed."

There was also an issue with translating the term *višestruko* in the sentence "Imunosne reakcije koje se zbivaju u organizmu redovito su višestruko nadzirane mehanizmima koji zahvaćaju različite razine imunosti." Although one of the first thoughts might be that the proper translation would be *multiple* or any derivative of this word, by taking into account the definition of *višestruk*, i.e., "više puta ponovljen ili koji se dogodio više puta"[71] (transl. which was repeated or which occurred multiple times), this leads to a better translation which is *repeated.* Therefore, the translation of the sentence is as follows: "Immune reactions that occur in the body are monitored repeatedly by mechanisms that affect different levels of immunity."

The last issue that will be mentioned in this part of the analysis refers to the translation of the word *kuja*. Although the sentence "U muških životinja atrofiraju spolne žlijezde, dok je u kuja poremećen spolni ciklus" could have been translated as "In male animals, the gonads atrophy, while in bitcehs the sexual cycle is disturbed", the noun *bitch* used for female dogs can easily be replaced by the word *female*, which makes the sentence sound more formal.

Overall, there were not as many issues in this chapter compared to the previous one. One of the reasons is that the majority of the literature from the field of veterinary science is written in the English language. During the translation, the translator knows that every term has its proper and accepted translation, unlike the terms in Croatian which sometimes do not have an official translation. Of great help are theses and other articles on the webpages of the Veterinary Institute which have their English equivalents included in the brackets. This helps not only in finding the appropriate term, but also in confirming that the chosen term is correct.

As opposed to the previous chapter, this one contained more problematic syntactic structures in terms of empty phrases, which the translator can always omit because they do not carry meaning, and redundancies such as *pasminska pripadnost* instead of *pasmina.*

[70] Retrieved from https://www.merriam-webster.com/dictionary/breakdown Accessed August 2021
[71] Retrieved from https://hjp.znanje.hr/index.php?show=search_by_id&id=f19vWRl%2B&keyword=vi%C5%A1estruk Accessed August 2021

4. Conclusion

The translation of texts belonging to veterinary medicine was challenging due to a certain number of terms which either do not have their equivalents in the Croatian language or their equivalents were difficult to find.

Generally, translation needs to be clear, straightforward and comprehensible. It is important to convey the same meaning while still maintaining the accuracy. It was crucial to properly research the topic and read numerous articles, research papers and books regarding immunology, i.e., the immune response and autoimmune diseases. It is always advisable to research the most commonly used terms, the choice of verbs and especially to see how certain terms are used by veterinarians (the difference between *B-limfocit, B limfocit* and *limfocit B*). In order to find that out, I consulted the *Veterinarski priručnik* and the repository of the Faculty of Veterinary Medicine in Zagreb, as well as the webpage of the Veterinary Institute. The veterinarians from the Institute in Rijeka were also of great help because they thoroughly explained to me every term I had trouble finding.

Luckily, both texts were from the field of immunology and there were some terms which were used in both of them, thus making it easier to translate the chapters. The sentences in the chapters were long and packed with information and had to be carefully read and analized in order to properly understand them. The vocabulary is very specific and the translations from English into Croatian were at times difficult to find. Some of the terms do not even have their translations which is why I translated most of them literally and added their English equivalents in brackets in order for the readers to be able to find more information about them.

5. Appendices

APPENDIX A

CHAPTER 8

Immune Response to Viral Infections

In response to the constant threat of invasion by infectious agents, including viruses, vertebrates have evolved an elaborate set of defensive measures, called, collectively, the immune system. During the initial encounter with a virus, the immune system of the host recognizes certain viral macromolecules (proteins, carbohydrates) called *antigens* as foreign which elicit several kinds of responses to eliminate the virus and to prevent reinfection. B lymphocytes respond (the humoral immune response) to an antigenic stimulus by producing and secreting *immunoglobulins* or *antibodies.* T lymphocytes respond (the cell-mediated immune response) by secreting cytokines that regulate the immune response by coordinating the activities of the various types of cells involved, including antibody production by B lymphocytes; T lymphocytes also have direct effector functions, such as cytotoxic functions. Both B and T lymphocytes bear highly specific receptor molecules that recognize discrete regions on viral proteins, known as *antigenic determinants* or *epitopes.*

Antigen-specific immune responses in concert with innate defense mechanisms terminate many viral infections before much damage has been done; this results in mild disease or even subclinical infection. This chapter deals with the role of the immune response in recovery from viral infection and resistance to reinfection. Later chapters address situations where the immune system does not function so effectively, where the immune response is actually harmful and a significant component in the pathogenesis of disease, and where the virus evades the immune system and establishes a persistent infection.

Cellular Components of the Immune System

The cells of the immune system include B and T lymphocytes, cells of the monocyte/macrophage lineage, dendritic cells, and natural killer (NK) cells (Figure 8.1). Lymphocytes have antigen-specific receptors on their surfaces, which are the basis for immunologic specificity. Any given T or B lymphocyte possesses receptors with specificity for a single epitope. When T or B lymphocytes bind antigen they signal the cell to divide to form an expanded clone of cells *(clonal expansion).* B lymphocytes differentiate into plasma cells, which are end cells that produce and secrete antibody. T lymphocytes secrete soluble factors known as *lymphokines* or *interleukins,* which are representatives of a large family of hormonelike molecules, known generically as *cytokines;* these molecules modulate the activities of the cells involved in the immune response. Some T and B cells revert to long lived small lymphocytes responsible for *immunologic memory.* Whereas antibodies and the receptors on B cells recognize epitopes on foreign antigens in their native conformation, T cell receptors recognize small peptides that are formed by the cleavage of viral proteins; they do this only when the foreign peptides are presented to them in association with membrane glycoproteins known as *major histocompatibility complex (MHC) proteins.*

Antigen-Specific Receptors

The antigen-specific receptors on the surface of B lymphocytes are modified immunoglobulin molecules composed of four polypeptides: two light (L) and two heavy (H) chains termed surface immunoglobulin (sIg). They are modified at the C terminus of the H chains to have a transmembrane domain that anchors them in the cell membrane where they serve their receptor function. Prior to primary antigen stimulation the sIg molecules are sIgM; after class switching (see later) the Ig of the class switch becomes the slg antigen-specific receptor.

The T cell antigen-specific receptor (TCR) is quite distinct; it is a two polypeptide heterodimer and although immunoglobulin like, it is encoded by an entirely different set of genes. The two polypeptides of the most common T cell receptors are designated α/β. A second T lymphocyte population bears a different T cell receptor designated *γ/β.*

Specific recognition and binding of either sIg or a T cell receptor to its epitope triggers, by signal transduction across the plasma membrane of the lymphocyte, a wide range of effector processes that attack and remove the invading virus and/or virus-infected cells (Figure 8.1). The resulting cascade of cell-cell interactions and cytokine secretion amplifies the immune response to match the scale of the virus infection and, in addition,

establishes a long-lived memory that enables the immune system to respond more quickly (secondary or anamnestic response) to reinfection with the same virus.

B Lymphocytes

Some of the pluripotent hematopoietic stem cells originating from fetal liver and later from bone marrow differentiate into B lymphocytes in the bursa of Fabricius in birds or its equivalent, the bone marrow, in mammals. They are characterized by the presence of specific antigen-binding receptors on their surface, plus receptors for complement (C3) and receptors for the Fc portion of immunoglobulin. During ontogeny, several hundred inherited V (variable) L and H chain immunoglobulin gene segments undergo somatic recombination. There are also multiple copies of J (joining) gene segments in the case of light chains and J and D (diversity) gene segments in the case of heavy chains that also somatically recombine with V genes. Somatic mutation (see later) also adds to the generation of antibody diversity to yield potentially more than 10^7 unique specificities.

Each individual B lymphocyte and its progeny express a set of immunoglobulin genes that are specific for a single epitope. During development such cells have three possible fates: (1) they may react with a self-antigen and be eliminated, (2) they may be nonviable and be eliminated, or (3) they may react with a foreign antigen and proliferate.

In contrast to T cells, the sIg receptors of B cells recognize antigens in their native and soluble state rather than as peptide-MHC complexes on the surface of cells, hence B cells interact directly with viral proteins or virions. When the particular clones of B cells bearing receptors complementary to any one of the several epitopes on an antigen bind that antigen, they respond, after receiving the appropriate signals from helper T cells, by division and differentiation into antibody-secreting plasma cells.

Each plasma cell secretes antibody of a single specificity, corresponding to the particular V (variable) region of the sIg receptor it expresses. Initially, this antibody is of the IgM class, but somatic genetic recombination (translocation) then brings about a class switch by associating V gene segments with different H chain constant domains. Various cytokines play an important role in isotype switching. Thus, after a few days, IgG, IgA, and sometimes IgE antibodies of the same specificity begin to dominate the immune response. Early in the immune response, when large amounts of antigen are present, antigen-reactive B cells may be triggered even if their receptors fit the epitope with relatively poor affinity; the result is the production of antibody that binds the antigen with low affinity. Later on, when only small amounts of antigen remain, B cells that have evolved by hypermutation in their V region

genes to produce receptors that bind the antigen with high affinity are selected *(affinity maturation)* and the affinity of the antibody secreted increases correspondingly.

T Lymphocytes

T lymphocytes are so named because of their dependence on the thymus for their maturation from pluripotent hematopoietic stem cells. Within the thymus there is positive selection for those cells able to recognize appropriate peptides on the surface of cells and negative selection to eliminate those T cells that recognize self antigens with possible autoimmune disease as a consequence. Only 1 or 2% of the lymphocytes that are produced in the thymus leave and populate the secondary lymphoid tissues. Functionally, T lymphocytes are classified into two subsets: *T helper (Th) lymphocytes,* which are further divided into Thl and Th2 cells, and *cytotoxic T (Tc) lymphocytes (CTLs).* Th cells are generally considered to have a regulatory function and Tc cells a direct effector function, i.e., target cell lysis. Close examination of T cell clones indicates that a single cell type can discharge both regulatory and effector functions and secrete a range of different lymphokines.

T Helper Lymphocytes

T helper cells carry a surface marker known as CD4. They recognize viral peptides in association with class II MHC protein, usually on the surface of an *antigen-presenting cell* (APC). They then secrete cytokines that further activate themselves and subsequently activate other cells, including other Th, Tc, and B lymphocytes, in the process helping Tc lymphocytes to become cytotoxic and B cells to produce antibody.

Thl cells *(inflammatory* T cells) are defined as typically (1) secreting the cytokines IL-2, IFN-γ, and TNF-β [plus granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-3]; (2) mediating delayed type hypersensitivity; and (3) promoting IgG2a production. Th2 cells are defined as typically (1) secreting IL- 4, IL-5, and IL-6 (plus GM-CSF and IL-3); (2) providing help, but not directly mediating delayed-type hypersensitivity responses; and (3) promoting the switch by B cells from IgG2 to IgG1 production in some species. Individual CD4+ T cell clones vary widely in the particular combinations of cytokines they produce; the two dominant patterns described earlier tend to emerge in chronic persisting infections.

Thl cells, i.e., cells expressing CD4 (and some expressing CD8), secrete lymphokines that set up the inflammatory response and greatly augment the immune response by attracting both monocytes/macrophages and other T cells to the site of the viral infection. These same lymphokines are self-activating, causing the cells that secrete them to be activated, to

proliferate, to differentiate, and to secrete other cytokines. This response is the basis for delayed-type hypersensitivity responses that are a recognized part of the pathogenesis of many viral infections. The same response occurs when an antigen is injected intradermallywthis is the basis for skin tests wherein a localized reaction is elicited in previously infected animals.

Some T cells can be demonstrated to down-regulate other T cell and/or B cell responses, which at one time suggested that there may be a further class of cell, once referred to as T suppressor cells. However, it has proved difficult to clone T cells that display this property and the view now is that suppressor functions are subsumed by Th and Tc cells. T cells may suppress various arms of the immune response in a variety of ways; e.g., by direct interaction with lymphocytes or via the production of immunosuppressive cytokines.

Cytotoxic T Lymphocytes

Cytotoxic T lymphocytes carry the CD8 surface marker and possess T cell receptors that recognize viral peptides presented on the surface of virus-infected target cells in association with class I MHC molecules. Activation and subsequent cytolysis of target cells by Tc cells require direct Tc-target cell contact in a manner reminiscent of a synapse (this contact has been called "the kiss of death"). Granules within the cytoplasm of the Tc cell polarize toward the target cell plasma membrane and their contents are released. A monomeric protein called perforin is secreted and polymerizes to form ~17-mer mushroom-shaped structures that insert themselves into the target cell plasma membrane, creating a pore that brings about the lysis of the cell. Perforin is structurally and functionally very similar to C9, which is responsible for complement-mediated lysis (see later). There is also evidence that both Tc and NK cells release lymphocyte-specific granules that have serine esterase activity (granzymes); these granules induce apoptosis in target cells.

The effector response of T cells is generally transient: in certain acute infections, Th and Tc activities peak about 1 week after the onset of viral infection and disappear by 2 to 3 weeks. It is not yet clear whether this is attributable to the destruction of infected cells with consequential removal of the antigenic stimulus or whether it is due to suppressor functions of T cells.

γ/δ T Lymphocytes

An entirely different class of T cells with a different type of T cell receptor composed of polypeptide heterodimers designated γ and δ (rather than the conventional α and β chains) is

found principally in epithelia such as the skin, intestine, and lungs. In mice and humans this classconstitutes a small minority (about 5%) of the T cell population. These cells appear to display a relatively limited immunologic repertoire, reflecting highly restricted V (variable) gene usage. There is emerging evidence, however, that these T cells are involved in the immune responses to viral infections that enter through those portals at which they are localized and there is evidence that they may recognize antigen in a non-MHC-restricted manner. These characteristics suggest that these cells may be more important than previously recognized, but their precise role and importance in specific infections have not been established. In swine, ruminants, and chickens, γ/δ cells represent about 30% of T lymphocytes and are distributed more widely in the body.

Monocytes, Macrophages, and Dendritic Cells

Monocytes, because of their mobility and homing capacity, and macrophages and dendritic cells, because of their key locations in various tissues (e.g., alveolar macrophages in the lung, Kupffer cells in the liver, Langerhans dendritic cells in the skin), are important initiators of the immune response against viral invasion. They are involved early in the host's response: (1) monocytes infiltrate tissue and differentiate to become macrophages, (2) macrophages often become the predominant cell in an infection focus by 24 hours after viral invasion, and (3) dendritic cells carry out afferent immune functions at all body surfaces and in key organs such as lymph nodes, spleen, and liver, where most phagocytic removal of foreign particles occurs. All three cell types bear immunoglobulin Fc and C3b receptors on their surfaces, which promotes the phagocytosis of immune complexes, i.e., virions coated with antibody. By serving as "professional" antigen-presenting cells, these cells exercise a controlling influence over the rapidity, magnitude, and dynamics of the immune response.

Macrophages then also give expression to the efferent limb of the immune response: cytokines secreted by activated T cells bring more monocytes into the infection focus and activate them as they differentiate into macrophages. Activated macrophages have increased chemotactic activity, phagocytic activity, and digestive powers.

Natural Killer Cells

Natural killer (NK) cells are a heterogeneous group of CD3-, CD16+, CD56+ large granular lymphocytes of uncertain lineage that have the capacity to kill virusinfected cells and tumor cells. The basis for their selectivity for virus-infected cells is related to the down-regulation of

the synthesis and expression of MHC class I proteins ("missing self-hypothesis"), which is an early feature of many virus-infected cells. They display no immunologic specificity for particular viral antigens, no memory, no MHC restriction, and no dependence on antibody. They are an important early defense mechanism, as their activity is enhanced greatly within 1 or 2 days of viral infection. Virus-induced activation of NK cells is mediated by interferons, acting synergistically with IL-2, and NK cells themselves secrete several cytokines, including interferon γ and tumor necrosis factor α.

Subcellular Components of the Immune System

Major Histocompatibility Complex

To understand antigen processing and presentation, one must first know something about the structure and intracellular production of MHC proteins. During ontogeny, the positive selection of developing T cells in the thymus by "self" MHC molecules results in mature T cells that can recognize foreign peptides, but only if they are located in the peptide-binding cleft of "self" MHC protein moleculesmnot when they are free in the extracellular space and not when they are associated with non-self MHC molecules (Figure 8.2). This phenomenon is known as *MHC restriction.*

There are two classes of MHC molecules, class I and class II; their structure is shown in Figure 8.3A. The two classes of T lymphocytes namely, Th and Tc, are defined by their interactions with class I or class II MHC proteins, respectively. The pathways used by cells to process and present antigenic peptides to Th and Tc cells are fundamentally different: they are referred to as the *exogenous pathway* for those peptides presented in association with MHC class II molecules and as the *endogenous pathway* for those peptides presented in association with MHC class I molecules.

The MHC is a genetic locus encoding three MHC class I proteins and up to 12 MHC class II proteins, each of which occurs in from 50 to 100 alternative allelic forms. Class I glycoproteins can be expressed on the plasma membrane of most types of cells (neurons are an exception), although they are not expressed constitutively, class II glycoproteins are expressed principally by "professional" antigen-presenting cells. At the distal tip of each class of MHC protein there is a cleft in which the antigenic peptide is bound and presented (Figures 8.3A and 8.3B). Peptide binding is determined by only two or three hydrophobic amino acids, called anchor residues, in a particular peptide and accordingly a particular MHC protein can bind numerous different peptides and some peptides can bind to several different MHC molecules. Peptides presented by class I molecules are usually 9 amino acids long (range 8- to

11-mers), whereas peptides binding to class II proteins range from 13 to 18 amino acids. The peptide-binding cleft in the case of class II is open at the ends whereas that of class I is closed. Specific amino acids that form pockets on the floor of the cleft of any particular MHC protein determine the particular range of peptides that can bind (Figure 8.3B). The peptide-MHC complex is in turn recognized, with absolute specificity, by the T cell receptor of the appropriate clone of T cells. Amino acid residues that do not bind in the MHC cleft are hydrophobic and project outward, inviting recognition by T cell receptors.

Although there is extensive polymorphism of MHC genes between individual animals, any individual has only a limited number of different MHC proteins and any given antigenic peptide binds only to certain MHC molecules. If certain peptide-MHC complexes are important in eliciting a protective immune response to a serious viral infection, animals lacking suitable MHC proteins will be genetically more susceptible to that disease. A further cause of increased susceptibility lies in the possible absence from an individual animal's T cell repertoire of lymphocytes bearing receptors for that particular MHC-peptide complex.

Antigen Presentation by Cells Expressing MHC Class II: The Exogenous Pathway

Only a restricted range of cells, defined as antigen-presenting cells, process and present antigens in association with MHC class II to Th cells. Antigen-presenting cells include dendritic cells, monocyte/macrophages, and, later in the immune response, B lymphocytes. Dendritic cells, including Langerhans cells of the skin and the dendritic cells of lymph nodes and the splenic red pulp and marginal zones, are so named because they form long finger-like processes that interdigitate with lymphocytes, thereby favoring antigen presentation. Unlike dendritic cells, macrophages express relatively low levels of MHC class II protein while resting, but more following activation, particularly by interferon γ. After primary activation, B lymphocytes become important antigen-presenting cells; they are especially important during the latter stages of an infection and during reinfection. Memory B cells serve as very efficient antigen-presenting cells. Viral antigen, or the virion itself, binds to the specific immunoglobulin receptors on the B lymphocyte and is endocytosed, cleaved into peptides that are presented on the surface of the B cell in association with class II MHC proteins. These peptides generally represent different epitopes from those of the same antigen recognized by the B cell for the production of antibody. CD4+ Th cells to which B cells present antigen respond by secreting cytokines that stimulate B cells to make antibody. Such *cognate* interaction, involving close physical association of T and B cells, ensures very efficient delivery of "helper factors" (cytokines) from the Th cell to the relevant primed B cell.

Virus or viral proteins taken up from an external source by antigen-presenting cells are said to enter the exogenous pathway; they pass progressively through early endosomes to late (acidic) endosomes and prelysosomes, where they are cleaved by proteolytic enzymes (Figure 8.4). Some of the resulting viral peptides are able to bind to class II MHC α and β polypeptides to form a trimeric complex that is then transported to the plasma membrane where they are recognized by CD4+ T cells, leading to a Th cell response.

Antigen Presentation by Cells Expressing MHC Class I: The Endogenous Pathway

Almost all cells can be induced to synthesize MHC class I proteins following virus infection; neurons are an exception. After synthesis, MHC class I α- and β-microglobulin polypeptides are transported to the endoplasmic reticulum where they assemble to form a stable complex in association with a molecular chaperone protein called calnexin (Figure 8.4). In virus-infected cells, some viral protein molecules are degraded (cleaved) in the cytoplasm by the large (26S) LMP-containing proteosome complex – these viral proteins are said to enter the endogenous pathway. The resulting peptides are then transported by a transporter molecule (TAP, for transporter associated with antigen processing) into the endoplasmic reticulum, where they assemble with class I MHC molecules to form a stable trimeric complex, which is then exported, via the Golgi complex, to the cell surface for presentation to Tc cells. Both LMP and TAP proteins are coded for within the MHC gene complex.

Cytokines

Cytokines are low molecular weight hormone-like proteins that stimulate or inhibit the proliferation, differentiation, and/or maturation of immune cells (Table 8.1; Figure 8.5). They differ from true hormones in a number of ways, including being produced by nonspecialized cells. Many are produced by T lymphocytes (lymphokines) or monocytes/macrophages (monokines) and serve to regulate the immune response by coordinating the activities of the various cell types involved. Thus, while cytokines are not antigen specific, their production and actions are often antigen driven.

Cytokines may act on the cell that produced them (autocrine) or on cells in the immediate vicinity (paracrine), particularly at cell-cell interfaces, where directional secretion may occur and very low concentrations may be effective, or they may act on cells at more distant locations (endocrine). Responsive target cells carry receptors for the particular cytokines. A single cytokine may exert a multiplicity of biological effects, often acting on more than one type of cell. Moreover, different cytokines may exert similar effects, although

perhaps via distinct postreceptor signal transduction pathways, resulting in synergism (Figure 8.6). There is much redundancy in the actions of cytokines, presumably linked to the need to provide fail-safe defense mechanisms; it is frequently the case that the use of *knockout* mice characterized by the deletion of a single cytokine gene fail to succumb to particular virus challenges.

Cytokines up-regulate or down-regulate the target cell, and different cytokines can antagonize one another. Typically, a cytokine secreted by a particular type of cell activates another type of cell to secrete a different cytokine or to express receptors for a particular cytokine, and so on in a sort of chain reaction (Figure 8.1). Because of the intricacy of the cytokine cascade, it is rarely possible to attribute a given biological event *in vivo* to a single cytokine.

Cytokines can influence viral pathogenesis in a number of ways: (1) augmentation of the immune response, e.g., of cytotoxic T cells by tumor necrosis factor α or by interferon γ, which up-regulates MHC expression; (2) regulation of the immune response, e.g., antibody isotype switching by interleukin 4, 5, 6, or interferon γ; (3) suppression of the immune response, e.g., interleukin 10 inhibits the synthesis of interferon γ; (4) inhibition of viral replication by interferons; and (5) upregulation of viral gene expression.

Table 8.1
Cytokines: Sources, Targets, and Effects[a,b,c]

CYTOKINE	PRINCIPAL SOURCE	PRINCIPAL TARGET/EFFECTS
IL-1α, β	Monocytes/macrophages, B cells, dendritic cells	Proliferation of T cells, IL-2 receptor expression, antibody, fever
IL-2	Th1 cells	Proliferation and differentiation of T cells
IL-3	T cells, NK cells, mast cells	Stem cells and mast cells; hematopoiesis, histamine release
IL-4	Th2 cells, mast cells, NK cells	Proliferation and differentiation of B cells, T cells and macrophages; switch from IgM to IgG1 and IgE; up-regulates MHC class II expression
IL-5	Th2 cells, mast cells	Proliferation and differentiation of B cells and eosinophils; class switch to IgA
IL-6	Th2 cells, macrophages, other cells	Proliferating B cells, plasma cells hepatocytes; promotes differentiation to plasma cells; synthesis of acute-phase proteins (fever)
IL-7	Bone marrow and thymic stromal cells	Proliferation of pre-B i pre-T cells; increases expression of IL-2 and its receptor
IL-8	Macropages, endothelial cells	Chemotaxis, adhesion, and diapedesis of neutrophils
IL-9	Th cells	Some Th cells; acts as a mitogen supporting proliferation in the absence of antigen
IL-10	Th2 cells	Inhibits cytokine production by macrophages and

		hence indirectly reduces cytokine production by T cells
IL-11	Bone marrow stromal cells	Pre-B cells, plasmocytoma cells, megakaryocytes, hepatocytes; growth and differentiation
IL-12	Macrophages, B cells	Acts synergistically with IL-2 to promote differentiation of Tc cells; proliferation of NK cells
IL-13	Th cells	Macrophages; inhibits activation and release of inflammatory cytokines
IL-15	T cells, intestinal epithelium, NK, and activated B cells	Growth and proliferation of intestinal epithelium and T cells; co-mitogen
IL-16	T cells (primarily Tc cells), macrophages, eosinophils	Th cells, chemotaxis, MHC class II expression, suppression of antigen-induced proliferation
TNF-α, β	Macrophages, Th1 cells, Tc, and mast cells	Antiviral; proliferation and differentiation of T cells, B cells, macrophages, NK cells and fibroblasts; fever; cytotoxiy, induces cachexia
TGF-β	Platelets, macrophages, lymphocytes, mast cells	Inhibits proliferation of T cells, B cells, and stem cells and induces increased IL-1 production, thereby inhibiting inflammation and promoting wound healing; induces class switch to IgA
IFN-α, β	Leukocytes, other cells	Antiviral; fever
IFN-γ	Th1, Tc, and NK cells	Antiviral; activation of Th2 cells, macrophages, and NK cells; IgM to Ig2a switch; blocks IL-4-induced class switch to IgE and IgG1; up-regulates MHC and Fc receptors
GM-CSF	T cells, macrophages, endothelium	Hematopoiesis, granulocytes, monocytes

[a]Cytokines are pleiotropic, i.e., single molecules have several distinct and seemingly unrelated phenotypic effects.
[b]Only certain major activities of the best-studied cytokines are listed in this condensed summary.
[c]lL, Interleukin; TNF, tumor necrosis factor; TGF, transforming growth factor; IFN, interferon; CSF, colony-stimulating factor.

Antibodies

The end result of activation and maturation of B cells is the production of antibodies, which react specifically with the epitope identified initially by their receptors. Antibodies fall into four main classes: two monomers, IgG and IgE, and two polymers, IgM and IgA. All immunoglobulins of a particular class have a similar structure, but they vary widely in the amino acid sequences comprising the antigen-binding site, which determines their specificity for a given antigenic determinant. The commonest immunoglobulin found in serum, IgG, consists of two H and two L chains, and each chain consists of a *constant* and a *variable* domain. The chains are held together by disulfide bonds. Papain cleavage separates the molecules into two identical *Fab fragments,* which contain the antigen-binding sites, and an

Fc fragment, which carries the sites for various effector functions such as complement fixation, attachment to phagocytic cells, and placental or colostrum transfer (Figure 8.7).

The immunologic specificity of an antibody molecule is determined by its ability to bind specifically to a particular epitope. The binding site, i.e., the *antibody-binding groove,* is located at the amino-terminal end of the molecule. The variable regions of both L and H chains comprise about 107 amino acids within which there are three hypervariable domains termed *complementary determining regions* interspersed between four conserved regions called *framework regions.* When the peptides fold to form the three-dimensional functional Ig structure, the six complementary determining regions (three each from L and H chains) are located in the antigen-binding groove. It is the variability of the complementary determining regions that accounts for the limitless range of different epitopes recognized by these molecules. (Similar principles underlie the generation of antigenic diversity found in T cell receptor variable regions.)

Antibodies directed against certain epitopes on the surface of virions neutralize infectivity; they may also act as opsonins, facilitating the uptake and destruction of virions by macrophages. In addition, antibody may attach to viral antigens on the surface of infected cells, leading to their destruction following activation of the classical or alternative complement pathways or by arming and activating Fc receptor-bearing cells such as NK cells, polymorphonuclear leukocytes, and macrophages (antibody-dependent cell-mediated cytotoxicity).

Immunoglobulin G

The major class of antibody in the blood is immunoglobulin G (IgG), which occurs as IgG1, IgG2, IgG3, and IgG4 subclasses. Following systemic viral infections, IgG continues to be synthesized for many years and is the principal mediator of protection against reinfection. The subclasses of IgG differ in the constant region of their heavy chains and consequently in biological properties such as complement fixation and binding to phagocytes.

Immunoglobulin M

Immunoglobulin M (IgM) is a particularly avid class of antibody, being a pentamer of five IgG equivalents, with 10 Fab fragments and therefore 10 antigen-binding sites. Because IgM is formed early in the immune response and is later replaced by IgG, specific antibodies of the IgM class are diagnostic of recent (or chronic) infection. Low levels of IgM may be found in

the fetus as it develops immunologic competence in the second half of pregnancy. In fact, because IgM does not cross the placentafrom dam to fetus in any species, the presence of IgM antibodies against a particular virus in a newborn animal may be indicative of intrauterine viral infection.

Immunoglobulin A

Immunoglobulin A (IgA) is a dimer, with four Fab fragments. Passing through epithelial cells, IgA acquires a J fragment (J, for joining, also called the secretory piece) to become *secretory IgA*, which is secreted through the epithelium into the respiratory, intestinal, and urogenital tracts. Secretory IgA is more resistant to proteases than other immunoglobulins and is the principal immunoglobulin on mucosal surfaces and, in some species of animals, in milk and colostrum. For this reason IgA antibodies are important in resistance to infection of the respiratory, intestinal, and urogenital tracts, and IgA antibody responses are much more effectively elicited by oral or respiratory than by systemic administration of antigen, a matter of importance in the design and route of delivery of some vaccines (see Chapter 13).

Immunoglobulins D and E

IgD and IgE are minor immunoglobulin species, accounting for less than 1% of total immunoglobulin levels: (1) most IgD is bound to the surface of B lymphocytes but its function there is not clear; (2) IgE, which is produced by subepithelial plasma cells in the respiratory and intestinal tracts, binds strongly to mast cells where it reacts with certain kinds of antigens (allergens). It stimulates the release of mediators of anaphylaxis such as serotonin and histamine.

Complement

The *complement system* consists of about 30 serum proteins, which can be activated to "complement" the immune response (Figure 8.8). As well as the classical complement activation pathway, which is dependent on the presence of antibody-antigen complexes, there is alsoan alternative antibody-independent pathway. Both are important in viral infections.

Activation of complement by the classical pathway may lead to the destruction of virions or virus-infected cells, as well as to inflammation. Virions are destroyed as a result of opsonization, enhancement of neutralization, or lysis of the viral envelope. Complement activation following interaction of antibody with viral antigens in tissues leads to inflammation and the accumulation of leukocytes. Activation of complement via the

alternative pathway appears to occur mainly after infections with enveloped viruses that mature by budding through the plasma membrane; because it does not require antibody, the alternate pathway can occur immediately after viral invasion of the body.

Immunologic Memory

Following priming by antigen and clonal expansion of lymphocytes, a population of long-lived *memory cells* arises that persists indefinitely. Memory T cells are characterized by particular surface markers (notably CD45RO) and homing molecules *(adhesins)* that are associated with distinct recirculation pathways. When reexposed to the same antigen, even many years later, they respond more rapidly and more vigorously than in the primary encounter. Memory B cells, on reexposure to antigen, also display an *anamnestic (secondary) response,* with the production of larger amounts of specific antibody.

Little is known about the mechanism of the longevity of immunologic memory in T or B lymphocytes in the absence of demonstrable chronic infection. The cells may be restimulated periodically by the original antigenic peptide retained for long periods as peptide-MHC complexes on follicular dendritic cells in lymphoid follicles or by surrogate antigen in the form of either fortuitously cross-reactive antigens or anti-idiotypic antibodies. Memory T and B lymphocytes may survive for years without dividing, until restimulated following reinfection.

Immune Responses to Viral Infection

An overview of the major features of the immune response to a typical acute viral infection is illustrated in Figure 8.1. As shown, at least three phenomena contribute to recovery from infection: (1) destruction of infected cells, (2) production of interferons, and (3) neutralization of the infectivity of virions. Shortly after infection, some virus particles are phagocytosed by macrophages. Except in the case of certain viruses that are capable of growing in macrophages, the engulfed virions are destroyed. Their proteins are cleaved into short peptides that are presented on the surface of the macrophage in association with class II MHC protein. This combination is recognized by the appropriate clones of CD4+ lymphocytes. Thl lymphocytes respond by clonal proliferation and release of lymphokines, which attract blood monocytes to the site and induce them to proliferate and differentiate into activated macrophages, the basis of the inflammatory response. Th2 lymphocytes respond by secreting a different set of lymphokines that assist the appropriate clones of B cells, following binding

of viral antigen, to divide and differentiate into plasma cells. Tc cells are activated following the recognition of viral peptides in association with MHC class I on the surface of infected cells. The Tc response usually peaks at about 1 week after infection, compared with the antibody response that peaks later (2 to 3 weeks). NK cell activity is maximal by 2 days, and interferon activity peaks in concert with the peak titer of virus.

Antibody synthesis takes place principally in the spleen, lymph nodes, gut-associated lymphoid tissues (GALT), and bronchus-associated lymphoid tissues (BALT). The spleen and lymph nodes receive viral antigens via the blood or lymphatics and synthesize antibodies mainly restricted to the IgM class early in the response and IgG subclasses subsequently. However, the submucosal lymphoid tissues of the respiratory and digestive tracts, such as the tonsils and Peyer's patches, receive antigens directly from overlying epithelial cells and make antibodies mainly of the IgA class.

Immune Cytolysis of Virus-Infected Cells

Destruction of infected cells is an essential feature of recovery from viral infections and it results from any of four different processes, involving cytotoxic T cells, antibody complement-mediated cytotoxicity, antibodydependent cell-mediated cytotoxicity, or NK cells. Because some viral proteins, or peptides derived therefrom, appear in the plasma membrane before any virions have been produced, lysis of the cell at this stage brings viral replication to a halt before significant numbers of progeny virions are released.

Antibody-complement-mediated cytotoxicity is demonstrable readily *in vitro* even at very low concentrations of antibody. The alternative complement activation pathway (Figure 8.8) appears to be particularly important in this phenomenon. *Antibody-dependent cell-mediated cytotoxicity (ADCC)* is mediated by leukocytes that carry Fc receptors: macrophages, polymorphonuclear leukocytes, and other kinds of killer cells. NK cells, however, are activated by interferon or directly by viral glycoproteins. They demonstrate no immunologic specificity, but preferentially lyse virus-infected cells. In addition, in the presence of antibody, macrophages can phagocytose and digest virus-infected cells.

Neutralization of Viral Infectivity

In contrast to T cells, B cells and antibody generally recognize epitopes that are *conformational,* i.e., critical residues that make contact with the antigen-binding site of the antibody molecule are not necessarily contiguous in the primary amino acid sequence but are brought into close apposition as a result of the folding of the polypeptide chain(s) to produce

the native conformation. Such B cell epitopes are generally located on the surface of the protein, often on prominent protuberances or loops, and generally represent relatively variable regions of the molecule, differing between strains of that species of virus.

While a specific antibody of any class can bind to any accessible epitope on a surface protein of a virion, only those antibodies that bind with reasonably high affinity to particular epitopes on a particular protein of the outer capsid or envelope of the virion are capable of neutralizing viral infectivity. The key protein is usually the one containing the ligand by which the virion attaches to receptors on the host cell. Mutations in critical epitopes on such a protein allow the virus to escape from neutralization by antibody, and the gradual emergence of mutations in a majority of these epitopes leads to the emergence of a novel strain (genetic/antigenic drift; see Chapter 4).

Neutralization is not simply a matter of coating the virion with antibody nor indeed of blocking attachment to the host cell. Except in the presence of such high concentrations of antibody that most or all accessible antigenic sites on the surface of the virion are saturated, neutralized virions may still attach to susceptible cells. In such cases the neutralizing block occurs at some point following adsorption and entry. One hypothesis is that whereas the virion is normally uncoated intracellularly in a controlled way that preserves its infectivity, a virion-antibody complex may be destroyed by lysosomal enzymes. For example, in the case of picornaviruses, the neutralizing antibody appears to distort the capsid, leading to loss of a particular capsid protein, which renders the virion vulnerable to enzymatic attack. With influenza virus, more subtle conformational changes in the hemagglutinin molecule may prevent the fusion event that precedes the release of the nucleocapsid from the viral envelope.

Recovery from Viral Infection

Cell-mediated immunity, antibody, complement, phagocytes, interferons, and other cytokines are all involved in recovery from viral infectionsmin most cases several of these arms of the immune system act in concert, again depending on the particular host-virus combination.

Role of T Lymphocytes

Lymphocytes and macrophages normally predominate in the cellular infiltration of virus-infected tissues; in contrast to bacterial infections, polymorphonuclear leukocytesm are not at all plentiful. T cell depletion by neonatal thymectomy or antilymphocyte serum treatment increases the susceptibility of experimental animals to most viral infections; for example, T cell-depleted mice infected with ectromelia virus fail to show the usual inflammatory

mononuclear cell infiltration in the liver, develop extensive liver necrosis, and die, despite the production of antiviral antibodies and interferon. Virus titers in the liver and spleen of infected mice can be reduced greatly by the adoptive transfer of immune T cells taken from recovered donors; this process is class I MHC restricted, implicating Tc cells, and is lifesaving.

Another approach used to "dissect" the immune response of experimentally infected inbred mice is to ablate completely all immune potential (using X-irradiation, cytotoxic drugs, etc.), then to separately add back individual components. In a now classic model, virus-primed cytotoxic T lymphocytes of defined function and specificity, cloned in culture and then transferred to infected animals, saved the lives of mice infected with lymphocytic choriomeningitis virus, influenza virus, and several other viruses. Generally, greater protection is conferred by CD8+ T cells than by CD4+ T cells. Moreover, transgenic mice lacking CD8+ T cells suffer higher morbidity and mortality than normal mice following virus challenge. Nevertheless, CD4+ T cells have been shown to play a significant role in recovery, as do the cytokines they secrete, notably interferon γ, and IL-2.

Although T cell determinants and B cell epitopes on surface proteins of viruses sometimes overlap, the immunodominant Tc determinants are often situated on the relatively conserved proteins located in the interior of the virion or on nonstructural virus-coded proteins that occur only in virus-infected cells. Hence T cell responses are generally of broader specificity than neutralizing antibody responses and display cross-reactivity between strains and serotypes. When the gene encoding a protein that fails to elicit any neutralizing antibody (e.g., the NP, M, or NS protein of influenza virus) is incorporated into the genome of vaccinia virus, the T cells elicited following infection with this construct can adoptively transfer complete protection to naive mice against challenge with influenza virus.

Role of Antibody

In generalized diseases characterized by a viremia in which virions circulate free in the plasma, circulating antibody plays a significant role in recovery. Data are not available for veterinary and zoonotic diseases, but there are good data from human diseases: human infants with severe primary agammaglobulinemia recover normally from measles virus infection, but are about 10,000 times more likely than normal infants to develop paralytic disease after vaccination with attenuated poliovirus vaccine. These infants have normal cell-mediated immune and interferon responses, normal phagocytic cells, and a normal complement system,

but cannot produce antibody, which is essential if poliovirus spread to the central nervous system via the bloodstream is to be prevented.

Although there is reasonably good evidence that antibody plays a key role in recovery from picornavirus, togavirus, flavivirus, and parvovirus infections in animals, it does not necessarily follow that antibody is acting solely by neutralizing virions. Indeed it has been shown that certain nonneutralizing monoclonal antibodies can save the lives of mice inoculated with various viruses, presumably by antibody-dependent cell-mediated cytotoxicity, antibody complement-mediated lysis of infected cells, or by opsonization of virions for macrophages.

Lessons from Experimental and Natural Congenital Immunodeficiencies

One approach to understanding the mechanisms involved in recovery from viral infection that is not subject to laboratory artifact is simple clinical observation of viral infections in animals or children suffering from primary immunodeficiencies. For example, athymic *(nude)* mice, which are congenitally deficient in T cells, are highly susceptible to many viral infections. In certain families of Arabian horses there is a total or near total absence of both B and T lymphocytes. Characteristic findings are lymphopenia and hypogammaglobulinemia, which render foals unusually susceptible to infections, especially equine adenovirus 1 infection. There are also several types of B lymphocyte deficiency that predispose newborn animals to very severe infections. Among these are a primary agammaglobulinemia of thoroughbred horses, a selective deficiency in foals of IgM-producing B cells, a deficiency of IgG2-synthesizing cells in some breeds of cattle, and dysgammaglobulinemia in certain lines of White Leghorn chickens. Furthermore, there are conditions characterized by a T cell deficiency due to thymic hypoplasia. Of different origin and significance, but of great practical importance, are secondary agammaglobulinemias and hypogammaglobulinemias in foals, piglets, lambs, and especially calves, associated with the failure of antibody transfer via colostrum (see later).

Immunity to Reinfection

Whereas a large number of interacting phenomena contribute to recovery from viral infection, the mechanism of acquired immunity to reinfection with the same virus appears to be much simpler. The first line of defense is antibody, which, if acquired by active infection with a virus that causes systemic infections, continues to be synthesized for many years, providing solid protection against reinfection. The degree of acquired immunity generally correlates

well with the titer of antibody in the serum. Further, transfer of antibody alone, whether by artificial passive immunization or by maternal antibody transfer from dam to fetus or newborn, provides excellent protection in the case of many viral infections. Thus it is reasonable to conclude that antibody is the most influential factor in immunity acquired by natural infection or by vaccination. If the antibody defenses are inadequate, the mechanisms that contribute to recovery are called into play again, the principal differences on this occasion being that the dose of infecting virus is reduced by antibody and that primed memory T and B lymphocytes generate a more rapid secondary response.

As a general rule, the secretory IgA response is short lived compared to the serum IgG response. Accordingly, resistance to reinfection with respiratory viruses and some enteric viruses tends to be of limited duration. For example, reinfection with the same serotype of parainfluenza virus or respiratory syncytial virus is not uncommon. Moreover, reinfection at a time of waning immunity favors the selection of neutralization-escape mutants, resulting in the emergence of new strains of viruses such as influenza virus by antigenic drift. Because there is little or no cross-protection between antigenically distinct strains of virus, repeated attacks of respiratory infections occur throughout life.

The immune response to the first infection with a virus can have a dominating influence on subsequent immune responses to antigenically related viruses, in that the second virus often induces a response that is directed mainly against the antigens of the original viral strain. For example, the antibody response to sequential infections with different strains of influenza A virus is largely directed to antigenic determinants of the particular strain of virus with which that individual was first infected. This phenomenon, irreverently called "original antigenic sin," is also seen in infections with enteroviruses, reoviruses, paramyxoviruses and togaviruses. Original antigenic sin has important implications for the interpretation of seroepidemiologic data, for understanding immunopathologic phenomena, and particularly for the development of efficacious vaccination strategies.

Passive Immunity

There is abundant evidence for the efficacy of antibody in preventing infection. For example, artificial *passive immunization* (injection of antibodies) temporarily protects against infection with canine distemper, feline panleukopenia, hog cholera, and many other viral infections (see Chapter 13). Furthermore, natural passive immunization, i.e., the transfer of maternal antibody from dam to fetus or newborn, protects the newborn for the first few months of life against most of the infections that the dam has experienced.

Natural Passive Immunity

Natural passive immunity is important for two major reasons: (1) it is essential for the protection of young animals, during the first weeks or months of life, from the myriad of microorganisms, including viruses, that are present in the environment into which animals are born and (2) maternally derived antibody interferes with active immunization of the newborn and must therefore be taken into account when designing vaccination schedules (see Chapter 13).

Transfer of Maternal Antibodies

Maternal antibodies may be transmitted in the egg yolk in birds, across the placenta in primates or via colostrum and/or milk in other mammals. Different species of mammals differ strikingly in the predominant route of transfer of maternal antibodies, depending on the structure of the placenta of the species (Table 8.2). In those species in which the maternal and fetal circulations are separated by relatively few (one to three) placental layers, antibody of the IgG (but not IgM) class is able to cross the placenta, and maternal immunity is transmitted mainly by this route. However, the placenta of most domestic animals is more complex (five to six layers) and, it is hypothesized, acts as a barrier even to IgG; in these species, maternal immunity is transmitted to the newborn via colostrum and, to a much lesser extent, via milk.

Table 8.2
Transfer of Natural Passive Immunity in Mammals

		Number of Placental Layers				
Species	Type of Placentation	Maternal	Fetal	Prenatal Transfer (via placenta)	Postnatal Transfer (via gut)	Translocation Cut-off Time (days)
Cattle, swine, horses	Epitheliochorial	3	3	0	+++	2
Sheep, goats	Syndesmochorial	2 or 3	3	0	+++	2
Dogs, cats	Endotheliochorial	1	2 or 3	+ -	+++	2
Mice, rats	Hemochorial	0	3	++	+	16-20

Different species differ in regard to the particular class or subclass of immunoglobulin that is transferred preferentially to the newborn in colostrum (Table 8.3), but in most domestic animals it is mainly IgG. In cattle and sheep there is a selective transfer of IgG1 from the serum across the alveolar epithelium of the mammary gland during the last few weeks of pregnancy, such that the level of IgG1 in colostrum may reach 40 to 70 g/liter, compared with

about 1.0 to 1.8 g/liter in milk and 13 g/liter in serum. Antibodies of the IgG1 class are important in protection against enteric infections as long as suckling continues.

The selective transfer of IgG from the maternal circulation across the mammary alveolar epithelium is a function of the Fc fragment of the molecule. The very large amounts of IgG present in colostrum are ingested and *translocated* in large intracytoplasmic vesicles by specialized cells present in the upper part of small intestine to reach the circulation of the newborn in an undergraded form. Small amounts of other antibodies (IgM, IgA) present in colostrum or milk may, in some species, also be translocated across the gut, but disappear quickly from the circulation of the young animal. The period after birth during which antibody, ingested as colostrum, is translocated (called the *translocation cutoff* time) is sharply defined and very brief (about 48 hours) in most domestic animals (Table 8.2).

In birds there is a selective transfer of IgG from the maternal circulation; the level of IgG in chicken egg yolk is 25 g/liter compared to 6 g/liter in the maternal circulation. A laying hen produces about 100 g of IgG per year for transfer to yolk, which is about as much as she synthesizes for her own needs. IgG enters the vitelline circulation and hence that of the chick from day 12 of incubation. Some IgG is also transferred to the amniotic fluid and is swallowed by the chick. Close to the time of hatching, the yolk sac with the remaining maternal immunoglobulin is completely taken into the abdominal cavity and incorporated into the wall of the small intestine of the chick.

Table 8.3
Concentrations of Immunoglobulin Classes IgG, IgA, and IgM in Colostrum and Milk of Some Mammalian Species[α]

	Immunoglobulin Concentration (grams/liter)					
	Colostrum			Milk		
Species	IgG	IgA	IgM	IgG	IgA	IgM
Cattle	<u>36-77</u>	4-5	3.2-4.9	<u>1.0-1.8</u>	0.2	0.04
Swine	<u>62</u>	10	3.2	1.4	<u>3.0</u>	1.9
Horse	<u>80</u>	9	4	<u>0.35</u>	0.8	0.04
Dog	2.0	<u>13.5</u>	0.3	0.01	<u>3.6</u>	0.06
Human	0.3	<u>120</u>	1.2	0.1	1.5	0.01

[α]An underbar indicates major components.

Maternal antibody in the bloodstream of the newborn mammal or newly hatched chick is destroyed quite rapidly, with first-order kinetics. The half-life, which is somewhat longer than in adult animals, ranges from about 21 days in the cow and horse through 8 to 9 days in the dog and cat to only 2 days in the mouse. Of course, the newborn animal will be protected against infection with any particular virus only if the dam's IgG contains specific antibodies,

and protection may last much longer than one IgG half-life if the initial titer against that virus is high.

Although the levels of IgA transferred via colostrum to the gut of the newborn animal are considerably lower than those of IgG, it helps to protect the neonate against enteric viruses against which the dam has developed immunity. Moreover, there is evidence that after translocation cut-off immunoglobulins present in ordinary milk, principally IgA but also IgG and IgM, may continue to provide some protective immunity against gut infections. Often the newborn encounters viruses while still partially protected. Under these circumstances the virus replicates, but only to a limited extent, stimulating an immune response without causing significant disease. The newborn thus acquires active immunity while partially protected by maternal immunity.

Failure of Maternal Antibody Transfer

The failure or partial failure of maternal antibody transfer is the most common immunodeficiency disease of domestic animals. For example, between 10 and 40% of dairy calves and up to 20% of foals fail to receive adequate levels of maternal antibody. Mortality during the neonatal period, particularly from enteric and respiratory diseases, is higher than at any other time of life and there is a strong correlation with failure of antibody transfer. Biologic reasons for failure are (1) premature birth of weak animals, (2) delay to first suckle, (3) death of the dam, (4) low colostrum production by the dam, (5) low antibody levels in maternal serum and thus in colostrum, (6) poor maternal instinct, particularly in primiparous dams, (7) premature lactation, (8) too many in the litter, and (9) domination of the weak in the litter by the strong. Of these, the most critical factors are the amount of colostrum available and the delay between birth and first suckling. Poor management also plays a major role by the imposition of unnatural conditions on parturition and early suckling. Especially in large production units, making sure that every newborn receives colostrum is a major challenge. Maternal immunization to protect newborn animals has become an important strategy in veterinary medical practice (see Chapter 13).

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APPENDIX B

AUTOIMUNOSNE BOLESTI

Opće je prihvaćena spoznaja da se u osnovne značajke imunosti ubraja i pojava nazvana prirodnom imunosnom podnošljivošću. To je značajka imunosnog sustava ljudi i životinja da antigene vlastita organizma razlikuju od drugih antigena koji u organizam dospiju iz okoliša i da na njih ne reagiraju imunosnom reakcijom. Takvo imunosno prepoznavanje vlastitih antigena i razlikovanje stranih nedvojbeno je jedno od odlučujućih načela na kojima se zasniva očuvanje ustroja svakog organizma. Međutim, ta važna značajka imunosnih mehanizama katkad može zatajiti, pa se imunosna reakcija različite jakosti pokrene i prema kemijskim biljezima vlastitih staničnih antigena. Takva se pojava naziva autoimunošću i tim se nazivom razumijeva imunosna reakcija usmjerena prema stanicama vlastita tkiva. Teorijski gledano, normalnu imunosnu reakciju s autoimunosnim obilježjima mogu pokrenuti i u nju biti uključeni izmijenjeni ili prikriveni autoantigeni ili je riječ o nenormalnoj imunosnoj reakciji na neizmijenjene (normalne) stanične antigene. Od ta dva osnovna imunopatogenetska mehanizma veće praktično značenje i učestalost ima imunosna reakcija na neizmijenjene antigene prisutne u organizmu. Katkad se autoimunost izjednačuje s bolešću, no tek bi kliničko očitovanje imunosne reakcije prema vlastitim stanicama trebalo nazivati autoimunosnom bolešću. Podjednako bi valjalo nadopuniti i djelomice izmijeniti stav da je autoimunost nepoželjna i za organizam u svakom slučaju štetna imunosna reakcija. Sve je više nepobitnih dokaza da su pojedine autoimunosne reakcije organizma prijeko potrebne za normalno održavanje nekih njegovih fizioloških funkcija. Klasični primjeri su imunosno prepoznavanje vlastitih antigena tkivne podudarnosti na staničnoj površini ili prepoznavanje vlastitih imunoglobulina s pomoću antiidiotipskih reakcija. Ipak, u ovom će se poglavlju pozornost ponajprije usmjeriti na patološka stanja uzrokovana autoimunosnim procesima, tj. opisat ćemo najvažnije autoimunosne bolesti ustanovljene do sada u životinja.

Kada se raspravlja o uzročnicima (poticateljima) autoimunosnih reakcija postoji opća suglasnost da oni mogu biti vrlo različiti i da su često uvijek nepoznati. Također, postoji suglasje da za pojedine autoimunosne bolesti životinja postoje predisponirajući čimbenici koji mogu biti povezani sa spolom, dobi, pasminom, genetskom sklonošću, pojedinim infekcijskim bolestima ili hranidbom.

Najvažniji geni povezani sa sklonošću prema autoimunosnim bolestima u ljudi i životinja jesu oni uključeni u glavni sustav gena tkivne podudarnosti (*major histocompatibility complex genes* ili MHC geni). Pojedine autoimunosne bolesti dovode se u vezu s određenim genom, dok su neke povezane s kombinacijom MHC molekula. Dokazano je da su u ljudi pojedine kombinacije MHC razreda II čvrsto povezane s nekim autoimunosnim bolestima. Tako se, primjerice, HLA DR2 povezuje sa sklonošću sistemskom eritematoznom lupusu i multiploj sklerozi, a kombinacija HLA DR4 s reumatoidnim artiritisom, pemphigus vulgarisom i šećernom bolesti tipa 1.

Među životinjama sklonost autoimunosnim bolestima također postoji. Najbolje je istražena u pasa, a dovodi se u vezu sa životinjama koje pripadaju pojedinim pasminama. Riječ je obično o malobrojnim pasminama unutar kojih su psi srodni pa je među njima neznatan polimorfizam gena sustava tkivne podudarnosti. Sklonost sistemskom eritematoznom lupusu ustanovljena je u pasa s DLA-12, a dijabetes melitus u onih s DLA-A3, A7 odnosno A10.

Kako je u uvodnom dijelu ovog poglavlja navedeno, autoimunosnim bolestima nazivamo kliničko očitovanje stanja koja se osnivaju na autoimunosnim procesima. Brojne su takve bolesti, a promatrano s kliničkog stajališta uobičajeno ih je razvrstavati s obzirom na značajke imunosnih mehanizama i njima zahvaćena tkiva i organe. Na osnovi takva pristupa autoimunosne bolesti dijele se na organospecifične i sistemske (ili organonespecifične), iako takva podjela ima određene nedostatke i mogu joj se uputiti pojedine primjedbe. Temeljni prigovor proizlazi iz činjenice da se specifični mehanizmi autoimunosti katkad međusobno preklapaju i nadopunjuju, pa se kod nekih pacijenata istodobno može razviti nekoliko autoimunosnih bolesti koje zahvaćaju različite organe ili organske sustave. No, bez obzira na iznijeto, podjela autoimunosnih bolesti na organospecifične i sistemske uglavnom je prihvaćena, pa u skladu s njom, nakon prikaza osnovnih imunosnih mehanizama, prikazujemo klinički najvažnije autoimunosne bolesti poznate u životinja.

Promatrano općenito, bez obzira na posebnosti pojedinih bolesti u životinja i njihovo razvrstavanje, sigurno je da su autoimunosne bolesti najbolje istražene u pasa, drugih kućnih ljubimaca i u pokusnih životinja koje često služe kao model za njihovo istraživanje. Razumljivo je da osim njih obolijevaju i druge životinje, ali su zbog praktičnih razloga u tih životinja dobro istražene. Naime, zbog čestih etipatogenetskih podudarnosti takvih stanja u životinja i čovjeka, njihovim sustavnim istraživanjima nastoji se pridonijeti boljem razumijevanju autoimunosnih bolesti u ljudi.

Imunosni mehanizmi nastanka autoimunosti

Premda se nastanak autoimunosnih bolesti u životinja može povezati s različitim pogodovnim učincima i uzrocima, nedvojbeno je da su oni imunosne naravi najvažniji. Kao i pri drugim imunosnim reakcijama i u autoimunosne mogu biti uključeni humorlani ili stanični mehanizmi. Pri pojedinim autoimunosnim bolestima sudjeluju isključivo autoprotutijela ili samo senzibilizirani T-limfociti, a postoje i autoimunosna stanja pri kojima se nadopunjuju oba tipa autoimunosne reakcije. Ne ulazeći podrobnije u objašnjavanje teorijskih spoznaja danas poznatih imunosnih mehanizama nastanka autoimunosnih bolesti, odnosno gubitka imunotolerancije, u najkraćim crtama navodimo njihove osnovne mehanizme odnosno patogenezu autoimunosti.

Reagiranje na vlastite prikrivene antigene

Pojedini tjelesni antigeni u normalnim fiziološkim okolnostima nedostupni su cirkulaciji i imunosnom sustavu organizma, pa cirkulacijski limfociti s njima ne dolaze u dodir. Takvi prikriveni antigeni sa značajkama autoantigena nalaze se u testisima, prednjoj očnoj komorici, središnjem živčanom sustavu, ali i u unutrašnjosti tkivnih stanica, primjerice jetara. Katkad se ipak takvi antigeni oslobode i dospiju u cirkulaciju gdje potaknu autoimunosnu reakciju. Primjerice, pri kroničnoj upali jetara u pasa mogu se ustanoviti autoprotutijela za proteinske antigene jetrene membrane. Imunosna reakcija na prikrivene antigene najčešće se ipak dogodi nakon ozljede određenog organa, ali i infekcija i njome uzrokovana oštećenja tkiva mogu pogodovati oslobađanju inače nedostupnih tjelesnih antigena. Poznato je da se pri tuberkulozi, koju često prate znatna tkivna oštećenja, u serumu oboljele životinje mogu ustanoviti protutijela za brojne tkivne antigene.

Autoimunosne reakcije na prikrivene antigene najčešće su kratkotrajne pa se zbog prolaznosti klinički znatnije i ne očituju odnosno opažaju. Tek kada postoji trajniji podražaj autoantigena, razvije se odgovarajuća autoimunosna bolest.

Poremećaji imunoregulacijskih mehanizama

Imunosne reakcije koje se zbivaju u organizmu redovito su višestruko nadzirane mehanizmima koji zahvaćaju različite razine imunosti. Dodatna važna značajka tih različitih nadzornih mehanizama jest da se oni nadopunjuju, a katkad i preklapaju. Njihova je osnovna zadaća kontrola početka, tijeka, trajanja, intenziteta i završetka svake imunosne reakcije. Taj inače specifičan i djelotvoran nadzor može se katkad poremetiti i omogućiti pokretanje

imunosne reakcije na antigene vlastita organizma, što može prouzročiti određenu autoimunosnu bolest. Poremećaji imunoregulacije mogu zahvatiti sve razine imunosnog nadzora, no njima su ipak najčešće zahvaćeni nadzorni sustavi koji upravljaju djelatnošću pomoćničkih i supresijskih T-limfocita.

Pri pojedinim autoimunosnim bolestima ustanovljen je smanjen broj supresijskih T-limfocita, što omogućuje povećanu djelatnost B-limfocita i tvorbu znatnih količina autoprotutijela. Primjer je sistemski eritematozni lupus čija je radovita značajka pojačana aktivnost B-limfocita, hiperglobulinemija i tvorba protutijela usmjerenih prema različitim antigenima vlastitih organa i tkiva. Autoimunosna reakcija poput opisane razvit će se pri sistemskom eritematoznom lupusu i onda kada je broj supresijskih T-limfocita u fiziološkim granicama, ali je smanjena njihova sposobnost potiskivanja imunosne reakcije.

Nastanak autoimunosnih bolesti može se katkad zasnivati i na zakazivanju regulacijske uloge pomoćničkih T-limfocita. U normalnim okolnostima limfociti te subpopulacije ne potiču autoreaktivne B-limfocite na tvorbu autoprotutijela. Takva imunoregulacijska uloga može im biti poremećena različitim učincima pa pomoćnički T-limfociti potaknu proliferaciju B-limfocita i njihovo lučenje autoprotutijela odgovornih za neku autoimunosnu bolest.

I u ljudi i u životinja zapaženo je da su pojedine autoimunosne bolesti povezane i učestalije u pacijenata koji boluju od tumora limfatičnog tkiva. U njihovoj je etiopatogenezi znakovito da nastaju zbog sloma ili slabljenja imunoregulacijskog nadzora pa su istodobno poremećeni i mehanizmi imunotolerancije. Klasičan primjer je miastenija gravis koja je često povezana s malignim tumorima timusa. Riječ je o autoimunosnoj bolesti koja zahvaća neuromuskularnu spojnicu pa se prilikom ponavljanja pokreta smanjuje mišićna snaga. Ljudima koji boluju od tumora limfatičnog tkiva ustanovljena je višestruko veća učestalost reumatoidnog artritisa.

Imunoregulacijski mehanizmi mogu biti poremećeni i zbog nedjelatnosti pojedinih citokina, što se najčešće odnosi na interleukine 4 i 10 (IL-4 i IL-10) te transformirajući faktor rasta beta (TGF β). Za njih se vjeruje da uz ostale učinke sprječavaju prekomjernu imunosnu reakciju.

Poliklonsko aktiviranje limfocita

Opće je poznato da tvorba protutijela izravno ovisi o suradnji B-limfocita s pomoćničkim T-limfocitima koji su prethodno bili potaknuti odgovarajućim antigenom. Jednako se tako zna da B-limfociti nisu tolerantni prema autoantigenima, ali imunosna reakcija izostane zbog izostanka nužnog podražaja pomoćničkih T-limfocita koji su prema istim autoantigenima

imunotolerantni. Nužno sudjelovanje pomoćničkih T-limfocita pri aktiviranju B-limfocita može u pojedinim prilikama biti zaobiđeno, kao što u rijetkim prigodama mogu biti aktivirani čak i T-limfociti. To se najčešće dogodi pri infekcijama što ih uzrokuju pojedine bakterije ili virusi. Takvo nespecifično ili poliklonsko aktiviranje B- i T-limfocita mogu prouzročiti tzv. Superantigeni. Riječ je o mikrobnim bjelančevinama, često egzotoksinima, koji su iznimno jaki mitogenici, imaju sposobnost limfocitne transformacije i izravno aktiviraju T-limfocite. Dok pri normalnoj imunosnoj reakciji sudjeluje, procjenjuje se, samo 0.001% ili manje cjelokupne populacije T-limfocita, superantigeni sposobni su aktivirati ih čak nekoliko desetaka posto. Tvore ih bakterije poput vrsta *Staphylococcus aureus, Streptococcus pyogenes, Streptococcus dysgalactiae, Streptococcus equi* subsp. *Equi, Yersina pseudotuberculosis* i *Mycoplasma arthritidis.* Podjednak učinak mogu prouzročiti i neki superantigeni kodirani pojedinim ljudskim i životinjskim virusima. Najbolje su istraženi i najpoznatiji: virus bjesnoće, herpesvirusi (citomegalovirus i Epstein-Barrov virus) te retrovirusi (virus mačje imunodeficijencije, virus humane imunodeficijencije i virus tumora mliječne žlijezde mišice). Na nespecifičan način, poliklonski, izravno se vežu na β-podjedinicu receptora T-limfocita, a dovoljne su i iznimno male količine superantigena da potaknu burnu aktivaciju tog dijela populacije limfocita. Kliničko očitovanje uključuje vrućicu, šok i uginuće životinje.

Postoje nagovještaji da superantigeni i njima potaknute imunosne reakcije T-limfocita mogu sudjelovati i pri autoimunosnim bolestima. Dokazom se smatra pokusno uzrokovani autoimunosni encefalomijelitis u miševa. Naime, davanje superantigena SEB (enterotoksin B bakterije *Staphylococcus aureus*) miševima koji su se oporavljali od autoimunosnog encefalomijelitisa uzrokovalo je izravnu stimulaciju autoreaktivnog peptida i brzi povratak simptoma encefalomijelitisa.

Katkad se poliklonski aktiviraju i B-limfociti, a njihovu aktivaciju bez sudjelovanja T-limfocita mogu potaknuti različite tvari. One su također često mikrobnog ili nametničkog podrijetla, a najpoznatiji su bakterijski lipopolisaharidi, PPD-tuberkulin, protein A, neke mikoplazme, dijelovi virusa te proteolitički enzimi. Osobito je dobro istražen protein A koji je 40-60 kD težak sastojak stanične stijenke bakterije *Staphylococcus aureus.* Djelovanjem proteina A ili drugih poliklonskih aktivatora B-limfocita može se potaknuti i tvorba protutijela za antoantigene, a osobito su važna ona razreda IgG.

Usprkos poznavanju mogućnosti poliklonskog aktiviranja B-limfocita i tvorbe autoprotutijela, nijednom se aktivatoru ne može sa sigurnošću pridati odlučujuća uloga pri nastanku neke određene autoimunosne bolesti u životinja. Zbog toga se pretpostavlja da poliklonsko aktiviranje B-limfocita u etiologiji autoimunosnih bolesti u životinja ima tek sekundarno značenje.

Poremećaji apoptoze i autoimunosti

Apoptoza ili programirana stanična smrt iznimno je važan mehanizam kojim se iz organizma uklanjaju stare, islužene, oštećene ili nenormalne stanice i njome se održava ravnovjesje prijeko potrebno za uravnoteženo i usklađeno obnavljanje tjelesnih stanica. Pokreće se unutar različitih fizioloških procesa ili zbog oštećenja koje stanice čine nekorisnima ili opasnima za organizam. To upućuje na tvrdnju da su stanice koje podliježu apoptozi morfološki i biokemijski različite od zdravih stanica, a pokretanje mehanizama programirane stanične smrti može biti vrlo raznoliko. Najvažnije je da se pomoću različitih posrednika pokreću kaskade proteolitičkih enzima kaspaza koje pripadaju skupini cisteinskih proteaza specifičnih za aspartat. Ti enzimi, koji sudjeluju pri apoptozi i njezini su izvršitelji, nalaze se u citoplazmi stanice kao proenzimi i mogu se podijeliti u dvije skupine. Prvu čine inicijacijske kaspaze koje sudjeluju u početnim procesima apoptoze, ali ujedno aktiviraju izvršne kaspaze koje obavljaju proteolitičko cijepanje brojnih i različitih staničnih bjelančevina. Njihova djelatnost očituje se deformiranjem stanica, kondenziranjem kromatina, „pupanjem“ dijelova stanične stijenke, nastankom apoptotskih tjelešaca i fragmentiranjem jezgrine DNA, što sve zajedno uzrokuje staničnu smrt. Stanice zahvaćene apoptozom na kraju brzo fagocitiraju lokalni fagociti, čime su trajno uklonjene iz tkiva. Ukratko opisani mehanizam smatra se iznimno važnim jer sprječava upalni odgovor organizma i druge imunosne reakcije prema vlastitim antigenima oslobođenim iz stanica. Pri uklanjanju apoptotičnih stanica ponajprije sudjeluju makrofagi i dendritične stanice, a uklanjaju mrtvih stanica pridonose i lokalne tkivne stanice poput epitelnih. Upravo ta značajka bitno razlikuje programiranu staničnu smrt od one koja se dogodi pri smrti stanice uzrokovane nekrozom. Pri apoptozi, usprkos dramatičnim biokemijskim promjenama u stanici, njezina cjelovitost ostaje sačuvana i stanični je sastojci ne napuštaju, dok je pri nekrozi raspadanje stanice i oslobađanje spojeva antigenskog potencijala redovito i neizbježno.

Proces programirane stanične smrti može se podijeliti u tri razdoblja. Početna ili inicijacijska faza započinje vanjskim ili unutrašnjim poticajima što pokreće mehanizam receptora smrti i

regulacijskih bjelančevina. Središnjim dijelom procesa apoptoze prevladava enzimska djelatnost kaspaza, a u završnoj fazi, vitalne stanične strukturne bjelančevine su pocijepane i nastupi smrt stanice.

U stanica sisavaca postoje dva osnovna puta pokretanja procesa apoptoze. Vanjskim putem uobičajeno je nazivati programiranu staničnu smrt potaknutu receptorima smrti, dok je značajka unutrašnjeg puta njegova potpuna ovisnost o metaboličkom stanju stanice i signalima u mitohondrijima.

Receptori smrti početno su mjesto na kojem se pokreće vanjski put pokretanja apoptoze, a pripadaju površinskim staničnim receptorima za faktor tumorske nekroze. S unutrašnje strane stanične stjenke dospijevaju u citoplazmu i na njima se nalaze domene smrti (DD od *death domain*). Vezanjem liganda na odgovarajući receptor smrti nastupi trimerizacija receptora i nastanak signalnog kompleksa koji inducira aktiviranje kaspaza i posljedičnu staničnu smrt.

Unutrašnjim putem programirane stanične smrti upravlja Bcl-2 porodica bjelančevina. Taj put najčešće pokreće nedostatak hormona rasta, stres stanice ili učinak citotoksičkih lijekova poput protutumorskih kemoterapeutika. Takvi učinci aktiviraju molekule koje potiču apoptozu ili inaktiviraju bjelančevine iz Bcl-2 porodice koje djeluju protuapoptotski. Na taj se način promijeni propusnost mitohondrija i iz njega se oslobađa citokrom c koji u kompleksu poznatom kao apoptosom aktivira kaspazu-9 odgovornu za pokretanje kaskade izvršnih kaspaza. Krajnji učinak njihova djelovanja jest uništenje i smrt stanice.

Kao i pri regulaciji odnosa među stanicama drugih tkiva, apoptoza je iznimno važan regulacijski mehanizam u nadzoru nad stanicama imunosnog sustava, osobito nad populacijama limfocita. Apoptoza osigurava uklanjanje aktiviranih limfocita nastalih tijekom imunosne reakcije. Smrt limfocita je brižno nadzirana i obično nastaju ozbiljne posljedice u prilikama kada se takav nadzor naruši. U prigodama kada izostane pokretanje apoptoze u limfocita mogu se razviti autoimunosni procesi i stvoriti autoimunosne bolesti. Pojedini su među njima posljedica zatajenja apoptoze ili se u njihovoj patogenezi predmnijeva da takvi mehanizmi sudjeluju.

Poremećaji apoptoze mogu prouzročiti izostanak nadzora nad trajanjem i završetkom imunosnog odgovora i nadzora nad aktiviranim limfocitima. U drugim prilikama, pokrenuti ali poremećeni mehanizmi apoptoze mogu osloboditi autoantigene i učiniti ih dostupnima imunosnim mehanizmima. Iako nedostatnosti programirane stanične smrti mogu potaknuti

autoimunosne mehanizme, i drugi regulacijski mehanizmi moraju zatajiti da bi se razvila određena autoimunosna bolest, a poznato je da je potrebna i genska sklonost za njihovo nastajanje. Najpoznatija je nasljedna nedostatnost sastojka Clq komplementa koji ima važnu ulogu pri uklanjanju apoptotičnih stanica.

Nekoliko je autoimunosnih bolesti za koje se pouzdano zna ili postoji osnovana sumnja da u njihovoj etiopatogenezi sudjeluju i mehanizmi poremećene apoptoze. To se ponajprije odnosi na sistemski eritematozni lupus, autoimunosni limfoproliferativni sindrom, multiplu sklerozu i reumatoidni artritis. Istraživanja na osnovi kojih su ostvareni rezultati koji upućuju na povezanost tih autoimunosnih bolesti i poremećaja apoptoze ponajprije se odnose na te bolesti u ljudi, ali i istraživanja na životinjama pridonijela su takvim spoznajama.

Sistemski eritematozni lupus, kroničnu bolest čija je značajka prisutnost niza autoprotutijela, osobito onih protiv jezgrinih sastojaka, karakteriziraju patološke promjene u različitim organima poput kože, bubrega i u krvnim žilama. Smatra se da su pri nastanku te autoimunosne bolesti upravo apoptotične stanice izvorište staničnih autoantigena. Mogućim razlozima neučinkovitog uklanjanja apoptotičnih stanica drže se nedjelatna fagocitoza makrofaga te poremećena djelatnost pojedinih sastojaka sustava komplementa, osobito Clq, C3 i C4. To je ustanovljeno u ljudi koji boluju od sistemskog eritematoznog lupusa, ali i u laboratorijskih miševa odgovarajućih sojeva. Na mišjem modelu ustanovljeno je da i poremećena apoptoza limfocita zbog nedjelotvornih mehanizama unutrašnjeg puta aktivacije programirane stanične smrti može uzrokovati bolest koja u tih pokusnih životinja nalikuje sistemskom eritematoznom lupusu.

Reumatoidni artritis je još jedna važna autoimunosna bolest ljudi i životinja za koju se vjeruje da poremećaji apoptoze imaju važnu ulogu u etiopatogenezi. Infiltracija upalnih stanica uzrokuje teška oštećenja sinovijske ovojnice te postoji naglašena hiperplazija sinovijskih stanica i sekrecija citokina koji potiču upalu (IL-6, TNF-α). U pokusnih miševa s reumatoidnim artritisom dokazana je hiperproliferacija pomoćničkih CD4+ T-limfocita što može dodatno potaknuti nakupljanje autoreaktivnih T-limfocita.

Idiotipske križne reakcije

Postoje dokazi da križne reakcije između idiotipova na protutijelima za neke viruse i receptora za te viruse na stanicama domaćina potaknu autoimunosnu reakciju zbog uplitanja antiidiotipskih protutijela. Iako postoje i druge spoznaje o mogućoj ulozi virusa pri pokretanju

autoimunosnih procesa, niti njima se, za sada, sa sigurnošću ne može pridati primarno značenje u etiologiji autoimunosnih bolesti u životinja.

Autoimunosne bolesti nakon cijepljenja

Kao i u humanoj medicini, tako je i u veterinarskoj medicinskoj praksi sve više pouzdanih dokaza da se pojedine autoimunosne bolesti mogu dovesti u vezu s aktivnom imunizacijom i primjenom pojedinih cjepiva. Već četrdesetak godina zna se da cijepljenje može u ljudi potaknuti pojavu neke autoimunosne bolesti. Iako se one relativno rijetko objektivno mogu dokazati kao najizravnija posljedica cijepljenja, vjeruje se da obično nastanu u osoba s genskom sklonošću prema autoimunosnim bolestima. Najbolje je istražena i dokumentirana masovnija pojava Guillan-Barréova sindroma u ljudi koji su sredinom sedamdesetih godina prošloga stoljeća u SAD-u bili cijepljeni protiv influence, cjepivom izrađenim od soja virusa svinjske influence A/New Jersey/76, subtipa H1N1. Tu bolest prati pareza pa čak i paraliza koja je posljedica upalnih promjena preifernih živaca potaknuta autoimunosnim mehanizmima.

Jedno se vrijeme vjerovalo da su takve nuspojave cijepljenja ponajprije vezane uz virusna cjepiva poput onih protiv influence, bjesnoće, zaušnjaka (mumpsa), rubeole, poliomijelitisa i hepatitisa B, no dokazano je da takva opasnost prijeti i nakon primjene cjepiva koja sadrže bakterijske antigene. To se posebice odnosi na cjepivo protiv tuberkuloze (BCG) i tetanusa (toksoid).

U posljednje su vrijeme sve učestalija izvješća o autoimunosnim bolestima koje se dovode u vezu s cijepljenjem životinja. To osobito vrijedi za pse koji se od svih domaćih životinja najčešće cijepe i za njih postoje vrlo različita cjepiva. Općenito se može ustvrditi da sve više jača i svijest da su brojna cijepljenja, primjerice, pasa nepotrebna i upravo se njima tumače različite nuspojave među kojima one na autoimunosnoj osnovi čine tek jedan manji dio. Pri tome se osobito optužuju različita polivalentna cjepiva koja katkad sadrže antigene pet pa i više uzročnika različitih psećih infekcijskih bolesti ili one vakcine koje sadrže pojedine potentnije adjuvanate. Osobita opasnost za razvitak takvih neželjenih reakcija postoji pri primjeni cjepiva sa živim modificiranim virusima. Cijepljenje takvim cjepivima može prouzročiti tvorbu niza različitih autoprotutijela. Ona se mogu razviti u kratkom vremenu nakon cijepljenja, ali i nakon nekoliko mjeseci. Obično im se titar brzo snizi, a nije poznato mogu li znatnije oštetiti ciljna tkiva i prouzročiti klinički izražene znakove bolesti. Kao primjer mogu poslužiti autoprotutijela za tiroglobulin koja se pojave nakon cijepljenja protiv

bjesnoće. Nije poznato mogu li ona značajnije oštetiti štitnu žlijezdu i prouzročiti autoimunosni tireoiditis, no razina tih protutijela u serumu može biti visoka.

Najbolje istražena i opisana autoimunosna bolest koja nastaje kao posljedica cijepljenja pasa jest autoimunosna hemolitička anemija. U jednom je sustavnom istraživanju dokazana u šezdesetak pasa, a njezinoj je pojavi, u znatnog dijela njih, prethodilo redovito godišnje cijepljenje. Ono je provedeno otprilike mjesec dana prije pojave autoimunosne hemolitičke anemije, a vrste i tipovi cjepiva bili su različiti. S obzirom na to da je autoimunosna hemolitička anemija vrlo teška autoimunosna bolest s visokom smrtnošću, ta se nuspojava smatra ozbiljnom posljedicom cijepljenja pasa.

Osim u pasa, u posljednje su vrijeme opisane i neke nuspojave cjepiva u mačaka, osnovane na autoimunosnim mehanizmima. Pri istraživanjima kroničnih bolesti bubrega, koje su u mačaka vrlo česte, dokazano je da su bubrežna oštećenja autoimunosne etiologije. Promjene su obično tako izražene da prouzroče zatajenje oba bubrega i najizravnije se mogu smatrati uzrokom smrti životinje. Razvitak promjena povezuje se s primjenom virusnih cjepiva, a među njima ponajprije onima izrađenim na staničnim kulturama izrađenim od mačjeg bubrežnog tkiva. Naime, mnogi se vakcinalni sojevi virusa od kojih se izrađuju cjepiva za mačke uzgajaju upravo na takvim staničnim kulturama. Pri tzv. žetvi virusa ne može se izbjeći prisutnost bjelančevina koje potječu od bubrežnih stanica i one postaju sadržajem cjepiva. Razumljivo je da će mačke imunizirane takvim cjepivima, osim na prisutnost virusnih antigena, reagirati i na antigene bubrežnih stanica, a stvorena će protutijela oštetiti bubrežne stanice cijepljenih mačaka.

Autoimunosne reakcije nastale nakon cijepljenja ne moraju uvijek biti nepoželjne. Naprotiv, u novije se vrijeme na autoimunosnim, ali i nekim drugim mehanizmima, osnivaju postupci kojima se smanjuje plodnost životinja cijepljenim tzv. antifertilitetnim cjepivima. Ona najčešće sadrže heterologne hormonske antigene koji potaknu tvorbu autoprotutijela za vlastite hormone, koja na autoimunosnoj reakciji poremete tvorbu spolnih hormona cijepljene životinje ili mijenjaju njezino spolno ponašanje. Na taj način može se postići imunokastracija muških svinja, pasa ili lisica. U tovnih svinja takvim se postupkom spriječi nepoželjan miris kakav ima meso zaklanih nekastriranih muških životinja, a u pasa i lisica tako se nadzire veličina njihove populacije i sprječava nekontrolirano i nepoželjno razmnožavanje. Svinje i psi mogu se aktivno imunizirati cjepivom protiv gonadotropin oslobađajućeg hormona (GnRH) čije inaktiviranje poremeti odlučujući dio hormonskog nadzora spolnog ciklusa. Pse

oba spola moguće je imunizirati i luteinizirajućim hormonom druge biološke vrste (ovčjim ili goveđim), a nastala će autoprotutijela i u ženskih i u muških životinja poremetiti fiziološke spolne funkcije. U muških životinja atrofiraju spolne žlijezde, dok je u kuja poremećen spolni ciklus. U oba slučaja posljedica je njihova neplodnost.

Organospecifične autoimunosne bolesti

Naziv te skupine autoimunosnih bolesti jasno upućuje da je riječ o bolestima koje ponajprije zahvaćaju pojedine organe i organske sustave i njih obrađujemo u ovom poglavlju. Pri tome napominjemo da redoslijed njihova iznošenja nije određen važnošću ili učestalošću pojedine bolesti, već je usklađen s organima ili organskim sustavima u kojima se autoimunosna oštećenja pojavljuju.

Autoimunosne kožne bolesti

Tu važnu skupinu autoimunosnih bolesti najčešće obilježava pojava mjehura (vezikula i bula) na koži oboljelih životinja. To se posebice odnosi na skupinu pemfigusa i pemfigusu sličnih bolesti, a pri drugima, glavne su značajke dermatitisi različite jakosti, ulcerozne i krustozne promjene na koži ili opadanje dlake uzrokovano autoimunosnim procesima.

SKUPINA PEMFIGUSA

Pemfigus (*pemphigus*) nije jedinstvena autoimunosna bolest, već se tim kliničkim pojmom zapravo označuje nekoliko sličnih bolesti koje imaju autoimunosnu osnovu i kojima je zajedničko pojava mjehura (vezikula i bula) na koži i sluznicama. Pemfigus se može nazvati i pemfigus kompleksom, jer ga čine: (1) pemfigus vulgaris, (2) pemfigus foliaceus, (3) pemfigus eritematozus i (4) pemfigus vegetans. Iako učestalost pojedinih pemfigusa u domaćih životinja nije podjednaka, općenito je riječ o rijetkim autoimunosnim bolestima, od kojih su neke poznate u pasa, mačaka, konja i koza. Kao i većina drugih autoimunosnih bolesti, i pemfigus je najsustavnije istražen u pasa, a jedan od osnovnih razloga je taj što su u pasa poznati svi oblici te bolesti. Najbolje je ipak istražen pemfigus vulgaris (iako u pasa nije najučestaliji), pa se tom „modelu“ unutar cijeloga kompleksa pemfigusa pridaje najveća pozornost.

TABLICA 12-1. SKLONOST PASA POJEDINIH PASMINA NAJVAŽNIJIM ORGANOSPECIFIČNIM I SISTEMSKIM AUTOIMUNOSNIM BOLESTIMA											
PASMINE	LT	DMI	ALP	MAS	UDS	AIHA	AITP	MG	SLE	DEL	DM
velika doga	+										
Borzoi	+										
Doberman	+										
zlatni retriver	+				+			+			
Jazavčar	+							+			
koker španijel	+					+	+				
mali šnaucer	+										
irski seter	+				+	+			+		
Bigl	+								+		
staroengleski ovčar	+				+	+	+				
Samojed		+			+	+					
njemački ovčar	+		+	+				+	+	+	
Bokser				+							
bernski planinski pas				+							
sibirski haski					+					+	
Bernardinac					+						
australski ovčar					+						
šetlandski ovčar					+				+	+	+
veliki japanski pas					+		+				
minijaturni jazavčar						+					
škotski terijer						+	+				
Vižla						+					
Pudl							+		+		
kratkodlaki poenter							+				
škotski ovčar			+						+	+	+

LT = limfocitni tireoiditis
DMI = dijabetes melitus ovisan o inzulinu
ALP = atrofični limfocitni pankreatitis
MAS = meningitis-arteritis osjetljiv na steroide
UDS = uveodermalni sindrom
AIHA = autoimunosna hemolitička anemija
AITP = autoimunosna trombocitopenija
MG = miastenija gravis
SLE = sistemski erimatozni lupus
DEL = diskoidni eritematozni lupus
DM = dermatomiozitis

Kod pasa pemfigus vulgaris obično nastaje kod životinja srednje dobi (između pet i šest godina), neovisno o spolu ili pasminskoj pripadnosti. Bolest se očituje pojavom znakovitih vezikula na koži i sluznicama ispunjenim bistrom tekućinom. Vezikule naknadno pucaju, na njihovu mjestu ostaju plitka oštećenja ili čak čirevi. Promjene su naročito česte na prijelazu kože u sluznicu (usnice, očni kapci, prepucij, anus), a također na jeziku i sluznici usta. Pri kroničnom tijeku bolesti česte su lokalne sekundarne bakterijske infekcije, koje mogu prijeći u septikemiju, pa i o tome ovise klinička slika te opće stanje pacijenta. Pri pregledu, pri prelasku jagodicom prsta po koži bolesnog psa može se zapaziti Nikolskvjev znak, koji se očituje time da se površinski sloj kože na većoj površini odvoji od svoje podloge.

Sva opisana zbivanja posljedica su autoimunosnih procesa koji započinju tvorbom autoprotutijela (uglavnom IgG) za površinske stanične antigene na keratocitima i/ili antigene međustanične tvari u koži ili sluznicama. Antigeni odgovorni za nastanak pemfigusa nisu još uvijek najpreciznije određeni, ali se vjeruje da glavnu ulogu ima glikoprotein na staničnoj površini. Daljnji slijed imunopatogenetskih zbivanja takav je da nastala autoprotutijela dospiju u epidermis i vežu se za odgovarajući antigen na keratocitima. Na taj način potakne se oslobađanje aktivatora plazminogena, koji prevede plazminogen u plazmin. Posljedica je njegova djelovanja akantoliza, odnosno gubitak međustanične kohezije, pa je tako omogućen nastanak karakterističnih mjehura. Svojedobno se sigurnim smatralo da i komplement ima važnu ulogu u patogenezi pemfigusa, ali rezultati pokusa provedenih u uvjetima *in vitro* nisu potvrdili to mišljenje. Zbog toga se može ustvrditi da je uloga komplementa u nastanku pemfigusa još uvijek dvojbena.

Za pemfigus vulgaris bitna je karakteristika, koja se histološki može dokazati, da se akantoliza i razdvajanje epidermisa zbivaju iznad stanica temeljnog sloja, pa red stanica toga sloja redovito ostane na dnu oštećene površine kože. Osim na osnovi te histološke značajke, pemfigus vulgaris može se dijagnosticirati i imunološkim postupcima. Vrlo je prikladna izravna imunofluorescencija, kojom se dokazuje taloženje imunoglobulina u međustaničnim prostorima epidermisa, dok je neizravna imunofluorescencija u životinja ograničenoga dijagnostičkog značenja. Razlog je u tome što su rijetki psi s pemfigusom koji imaju znatan titar specifičnih serumskih autoprotutijela.

Točno dijagnosticiranje i međusobno razlikovanje pemfigusa u pasa naročito je važno s prognostičkog stajališta. Naime, za životinje koje imaju pemfigus vulgaris prognoza bolesti uglavnom je loša, dok je kod ostalih oblika pemfigusa u načelu povoljnija. Pemfigus

foliaceus, koji je u pasa češći od pemfigus vulgarisa, blaža je bolest, a zbog diferencijalnodijagnostičkih razloga može se spomenuti da tu autoimunosnu bolest također karakterizira akantoliza, ali se mjehuri pojavljuju odmah ispod rožnatog sloja epidermisa. Osim toga, promjene vrlo rijetko zahvaćaju sluznice, a one na koži obično su opsežne. Obuhvaćaju otpadanje dlake i češće se nalaze na koži glave, na uškama i njušci. Inače, izravnom imunofluorescencijom dobije se podjednak nalaz kao pri pemfigus vulgarisu.

Pemfigus eritematozus sliči blažem obliku pemfigus foliaceusa i obično zahvaća kožu lica i vrata. Simptome bolesti pojačava sunčevo svjetlo, a na osnovi imunosnih karakteristika pemfigus eritematozus sliči sistemskom eritematoznom lupusu i pemfigus foliaceusu. Pemfigus vegetans je dosad najrjeđe ustanovljen unutar cijelog kompleksa, a u pasa klinički, imunološki i histološki najviše nalikuje na pemfigus vulgaris.

Bez obzira na oblik pemfigusa, životinje se liječe ponajprije glukokortikoidima, koji se najčešće moraju kombinirati s antibioticima. Uobičajeno je da su u početku liječenja doze glukokortikoida visoke, a nakon postignutog ublažavanja simptoma bolesti doza odgovarajućeg pripravka smanji se. Liječenje je redovito dugotrajno, traje tjednima, pa i mjesecima, a mogu se pojaviti i neželjene posljedice imunosupresijskog učinka glukokortikoida. Zbog takve mogućnosti životinje moraju biti pod stalnim nadzorom, a popratne pojave liječenja osnovne bolesti mogu biti raznolike i katkad vrlo teške (infekcije, degeneracija vitalnih organa, krvarenja i drugo). Osim glukokortikoida, mogu se primijeniti i drugi pripravci (npr. soli zlata), ali je njihov učinak općenito slabiji.

Kao što je već spomenuto, pojedini oblici pemfigusa zabilježeni su i u drugih domaćih životinja. U mačaka su poznati svi oblici osim pemfigus vegetansa, a najučestaliji je pemfigus foliaceus. Liječenje mačaka koje boluju od pemfigusa visokim dozama glukokortikoida nije osobito uspješno i djelotvorno je tek u šezdesetak posto tako liječenih životinja. Katkad se vrlo povoljan ljekoviti učinak može postići primjenom pripravaka koji sadrže soli zlata. U konja je pemfigus foliaceus najčešća autoimunosna bolest uopće, a taj oblik pemfigusa zabilježen je i u koze.

BULOZNI PEMFIGOID

Riječ je o autoimunosnoj bolesti koja se naročito očituje promjenama na koži i za koju je također znakovita pojava mjehurastih izbočenja epidermisa, tj. pojava bula ili vezikula. Na

osnovi kliničkih znakova bulozni pemfigoid vrlo nalikuje na pemfigus vulgaris, ali se imunopatogenetski i patohistološki od njega jasno razlikuje.

Patogeneza buloznog pemfigoida također se osniva na djelovanju autoprotutijela, pretežno IgG razreda, međutim, ona su usmjerena prema bjelančevinskim sastojcima temeljne membrane koja se nalazi na spoju epidermisa i korijuma. Vezanjem autoprotutijela za tip XVII kolagena na odgovarajuće antigene temeljne membrane aktivira se sustav komplementa i na tom se mjestu razvije jaka upalna reakcija s infiltracijom monocita i eozinofilnih leukocita te odlaganjem fibrina. Posljedica je svih tih imunopatogenetskih zbivanja nastanak mjehura, koji su redovito smješteni ispod epidermisa. Njihovim pucanjem nastanu oštećenja i znakoviti čirevi.

Među domaćim životinjama od buloznog pemfigoida najčešće obole psi, a skloniji su oni koji pripadaju pasminama koli, doberman i šetlandski ovčar. O toj bolesti u mačaka, svinja i konja postoje tek pojedinačna izvješća. U pasa su promjenama obično zahvaćeni dijelovi kože na uškama, glavi, vratu, u pazuhu i po trbuhu. Pojava vezikula ili bula česta je i na sluznici usta, a opće stanje životinje ovisi o proširenosti promjena, njihovoj intenzivnosti i sekundarnim bakterijskim infekcijama.

Bulozni pemfigoid se osim histološkom pretragom može dijagnosticirati i izravnom imunofluorescencijom, kojom se dokazuju taloženje imunoglobulina i prisutnost komplementa uzduž temeljne membrane. U promijenjenu tkivu prevladava IgG, dok je prisutnost IgA i IgM izrazito manja.

Načela liječenja životinja koje boluju od buloznog pemfigoida podjednaka su onima koja se primjenjuju pri liječenju pemfigusa. Pripravci glukokortikoida također su lijekovi izbora, a i antimikrobno liječenje obično je prijeko potrebno zbog prisutnosti sekundarnih bakterijskih infekcija. Pri blagim i lokaliziranim promjenama moguće je zadovoljavajuće rezultate liječenja ostvariti i malim dozama glukokortikoida, iako primjenu tih lijekova uvijek prati opasnost od neželjenih posljedica. Za pacijente s težim oblicima buloznog pemfigoida prognoza bolesti uglavnom je nepovoljna.

BULOZNA DERMATOZA S LINEARNIM ODLAGANJEM IgA

Bulozna dermatoza s linearnim odlaganjem IgA, poznata i pod imenom linearna IgA dermatoza, pripada skupini autoimunosnih bolesti kože ili katkad sluznica koje klinički otkriva pojava subepidermalnih mjehura. Riječ je o rijetkoj bolesti u ljudi, a među životinjama

vrlo slična bolest dokazana je i opisana u pasa. Za razliku od buloznog pemfigoida pri kojem autoprotutijela prepoznaju transmembranski kolagen tipa XVII (bjelančevina BPAG2), pri buloznoj dermatozi s linearnim odlaganjem IgA, autoprotutijela te klase usmjerena su prema antigenu LAD-1 koji je ekstracelularni oblik kolagena tipa XVII. Pri tome je karakterističan linearni depozit IgA u području bazalne membrane, iako se na tom mjestu odlagati mogu i autoprotutijela imunoglobulinskog razreda G.

U samo nekoliko slučajeva bulozna dermatoza s linearnim odlaganjem IgA objektivno je dokazana u odraslih pasa, a klinički se očitovala erozivnim, ulcerativnim i krustoznim promjenama na koži lica i nogu te na sluznici usta. Također su ustanovljene pukotine u bazalnoj membrani bez upale i s umjerenom infiltracijom neutrofilnih leukocita. Dokazano je i odlaganje imunoglobulina (IgA i IgG) u zonu bazalne membrane i cirkulirajućih protutijela za topljivi protein LAD-1.

STEČENA BULOZNA EPIDERMOLIZA

Najvažnije imunološke značajke te rijetke autoimunosne kožne bolesti jesu linearna odlaganja IgG i IgA te pojedinih sastojaka sustava komplementa u području bazalne membrane. Specifična su za antigen kolagena tipa VII koji sačinjava vlakna kojima je dermis povezan s epidermisom. U tkivo odložena cirkulirajuća protutijela mogu se dokazati različitim imunološkim postupcima. Prikladni postupci za njihovo dokazivanje su pojedine imunoenzimske metode i imunobloting, a specifična mjesta njihova odlaganja mogu se precizno ustanoviti imunoelektronskom mikroskopijom.

Osim u ljudi, stečena bulozna epidermoliza do sada je u prirodnim okolnostima ustanovljena samo u pasa. U pokusnim uvjetima, serumom pacijenata koji je sadržavao specifična protutijela prenijeta je na odrasle imunokompetentne miševe.

U prirodnim okolnostima stečenu buloznu epidermolizu u pasa karakterizira pojava brojnih mjehura i ulceroznih promjena na koži i sluznicama uz izraženu urtikariju. U kasnijoj fazi bolesti nastaje nekroza i opsežne bakterijske infekcije. Upravo su bakterijske infekcije glavna prijetnja pri imunosupresijskom liječenju koje načelno može imati povoljan učinak.

ALOPECIJA AREATA

Alopecija areata ili limfocitni folikulitis je autoimunosna kožna bolest koja je do sada opisana u čovjeka i nekoliko različitih životinjskih vrsta. Među životinjama najčešće je ustanovljena u

pojedinih pasmina pasa, a to su ponajprije: jazavčar, doberman, njemački ovčar, madžarska vižla, minijaturni pudl, ali nisu iznimka ni psi križanci. Osim u pasa, uglavnom pojedinačni slučajevi opisani su u sijamskih mačaka, goveda holsteinske pasmine, konja, nekoliko vrsta primata te pojedinih sojeva laboratorijskih miševa i štakora. Bolest karakterizira pojava većih ili manjih, uglavnom pravilnih, okruglih ili ovalnih bezdlačnih mjesta. Ona su najčešće oštro ograničenih rubova i mogu biti razmještena na različitim dijelovima tijela. Koža bezdlačnog područja nije upalno promijenjena ili je upala tek neznatna. Iznimno su rijetki generalizirani slučajevi kad je zahvaćeno cijelo životinjsko tijelo.

Autoimunosni procesi usmjereni su prema stanicama i keratinu dlačnih folikula, a osim imunoglobulina G i M specifičnih za te dijelove i sastojke kože, u pasa je dokazana infiltracija T-limfocita s biljezima CD4 i CD8. Pretpostavlja se da u patogenezi sudjeluje i sastojak C3 komplementa.

Liječenje životinja koje boluju od alopecije areate obično je povoljnije što je zahvaćeno područje manje i ako ono započne ubrzo nakon pojave bolesti. Pripravcima s glukokortikoidima postižu se najbolji terapijski učinci u pasa, primata, konja, miševa i štakora premda se bolest katkad može vratiti nakon prestanka liječenja.

U pokusima provedenima na miševima također je dokazana povoljna djelotvornost mekloretamina koji inhibira učinak faktora tumorske nekroze, interleukina 12 i gamainterferona.

Autoimunosne bolesti lokomotornog sustava

Autoimunosne bolesti lokomotornog sustava u životinja ustanovljene su do sada kod nekoliko vrsta domaćih i divljih životinja, no najveću važnost imaju u kućnih životinja, osobito pasa. Iako je riječ o rjeđim bolestima, one mogu biti vrlo teške i neugodne oboljelim životinjama, ali i zahtjevne njihovim vlasnicima.

MIASTENIJA GRAVIS

Miastenija gravis jest bolest s neuromuskularnim poremećajima, što se klinički jasno očituje izrazitom mišićnom slabošću. Riječ je o slabosti pojedinačnih voljnih mišića ili mišićnih skupina, a nastaje zbog poremećene neuromuskularne provodljivosti. Među domaćim životinjama miastenija gravis je opisana u pasa i mačaka, uz napomenu da je ta bolest bez dvojbe najbolje istražena u ljudi, koji od nje također obole. U mačaka se miastenija gravis

zapravo rijetko ustanovi, a u pasa, jednako kao i u ljudi, bolest je češća i pojavljuje se u dva oblika. Vidi str. 2373.

Jedan je oblik miastenije gravis nasljedan i poznat u nekih pasmina terijera i španijela, ponajprije u štenadi. Bolest se nasljeđuje autosomno recesivno i nema izraženu imunosnu osnovu. Taj se prirođeni oblik miastenije gravis zasniva na poremećaju acetilkolinskih receptora i sprječavanju neuromuskularnog prijenosa podražaja.

Autoimunosnu osnovu ima oblik stečene miastenije gravis, koja se pojavi kao posljedica djelovanja autoprotutijela na površinske acetilkolinske receptore na mišićnim stanicama. Specifična antireceptorska protutijela (IgG) vežu se na acetilkolinski receptor, zakoče ga i tako onemoguće acetilkolinsko aktiviranje. Gubitak acetilkolinskih receptora odgovoran je za smanjenu motoričku djelatnost, a ona se očituje izostankom mišićnih kontrakcija.

U patogenezi miastenije gravis osim autoprotutijela sudjeluje i komplement koji se može dokazati na mjestu imunopatoloških zbivanja u neuromuskularnom sklopu. Zamršenosti imunopatogeneze pridonosi i vjerovanje da nenormalnosti timusa i njegovi poremećaji također mogu sudjelovati u nastanku miastenije gravis. Smatra se da su najvažniji poremećaji na razini diferencijacije T-limfocita, osobito pomoćničkih i supresijskih limfocita. U skladu s takvim mišljenjem pretpostavlja se, nadalje, da nenormalnost pomoćničkih T-limfocita omogućuje stvaranje antireceptorskih protutijela, a nedjelatnost supresijskih limfocita i nedostatak supresijskih faktora što ih oni izlučuju omogućuju gubitak imunosne podnošljivosti prema proteinskim acetilkolinskim receptorima. Posljedica je takva poremećaja tvorba protutijela za taj vlastiti antigen.

Od toga oblika miastenije gravis, koji ima autoimunosna obilježja, obično obole psi koji pripadaju tzv. velikim pasminama (primjerice njemački ovčari), iako pasminska sklonost bolesti nije sasvim sigurno dokazana. U životinja se znakovi bolesti razvijaju postupno, a vrlo je uočljiv simptom slabost voljnih mišića. Njihova malaksalost pojačava se pri ponavljanju pokreta ili pri nekoj dugotrajnijoj mišićnoj aktivnosti. Mirovanjem ili prekidanjem mišićnog rada stanje se popravi, ali se to obično ne odnosi na skupine stalno aktivnih mišića. To su naročito mišići glave i vrata, pa se u pasa koji boluju od miastenije gravis nekontrolirano spuštaju očni kapci, nastupe poteškoće pri žvakanju hrane i njezinu gutanju, a mogu se opaziti i drugi karakteristični znakovi.

Jednostavno i pouzdano dijagnosticiranje bolesti omogućuje karakteristična klinička slika, ali se miastenija gravis može dijagnosticirati i različitim farmakološkim, elektromiografskim i imunološkim postupcima. Vrlo je prikladan test pri kojem se radi dijagnostike psu ubrizga pripravak antikolinesteraze kratkotrajna učinka. U životinje koja boluje od miastenije gravis znakovi izrazitog poboljšanja pojave se obično već za minutu od trenutka davanja lijeka. Učinak antikolinesteraze takav je da zakoči enzim kolinesterazu i njegovu razgradnju acetilkolina. Na taj je način omogućeno nakupljanje acetilkolina u količinama dovoljnim da podraže preostale acetilkolinske receptore u neuromuskularnom spoju, pa se mišićne kontrakcije odvijaju nesmetano.

Za dijagnosticiranje miastenije gravis serološki se postupci ne primjenjuju osobito često, iako se njima mogu dokazati antireceptorska protutijela. Ona su ustanovljena u devedesetak posto pretraženih životinja, a prikladan je dijagnostički postupak radioimunski test (RIA) ili neki od testova pri kojima se upotrebljava stafilokokni protein A (protein A vrste *Staphylococcus aureus*). Određenoga je dijagnostičkog značenja i neizravna imunofluorescencija.

Liječenje pasa koji boluju od miastenije gravis provodi se ponajprije pripravcima antikolinesteraze dugotrajnog učinka koji sadrže edrofonijev klorid. Takvo se liječenje može nadopuniti istodobnim davanjem glukokortikoida, a uspjeh liječenja može biti vrlo različit. U nekih se životinja postigne samo prolazno poboljšanje, dok se u drugih mogu postići iznimno dobri učinci. Ishod bolesti često ovisi o popratnim pojavama koje se razviju uz osnovnu bolest, a naročito je povezan s pravodobno započetim liječenjem. Ipak, može se izreći općenita tvrdnja da je ishod bolesti najčešće povoljan.

AUTOIMUNOSNI POLIMIOZITIS

Među autoimunosnim bolestima lokomotornoga sustava pasa najučestalija je skupina mišićnih bolesti koje se zajedničkim imenom mogu nazvati autoimunosni polimiozitis. Iako se mogu klasificirati i različito (npr. atrofični miozitis, autoimunosna miopatija žvačnih mišića i dr.) svim su tim bolestima zajedničke značajke idiopatske autoimunosne promjene u mišićnom tkivu i djelotvornost glukokortikoida pri liječenju. Osim toga, imaju i druge sličnosti kojih je više od onih koje ih razlikuju pa je uputno i opravdano nazivati ih jednim imenom. Bez obzira na simptome i njihovu lokalizaciju primijećeno je da je autoimunosni polimiozitis češći u pasa velikih pasmina.

Najupečatljiviji klinički znakovi obično su povezani s promjenama na žvačnim mišićima koji mogu biti bolni, natečeni ili atrofični. To je najčešće povezano s nemogućnošću ili otežanim otvaranjem usta. Trizam može toliko jak da postoji čak i tijekom opće anestezije. Promjene na mišićima dušnika i ždrijela mogu biti tako izražene da otežavaju glasanje bolesnih pasa. Budući da su pri autoimunosnom polimiozitisu zahvaćene različite skupine mišića, i simptomi mogu biti različiti. U pojedinih pasa primjetan je otežan i sputani hod, ukočenost vratnog mišićja ili opća mišićna slabost.

Dijagnoza autoimunosnog polimiozitisa može se potvrditi nalazom visoke razine serumske keratin-fosfokinaze, pretragom bioptata zahvaćenih mišića ili autoprotutijela specifičnih za pojedine sastojke mišićnoga tkiva. Histološkom se pretragom obično ustanove nekrotične, degenerativne i upalne promjene sa znakovima fibroze. Oboljelo tkivo može biti infiltrirano limfocitima i plazma-stanicama, a katkad i eozinofilnim leukocitima, premda se histološki nalazi mogu međusobno vrlo razlikovati.

Autoimunosne bolesti krvi i krvotvornih tkiva

Među životinjama, osobito kućnim, od autoimunosnih bolesti krvi i krvotvornih tkiva najbolje su istražene i najučestalije autoimunosna hemolitička anemija i autoimunosna trombocitopenija.

AUTOIMUNOSNA HEMOLITIČKA ANEMIJA

Autoimunosna hemolitička anemija najčešće je akutna autoimunosna bolest poznata u pasa, mačaka, konja i goveda i njezina je glavna značajka da se hemolizni poremećaji osnivaju na autoprotutijelima za eritrocite domaćina. S obzirom na sudjelovanje različitih imunosnih mehanizama, autoimunosna hemolitička anemija obično se dijeli na nekoliko tipova, a jedno od njihovih važnih dodatnih obilježja jest odsutnost ili prisutnost komplementa pri razaranju eritrocita. Osim toga, pri pojedinim tipovima autoimunosne hemolitičke anemije izrazitije su razlike s obzirom na mjesto u organizmu gdje se hemoliza događa. Pri nekima je to unutar krvnih žila, a druge tipove autoimunosne hemolitičke anemije označuje propadanje eritrocita izvan krvnog optoka. Budući da je autoimunosna hemolitička anemija najsustavnije istražena u pasa, tu autoimunosnu bolest prikazujemo prije svega na osnovi spoznaja stečenih u te životinjske vrste, dok ćemo osobitosti te bolesti u drugih domaćih životinja iznijeti nakon toga opisa.

U pasa se autoimunosna hemolitička anemija obično pojavljuje u dobi od dvije do osam godina, a postoji li pasminska sklonost bolesti, nije potpuno jasno. Obole psi svih pasmina, ali su staroengleski ovčarski psi, pudli, koker španijeli, irski seteri i njemački ovčari ipak najosjetljiviji. Zanimljivo je da je u kuja tri do četiri puta učestalija nego u muških životinja, a pomišlja se da bolest ima i genetsku osnovu.

Svi činitelji što sudjeluju u patogenezi autoimunosne hemolitičke anemije nisu poznati. Jedno je od mogućih tumačenja da protueritrocitna protutijela nastanu zbog biokemijskih promjena i na taj način izmijenjene antigeničnosti eritrocita, a pretpostavlja se da bi takve promjene mogle biti potaknute nekim lijekovima, učincima drugih kemijskih spojeva ili pojedinim mikrobima.

Više se zna o učinku nastalih autoprotutijela i o sudbini domaćinovih eritrocita. Način njihova uništavanja može biti različit i uslijediti zbog intravaskularne aglutinacije, intravaskularne hemolize ili zbog ekstravaskularne hemolize, a dodatni podatci o značajkama tipova autoimunosne hemolitičke anemije u pasa (tipovi I do V) iznijeti su u tablici 12-2.

Na osnovi podataka prikazanih u tablici 12-2 uočljiva je sličnost tipova I i IV, odnosno tipova II i V autoimunosne hemolitičke anemije. Pri tipovima I i IV pojavljuje se intravaskularna aglutinacija, nakon koje slijedi fagocitiranje aglutiniranih eritrocita u slezeni odnosno jetrima. Bitna je razlika među tim tipovima što se pri tipu IV aktivira i sustav komplementa. Tipovi II i V autoimunosne hemolitičke anemije međusobno su još sličniji. Posebnost je tipa V da pri tom obliku autoimunosne hemolitičke anemije sudjeluju „hladna“ protutijela, a tako se nazivaju jer su naročito aktivna pri niskim temperaturama, pa se i njihova djelatnost određuje pri 4C. Autoprotutijela što sudjeluju pri tipu IV također pripadaju „hladnim“ protutijelima (tablica 12-2).

Osobina autoprotutijela utječe i na kliničku sliku bolesti, pa tipove autoimunosne hemolitičke anemije s „hladnim“ protutijelima karakterizira naročita osjetljivost pasa na hladnoću. U takvih se životinja za hladna vremena u kapilarama nogu, na krajevima uški i repa mogu aglutinirati eritrociti, te se na taj način razvije krvni zastoj koji može pridonijeti nastanku nekroze tkiva.

TABLICA 12-2. OSOBITOSTI POJEDINIH TIPOVA AUTOIMUNOSNE HEMOLITIČKE ANEMIJE U PASA						
TIP AIHA	RAZRED IMUNOGLOBULINA	UČINAK IMUNOGLOBULINA	SUDJELOVANJE KOMPLEMENTA	OPTIMALNA TEMPERATURA	MJESTO UKLANJANJA ERITROCITA	KLINIČKO OČITOVANJE
I	IgG, IgM	aglutinacija	-	37 °C	slezena	intravaskularna aglutinacija
II	IgM	hemoliza	+	37 °C	jetra	intravaskularna hemoliza
III	IgG	nekompletan	+	37 °C	slezena	anemija
IV	IgM	aglutinacija	+	4 °C	jetra	cijanoza nogu
V	IgM	nekompletan	+	4 °C	jetra	anemija

Inače, jaka anemija redovit je znak bolesti, a u tipičnim slučajevima riječ je o makrocitnoj anemiji sa sferocitozom. Ostali najčešći simptomi u izravnoj su vezi s anemijom, pa su životinje nujne, slabe i teško podnose napore. Vidljive sluznice su im blijede, katkad sa znakovima žutice, a mogu biti izraženi i znakovi limfadenopatije i hepatosplenomegalije. Jetra i slezena naročito su povećani u pasa u kojih se eritrociti uništavaju izvan krvotoka. Iako je autoimunosna hemolitička anemija zasebna autoimunosna bolest, kod otprilike jedne trećine bolesnih životinja pojavi se zajedno s drugim autoimunosnim bolestima autimunosne trombocitopenije ili sistemskog eritematoznog lupusa, pa postoje i dodatni klinički znakovi. O udruženosti više autoimunosnih oštećenja također ovise i rezultati laboratorijskih pretraga. Glavni kriteriji za dijagnosticiranje autoimunosne hemolitičke anemije zasnivaju se na karakterističnim hematološkim i biokemijskim nalazima, dok je dijagnostički najznačajniji izravni antiglobulinski test (Coombsov test). Mogu se primijeniti i drugi imunološki postupci, poput neizravnoga antiglobulinskog testa ili aglutinacija na predmetnici, ali se tipovi II, III i V autoimunosne hemolitičke anemije ipak najpouzdanije dijagnosticiraju s pomoću izravnoga Coombsova antiglobulinskoga testa.

Različiti se terapijski postupci mogu poduzeti pri liječenju pasa koji boluju od autoimunosne hemolitičke anemije, međutim, najbolji rezultati liječenja obično se postižu visokim dozama glukokortikoida. Njima se ne sprječava tvorba antieritrocitnih protutijela, ali se onemogućuje fagocitiranje eritrocita na koje su ona vezana. Takav učinak glukokortikoida najbolje je izražen prema eritrocitima opsoniziranim s IgG (pri tipu III AIHA), a općenito se može ustvrditi da uspješnost liječenja ovisi o tipu bolesti.

O tipu autoimunosne hemolitičke anemije u pasa ovisi i prognoza bolesti. Smatra se da su tipovi II, III i V uglavnom prognostički povoljniji nego tipovi I i IV.

Mnogo je manje poznata autoimunosna hemolitička anemija u drugih domaćih životinja. Zabilježena je u mačaka, goveda i konja, ali se zbog malobrojnih opisa bolesti još uvijek ne mogu iznijeti potpunije značajke te autoimunosne bolesti u tih životinjskih vrsta. Kao i u pasa, i u njih je anemija najočitiji i najvažniji simptom. Bolest se u mačaka, goveda i konja također pouzdano dijagnosticira na osnovi pozitivnog rezultata izravnoga antiglobulinskog testa, a i liječenje se provodi s pomoću pripravaka glukokortikoida. Mačkama koje boluju od autoimunosne hemolitičke anemije uputno je takvo liječenje nadopuniti davanjem nekoga tetraciklinskog antibiotika, da bi se spriječilo izbijanje pritajene infekcije što je u tih životinja uzrokuje mikrobna vrsta *Mycoplasma haemofelis.* Prije je bila klasificirana kao rikecija i poznata kao vrsta *Haemobartonella felis,* pa se i bolest nazivala hemobartonelozom.

AUTOIMUNOSNA TROMBOCITOPENIJA

Primarna autoimunosna trombocitopenija, u starijoj literaturi poznata kao autoimunosna trombocitopenična purpura, autoimunosna je bolest nerazjašnjene etiologije koju karakteriziraju autoprotutijela za krvne pločice (trombocite) u krvnom optoku i megakariocite u koštanoj srži. Bolest se klinički očituje pojavom točkastih i mrljastih krvarenja (purpura) u koži i sluznicama, te seroznim ovojnicama, a može se pojaviti i krvarenje u neku tjelesnu šupljinu ili iz nekoga tjelesnog otvora. Među domaćim životinjama autoimunosna trombocitopenija je najpoznatija i najučestalija u pasa, dok se rjeđe pojavljuje u mačaka i konja.

U pasa je primijećeno da od autoimunosne trombocitopenije najčešće obole pudli, staroengleski ovčarski psi i koker španijeli, a dob bolesnih životinja može biti različita. Raspon dobi obično je od jedne do dvanaest godina, ali je bolest ipak najčešća u petogodišnjih i šestogodišnjih životinja. Također je poznato da ženke obole dvostruko češće od mužjaka. Autoimunosna trombocitopenija može nastati kao samostalna bolest ili je udružena s nekom drugom autoimunosnom bolešću poput sistemskog eritematoznog lupusa, autoimunosne hemolitičke anemije ili reumatoidnog artritisa.

Iako je patogeneza bolesti nerazjašnjena, poznato je da u bolesnih pasa postoje autoprotutijela specifična za krvne pločice i megakariocite koštane srži. U osamdesetak posto životinja s autoimunosnom trombocitopenijom dokazana su antitrombocitna protutijela koja pripadaju razredu IgG. Ona nisu sposobna aktivirati sustav komplementa, nego opsoniziraju krvne pločice omogućujući njihovo fagocitiranje. Najintenzivnija fagocitoza trombocita zbiva se u slezeni, djelomice i u jetrima, a na taj se način razvije za bolest znakovita trombocitopenija.

Ona može biti tako jaka da je broj krvnih pločica manji od 20 x 10^9 /L krvi, a vrijeme krvarenja izrazito produljeno. Zbog antigenske sličnosti krvnih pločica i njihovih preteča megakariocita, nastala antitrombocitna protutijela reagiraju i s megakariocitima, pa se poremeti i trombocitopoeza. Međutim, ona nije primarni uzrok trombocitopeniji.

Klinički znakovi autoimunosne trombocitopenije i njihova izraženost u naizravnijoj su vezi sa stupnjem trombocitopenije i poremećenim grušanjem krvi. Znakoviti su simptomi bolesti točkasta krvarenja u koži, po zubnom mesu, očnim spojnicama i drugim sluznicama, a nakon palpiranja ili uobičajenog postupka s pacijentom pri pregledu na mjestu dodira mogu se pojaviti ehimoze. Opsežnija krvarenja su rjeđa, ali mogu biti toliko jaka da čak ugroze i život životinje. U pasa, krvarenja u želučano-crijevnom sustavu katkad mogu biti toliko jaka da životinja ugine zbog iskrvarenja.

Postoje utemeljene pretpostavke da se u mačaka autoimunosna trombocitopenija razvije u tijeku kronične infekcije virusom mačje leukemije.

Laboratorijsko dijagnosticiranje autoimunosne trombocitopenije može se zasnivati na različitim hematološkim pretragama i imunološkim testovima. Njima se obično provjerava broj krvnih pločica, poremećaji zgrušavanja krvi i drugo, ali najčešće primjenjivani laboratorijski postupci za dijagnosticiranje autoimunosne trombocitopenije obuhvaćaju određivanje trombocitnih fosfolipida nazvanih trombocitni faktor 3 i primjenu postupka izravne imunofluorescencije.

Dokazivanjem trombocitnog faktora 3 provjerava se zapravo prisutnost antitrombocitnih protutijela u krvnom serumu pacijenta i njihov učinak na krvne pločice u krvnoj plazmi zdravog psa. U životinja koje boluju od autoimunosne trombocitopenije antitrombocitna protutijela vežu se za normalne krvne pločice i oštete ih tako da se iz njih oslobodi spomenuti faktor, koji onda potakne zgrušavanje krvne plazme. Budući da se tim postupkom katkad mogu dobiti prilično nepouzdani rezultati, sigurnijom dijagnostičkom metodom smatra se pretraga koštane srži izravnom imunofluorescencijom. Tom se pretragom dokazuju antitrombocitna protutijela vezana na megakariocite u aspiriranu uzorku pacijentove koštane srži.

Uspješnost liječenja i prognoza bolesti često ovise o pravodobnom dijagnosticiranju te upornom i dugotrajnom liječenju. Pravilan izbor, primjerene doze izabranih lijekova i trajanje liječenja često je presudno jer je i pri pravodobno započetom liječenju koje kratko traje

moguće ponovno izbijanje simptoma autoimunosne trombocitopenije. Bolesne životinje obično najbolje reagiraju na liječenje glukokortikoidima. Velikim dozama takvih pripravaka, primjerice prednizolona, ponajprije se smanjuje fagocitna djelatnost makrofaga i vezanje antitrombocitnih protutijela za krvne pločice. Također se smanjuje razina autoprotutijela u krvi, a istodobno povećava čvrstoća kapilara i tako spriječi njihovo pucanje. Poželjni imunosupresijski učinak može se postići i drugim pripravcima poput ciklofosfamida, vinkristin sulfata ili azatioprina. Moguća je također istodobna upotreba pojedinog od navedenih lijekova i odgovarajućeg glukokortikoida. Ona se čak i preporučuje ako se 7 – 10 dana nakon započete monoterapije glukokortikoidom ne ustanovi značajniji porast broja krvnih pločica. U pasa u kojih se razvije akutni oblik autoimunosne trombocitopenije popraćen jakim krvarenjima stanje se može poboljšati transfuzijom krvi, a u kronično bolesnih životinja sa stalnim znakovima autoimunosne trombocitopenije ili u onih s povremenim izbijanjem bolesti splenektomija može biti preporučljiva kao i prikladna terapijska mogućnost.

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