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1 **Chapter 6**

2  
3 **The Role of the Immune System from an Evolutionary Perspective**

4  
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31 **ABSTRACT**

32

33 "Nothing in Biology makes sense, except in the light of evolution." This famous citation of  
34 Theodosius Dobzhansky also underlies the integrative field of evolutionary medicine,  
35 which faces the challenge to combine (patho-)physiological mechanisms with evolutionary  
36 function. Here we introduce a concept from the study of animal behaviour, which are the  
37 four questions of Tinbergen that consider 1) the ontogeny of an individual describing its  
38 development, 2) its physiological machinery, which 3) has fitness consequences influenc-  
39 ing 4) the evolutionary history (phylogeny) of future generations. It is shown how this con-  
40 cept can be applied to infectious disease and to chronic inflammatory systemic diseases.  
41 Evolutionary medicine takes lifetime reproductive success into account. The hypothesis to  
42 be tested is that mechanisms underlying a disease in old age might have higher fitness  
43 benefits in the pre-reproductive and / or reproductive life history stage. We emphasize that  
44 our human aim is not to increase evolutionary fitness but to reduce suffering and costs of  
45 public health. Thus, medical research might be most successful in diseases that have no  
46 lifetime fitness cost, as otherwise evolution would already have acted against it. Impor-  
47 tantly, while no selection pressure existed to favour physiological mechanisms acting  
48 against such diseases, such mechanisms might become available via biomedical research.  
49 We conclude that for a comprehensive understanding of the pathophysiology of a disease,  
50 its fitness consequences and its evolutionary history should be considered. The special  
51 situation of the immune system and chronic inflammatory systemic diseases is highlighted.

52

53 **KEYWORDS:** evolutionary fitness; life history; reproductive success; disease; public  
54 health

55

56

## 57 **6.1 INTRODUCTION**

58 Evolutionary medicine emphasizes that to better understand modern human health and  
59 disease, the underlying evolutionary history and evolutionary consequences must also be  
60 understood. Thus, evolutionary medicine will contribute significantly to our understanding  
61 of the fitness consequences and the phylogeny (evolutionary history) of diseases and dis-  
62 ease related traits, explaining why disease exist even though it reduces fitness (Gluckman  
63 et al. 2009, Perlman 2013, Stearns et al. 2016).

64 For example, when trying to understand why chronic inflammatory systemic diseases  
65 (CIDs) occur, evolutionary biologists pointed out that it is crucial to consider the effect of  
66 CIDs on lifetime reproductive success depending on the species-specific life history traits  
67 such as age at first reproduction, reproductive lifespan, and life expectancy (Straub et al.  
68 2016). However, evolutionary medicine faces the challenge and difficulty to integrate  
69 physiological mechanisms with evolutionary function (Gluckman et al. 2009, Lozano  
70 2010, Nesse et al. 2012). This challenge is not unique to evolutionary medicine, but is one  
71 of the main topics in organismal research in biology, and has been especially addressed in  
72 the research on animal behaviour (Tinbergen 1963).

73 Biological research has traditionally been divided into the study of proximate (physiologi-  
74 cal or pathophysiological) mechanisms on the one hand and ultimate (evolutionary) causes  
75 on the other hand (Mayr 1961). Most researchers take only one of these two approaches  
76 into account (Drickamer 1998). For example, immunological research is mainly proximate,  
77 focusing on the pathophysiological mechanisms underlying the most prevalent infectious  
78 diseases, allergic diseases, and CIDs. Studies in behavioural ecology, on the other hand,  
79 are primarily ultimate, focusing on the fitness consequences of behaviour, which means  
80 whether individuals showing a specific behaviour have more offspring than other individu-  
81 als (Krebs et al. 1993, Wilson 1975). Behavioural ecologists have realized that studying  
82 physiological mechanisms as evolved traits that increase fitness provides an integrative  
83 understanding of animal behaviour (Wikelski et al. 2001, Wingfield 2008).

84 For example, the major histocompatibility complex (MHC), a molecule that plays a sig-  
85 nificant role in the immune response (a proximate factor), is known to affect behaviour,  
86 enabling females to choose mates with complementary MHC alleles, which increases fit-  
87 ness of common offspring (Kamiya et al. 2014, Lerner et al. 1991). Thus, behavioural  
88 ecologists came to a more comprehensive understanding of behaviour by taking into ac-  
89 count the fitness consequences of its underlying physiological mechanisms.

90 Based on the four questions of Tinbergen that he applied to animal behaviour (Tinbergen  
91 1963), we want to tackle the role of the immune system from an evolutionary perspective.  
92 This will be addressed in this chapter by using the special situation of CIDs as an example.

93

## 94 **6.2 THE FOUR QUESTIONS OF TINBERGEN**

95 Tinbergen formulated in 1963 four questions (Tinbergen 1963), which are the basis for an  
96 integrative approach to understand biological traits (Krebs et al. 1993). Each question is of  
97 equal importance. The four questions are (see also (Bateson et al. 2013, Nesse 2013)):

98

- 99 • What is the **Function**, which means the fitness value of the trait?
- 100 • What is the **Phylogeny**, which means the evolutionary history of the trait?
- 101 • How did the trait develop in individuals over their lifetime (**Ontogeny**)?
- 102 • What physiological machinery causes the observable trait (**Causation**)?

103

104 The questions concerning the function and phylogeny address ultimate factors, whereas  
105 questions concerning ontogeny and causation address proximate factors. Evolutionary  
106 medicine focusses on the two ultimate factors. The question about the function concerns  
107 the fitness consequences of behavioural patterns, i.e., why did they evolve? In order to  
108 evolve through the process of natural selection, a specific trait must have fitness benefits  
109 for the individual, which means increase the number of offspring produced during the indi-  
110 vidual's lifetime. The question regarding the phylogeny of a trait concerns the evolutionary  
111 history. Tinbergen regarded the responding central nervous system as the machinery caus-  
112 ing animal behaviour. He defined ontogeny of behaviour as the “change of behavioural  
113 machinery during development“. Thus, the question addressing causation is the question  
114 about the behavioural machinery leading to the observed behavioural pattern, and the ques-  
115 tion about ontogeny asks how this machinery develops until the behaviour is shown for the  
116 first time (Tinbergen 1963). In the context of an immune response, this machinery is called  
117 the “immune machinery.”

118

119

## 120 **6.3. THE FOUR QUESTIONS OF TINBERGEN AND THE IMMUNE RESPONSE**

121

### 122 6.3.1 Function - fitness value of the trait

123 Reactions to acute inflammation serve the body to overcome short-lived infectious diseases  
124 and other threats such as exposure to allergic antigens. In both situations, the bod tries to  
125 get rid of the stimulus. The mechanisms are thus adaptive, increasing individual fitness.

126 Typically, inflammatory responses are highly adaptive, enabling individuals to overcome  
127 infections, to combat allergic threats, and to heal wounds. Thus, alleles of genes enabling  
128 this adaptive response got fixed within the gene pool.

129 Thanks to the last two decades of genome-wide association studies, we now recognize that  
130 hundreds of genetic loci associated with CIDs overlap with genes relevant in infectious and  
131 allergic diseases (Brinkworth et al. 2014). While in earlier time (before 2000), CIDs were  
132 thought to have one unique immune disease pathways, it is now very clear that this is in-  
133 correct. In CIDs inflammation is typically regulated by a network of genes that are impli-  
134 cated in multiple diseases (Cotsapas et al. 2011). The unique disease pathway is known in  
135 monogenic autoinflammatory diseases, which also employ immune pathways relevant to  
136 infections and allergies.

137

### 138 6.3.2 Phylogeny - evolutionary history of the trait

139 The evolutionary history of human immunological pathways is shared with sharks, birds,  
140 and rodents, spanning more than 420 million years (Boehm 2011). The best known asso-  
141 ciation between infections and genes has been established for the MHC allele system,  
142 which is an important element of antigen presentation in the human leukocyte antigen  
143 molecules (HLA). Polymorphic MHC alleles have been retained because they helped to  
144 overcome various infections (Mangalam et al. 2013), leading to positive selection. For ex-  
145 ample, the genetic factor HLA-DR4 (DRB1\*04) protects from dengue hemorrhagic fever  
146 (LaFleur et al. 2002). Furthermore, clearance of virus infections is much better for hepatitis  
147 B virus in the presence of HLA-DR13 (Wang et al. 2016) and for human immunodeficiency  
148 virus in the presence of HLA-B27 (Chakrabarti et al. 2010). There are many more  
149 examples also outside the MHC allele system, presentation of which would go beyond the  
150 scope of this chapter. The reader is referred to important reviews (Brinkworth et al. 2014).

151

152 6.3.3 Ontogeny – development of the trait in individuals over a lifetime

153 The environment of an individual during development and adult life together with the  
154 genotype determine how the inflammatory response system develops and will later re-  
155 spond. The immune system is equipped with a system to memorize antigens, and this in-  
156 fluences its later responsiveness to the same antigens. We call it immunological memory  
157 (Murphy et al. 2011), which is very personal depending on the exposure of the individual  
158 to infectious agents during the lifetime. For example, most people in Europe have been  
159 exposed to small pox virus and are thus immune to it. This was completely different for  
160 native Americans at a time point of arrival of European seafarers in the 16<sup>th</sup> century, lead-  
161 ing to mass extinction of local inhabitants (Patterson et al. 2002).

162 Another example in the neuroendocrine immune field further demonstrates the impact of  
163 ontogeny. Neonatal exposure of a new-born rat to lipopolysaccharide changes the hypotha-  
164 lamic-pituitary adrenal axis markedly (Shanks et al. 1995). As adults, neonatally en-  
165 dotoxin-treated animals exhibited significantly greater adrenocorticotrophic hormone and  
166 corticosterone responses to restraint stress than controls. Neonatal endotoxin treatment  
167 reduced glucocorticoid receptor density across a wide range of brain regions (Shanks et al.  
168 1995). Exposure to gram-negative lipopolysaccharide in early life can alter the develop-  
169 ment of neural systems, which govern endocrine responses to stress and may thereby pre-  
170 dispose individuals to stress-related pathology. Indeed, it has been demonstrated that neo-  
171 natal endotoxin treatment of rats protects animals from experimental arthritis later in life  
172 (Shanks et al. 2000). This long-term imprinting of central nervous changes in the early  
173 phase of ontogeny can also change the behaviour of the immune system throughout life.

174

175 6.3.4 Causation – the “immune machinery”

176 Inflammation is caused by specific antigens, including pathogens or cell material of dam-  
177 aged tissue (wounds), to which the immune system responds (Murphy et al. 2011). There  
178 are several supportive reactions of the neuronal and endocrine systems that foster the im-  
179 mune response in acute infectious diseases (Straub 2015), altogether representing the cau-  
180 sation of inflammation and immune response. In line with Tinbergen’s terminology (i.e.,  
181 behavioural machinery), this might be called the immune machinery. The immune machin-  
182 ery consists of immune cells (neutrophils, lymphocytes, macrophages, dendritic cells, natu-  
183 ral killer cells, and many others) with specific surface receptors to activate these cells,  
184 causing the release of inflammatory mediators (Murphy et al. 2011).

185 The immune machinery is highly dependent on the availability of energy-rich substrates in  
186 the body because immune cells demand enormous amounts of energy (Gaber et al. 2017,  
187 Straub et al. 2010). We may call the immune system selfish, because during infection it is  
188 the major dominating factor operating at the highest hierarchical level to acquire energy-  
189 rich substrates (Straub 2014). This selfishness has been positively selected for infectious  
190 diseases, and it is an important determining aspect of the immune machinery (causation).

191

192 6.3.5 Integrative approach - the immune system in evolutionary medicine (Fig 1)

193 The immune machinery has been positively selected for short-lived infectious diseases  
194 (causation), which leads to measurable immune responses and inflammation (diagnostic,  
195 red box in Fig. 1), protecting the individual from infections / helping during wound heal-  
196 ing. This increases the chance of survival and reproduction at a later stage, increasing evo-  
197 lutionary fitness (Schmid-Hempel 2011). Genes improving the immune response increased  
198 in frequency in the gene pool (phylogeny). The individual genotypes together with the in-  
199 dividual specific environment lead to an individual specific development of the immune  
200 system (ontogeny). A classical ontogenetic factor of the immune response is immunologi-  
201 cal memory of the adaptive immune system towards pathogen-specific antigens (Murphy  
202 et al. 2011). If a microbial antigen is known to the immune machinery (causation), then it  
203 is rapidly activated, i.e. an immediate response towards an infectious agent is generated.  
204 The immune machinery with memory consists of educated specific T or B cells (physio-  
205 logical response) that can be observed as a phenotypic trait, causing a stronger and faster  
206 immune reaction towards the antigen (causation).

207

208 ----- Figure 1 here -----

209

210

## 211 **6.4 THE FOUR QUESTIONS OF TINBERGEN AND CHRONIC INFLAMMA-** 212 **TORY SYSTEMIC DISEASES**

213

214 CIDs are characterized by a continuous immune response towards harmless autoantigens  
215 (reaction against innocuous self) or harmless microbes on the surface of the body (reaction  
216 against innocuous foreign) (Firestein et al. 2013). Examples for CIDs are rheumatoid ar-  
217 thritis, multiple sclerosis, ankylosing spondylitis, systemic lupus erythematosus, Sjögren  
218 syndrome, pemphigus vulgaris, and many others. While an immune response is usually



219 confined to a small space, it becomes chronic and widespread in CIDs (Hochberg et al.  
220 2015, Straub 2015). A CID leads to new energy requirements in an affected person, which  
221 supports many unwanted disease-related signs and symptoms recently demonstrated  
222 (Straub et al. 2016).

223

#### 224 6.4.1 Ultimate factors - Function and Phylogeny

225 While reactions to acute inflammation serve the body to overcome short-lived infectious  
226 diseases (see 6.3.1), a long-term CID is detrimental. In CIDs, the positively selected im-  
227 mune mechanisms, which usually support fitness and function (Fig. 1), are continuously  
228 activated by harmless antigens, and the response becomes maladaptive (Straub et al. 2016).  
229 Importantly, a CID - while costly - will not have a significant influence on fitness (func-  
230 tion), because it typically happens after the reproductive phase (Fig. 2).

231

232 ----- Figure 2 here -----

233

234 CIDs have a multifactorial genetic background discussed above (section 6.3.1). The MHC  
235 allele system plays an important role in CIDs. For some MHC alleles, the risk to develop a  
236 CID is 90 times increased (Brewerton et al. 1973, Schlosstein et al. 1973). However, nega-  
237 tive selection against specific MHC alleles was most probably weak, because in most indi-  
238 viduals carrying these alleles the disease did not develop due to the lack of additional risk  
239 factors (Straub et al. 2016) that are important during ontogeny. MHC alleles were posi-  
240 tively selected due their role in infection (see section 6.3.2). We described the link between  
241 HLA-DR4 (DRB1\*04) and dengue hemorrhagic fever, but the same MHC allele is known  
242 to be positively associated with rheumatoid arthritis, type I diabetes mellitus, and other  
243 CIDs.

244 We described HLA-B27 as an important factor to overcome human immunodeficiency  
245 virus infection (see section 6.3.2), but the same allele is linked to ankylosing spondylitis  
246 (Brewerton et al. 1973, Schlosstein et al. 1973). Thus, many traits have an evolutionary  
247 history (phylogeny) developed in the context of infectious disease, but these traits are used  
248 again in another somatic environment in later life (Williams 1957). This phenomenon is  
249 called antagonistic pleiotropy (Williams 1957), which means fitness benefits at one life  
250 history stage being higher than fitness costs at another life history stage. Here, they can  
251 support the development of a CID.

252

#### 253 6.4.2 Ontogeny – development of the trait in individuals over a lifetime

254 We learned that the immune system has a memory for antigens. However, cross-reactivity  
255 towards harmless autoantigens (reaction against innocuous self) or harmless microbes on  
256 the surface of the body (reaction against innocuous foreign) as in CIDs can also occur.

257 Now, the immune memory is directed against the harmless antigens, which leads to a  
258 chronic immune attack in CIDs.

259 Sometimes autoantigens are posttranslationally processed, which can be supported by fac-  
260 tors that appear during individual development. For example, smoking may change self-  
261 peptides leading to an exchange of arginine with citrulline (Quirke et al. 2011). This post-  
262 translational modification with the new citrulline is foreign to the immune system and may  
263 be attacked as an antigen. Thus, smoking is one environmental factor during development  
264 known to increase the risk that the immune system later attacks harmless autoantigens fos-  
265 tering CIDs (Klareskog et al. 2011, Mathews et al. 1973). Another environmental risk fac-  
266 tor for some CIDs is silica exposure, for example during construction work, which might  
267 overstimulate the immune system and trigger the autoimmune process leading to chronic  
268 inflammation (Pollard 2016).

269 Another environmental risk factor is psychological stress. We already saw that neonatal  
270 endotoxin exposure can change the adult immune system response, and it seems that the  
271 childhood immune system is more vulnerable to stressors as compared to the adult immune  
272 system (see 6.3.3). In several studies, it was demonstrated that childhood trauma (death of  
273 a parent, sexual abuse, violence in the family etc.) was positively linked to later appearance  
274 of CIDs (Dube et al. 2009, Neufeld et al. 2013, Spitzer et al. 2013). These examples are  
275 indicative of how the individual development can manipulate the immune system and the  
276 appearance of overt CIDs.

277

#### 278 6.4.4 Causation – the immune machinery

279 In CIDs, the role of the immune machinery was described for more than 100 years, reach-  
280 ing enormous detail since the start of molecular biology and functional genomics in the  
281 1980s and 1990s. Today, we realize that many important pathways have been discovered  
282 that cause and support CIDs (Firestein et al. 2013, Hochberg et al. 2015). These novel fac-  
283 tors led to the development of biological therapy such as anti-TNF strategies (Feldmann et  
284 al. 2010). Nevertheless, much detail needs to be learned, particularly, with respect to hu-  
285 man CIDs. Importantly, the immune machinery for CIDs is the same as the immune ma-  
286 chinery for infectious diseases and allergy.

287 On top of the specific immune machinery, which was called selfish (see 6.3.4), a general  
288 bodily reaction supports the immune system (Straub et al. 2013). The immune system is  
289 selfish because it makes use of other systems (nervous and endocrine) to redistribute en-  
290 ergy-rich fuels (Straub 2014). While this has been positively selected for short-lived infec-  
291 tious diseases, the long-term application of these adaptive programs leads to many unfav-  
292 ourable signs and symptoms in CIDs (Straub et al. 2016). These are daytime fatigue, low  
293 mood, sleeping alterations, anorexia, inflammation type of anaemia, muscle loss (sarco-  
294 penia), bone loss, insulin resistance, decreased fertility & libido, high blood pressure &  
295 volume overload, and increased blood coagulation (Straub et al. 2016). These phenomena  
296 were positively selected as the non-immune machinery that supports the immune machin-  
297 ery. However, if the non-immune machinery is used too long, many problems appear that  
298 need specific extra treatment besides immunosuppression. Long-term use of these pro-  
299 grams is maladaptive (Straub et al. 2016).

300

#### 301 6.4.5 Integrative approach to understand CIDs in evolutionary medicine (Fig. 3)

302 Ultimate factors have been positively selected for short-lived infectious diseases and not  
303 for CIDs (Straub et al. 2016). Net fitness is increased because the fitness benefits in early  
304 life are much higher than fitness costs in post-reproductive life, so that favourable genes  
305 stay in the gene pool (function and phylogeny). The individual genotypes together with the  
306 individual specific environment lead to an individual specific development of the immune  
307 system (ontogeny). Here, environmental factors such as smoking, silica exposure, and  
308 childhood stress can prepare the immune machinery for the unfortunate development of a  
309 CID. When several factors come together (genetic & environmental), the individual can  
310 develop an immune response towards harmless self and harmless foreign antigens. Then,  
311 the response is imprinted in the immune memory, which leads to measurable immune re-  
312 sponses such as autoantibodies towards citrullinated peptides (diagnostic, red box in Fig.  
313 3).

314

315 ----- Figure 3 here -----

316

### 317 **CONCLUSIONS: APPLICATION OF THE FOUR QUESTIONS OF TINBERGEN** 318 **IN EVOLUTIONARY MEDICINE**

319 Many chronic diseases might be studied and understood using the same framework as out-  
320 lined in figure 3. The evolutionary approach here considers three points:

- 321 1. One must take into account the fitness consequences of the trait leading to disease
- 322 2. To be done at the different life history stages (pre-reproduction, reproductive age,  
323 and post-reproductive; Fig. 2)
- 324 3. To determine life-time reproductive success

325 This will enable us to understand the evolutionary history of the disease, especially why  
326 alleles favouring the disease have been established in the gene pool. This approach might  
327 then also benefit clinicians: it is often less relevant to know which genes and alleles favour  
328 the expression of a specific disease, but the environmental factors triggering the disease.  
329 This is because we cannot easily change the genotype of individuals, but we can interfere  
330 with environmental threats in the individual live.

331 Finally, the absence of physiological mechanism acting against a disease is no indicator  
332 that such a mechanism is impossible; it only indicates that such a mechanism would not  
333 significantly increase fitness. However, our human aim is to reduce suffering and costs of  
334 public health, not to increase evolutionary fitness. This leads to the conclusion that bio-  
335 medical research might be most successful in diseases that have no or low lifetime fitness  
336 cost, but high costs for public health and a high load of individual suffering.

337 Last but not least, current research topics in evolutionary medicine where our graphical  
338 model might fail could nevertheless benefit by taking the four questions into account. Ex-  
339 amples could be maladaptation, environmental mismatch and evolved traits that are not  
340 adaptive in the current modern environment. By applying the model and then identifying  
341 where it fails, the reason as well as the consequences why the trait is not adaptive or why  
342 environmental mismatch occurs could be identified. Thus, not all disease can be explained  
343 and described by Tinbergen`s four question, but identifying why and when this concept  
344 fails will nevertheless improve our understanding why our body is constructed in a way  
345 that sometimes leads to disease.

346

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## References

- Bateson, P. and Laland, K.N. (2013). Tinbergen's four questions: an appreciation and an update. *Trends Ecol. Evol.*, 28, 712-8.
- Boehm, T. (2011). Design principles of adaptive immune systems. *Nat. Rev. Immunol.*, 11, 307-17.
- Brewerton, D.A., Hart, F.D., Nicholls, A., Caffrey, M., James, D.C. and Sturrock, R.D. (1973). Ankylosing spondylitis and HL-A 27. *Lancet.*, 1, 904-7.
- Brinkworth, J.F. and Barreiro, L.B. (2014). The contribution of natural selection to present-day susceptibility to chronic inflammatory and autoimmune disease. *Curr. Opin. Immunol.*, 31, 66-78.
- Chakrabarti, L.A. and Simon, V. (2010). Immune mechanisms of HIV control. *Curr. Opin. Immunol.*, 22, 488-96.
- Cotsapas, C., Voight, B.F., Rossin, E., Lage, K., Neale, B.M., Wallace, C., Abecasis, G.R., Barrett, J.C., Behrens, T., Cho, J., De Jager, P.L., Elder, J.T., Graham, R.R., Gregersen, P., Klareskog, L., Siminovitch, K.A., van Heel, D.A., Wijmenga, C., Worthington, J., Todd, J.A., Hafler, D.A., Rich, S.S., Daly, M.J. and FOCiS Network of Consortia (2011). Pervasive sharing of genetic effects in autoimmune disease. *PLoS. Genet.*, 7, e1002254.
- Drickamer, L.C. (1998). Vertebrate behavior: integration of proximate and ultimate causation. *American Zoologist*, 38, 39-42.
- Dube, S.R., Fairweather, D., Pearson, W.S., Felitti, V.J., Anda, R.F. and Croft, J.B. (2009). Cumulative childhood stress and autoimmune diseases in adults. *Psychosom. Med.*, 71, 243-50.
- Feldmann, M., Williams, R.O. and Paleolog, E. (2010). What have we learnt from targeted anti-TNF therapy? *Ann. Rheum Dis.*, 69 (Suppl 1), i97-i99.
- Firestein, G.S., Kelley, W.N., Budd, R.C., Gabriel, S.E., McInnes, I.B. and O'Dell, J.R. (2013). *Kelley's textbook of rheumatology*. Elsevier/Saunders, Philadelphia, PA.
- Gaber, T., Strehl, C. and Buttgerit, F. (2017). Metabolic regulation of inflammation. *Nat. Rev. Rheumatol.*, 13, 267-79.
- Gluckman, P., Beedle, A. and Hanson, M. (2009). *Principles of evolutionary medicine*. Oxford University Press, Oxford New York.
- Hochberg, M.C., Silman, A.J., Smolen, J.S., Weinblatt, M.E. and Weisman, M.H. (2015). *Rheumatology*. Elsevier Mosby, Philadelphia.
- Kamiya, T., O'Dwyer, K., Westerdahl, H., Senior, A. and Nakagawa, S. (2014). A quantitative review of MHC-based mating preference: the role of diversity and dissimilarity. *Mol. Ecol.*, 23, 5151-63.
- Klareskog, L., Malmstrom, V., Lundberg, K., Padyukov, L. and Alfredsson, L. (2011). Smoking, citrullination and genetic variability in the immunopathogenesis of rheumatoid arthritis. *Semin. Immunol.*, 23, 92-8.
- Krebs, J.R. and Davies, N.B. (1993). *An Introduction to Behavioural Ecology*. Blackwell Science Ltd., Oxford.
- LaFleur, C., Granados, J., Vargas-Alarcon, G., Ruiz-Morales, J., Villarreal-Garza, C., Higuera, L., Hernandez-Pacheco, G., Cutino-Moguel, T., Rangel, H., Figueroa, R., Acosta, M., Lazcano, E. and Ramos, C. (2002). HLA-DR antigen frequencies in Mexican patients with dengue virus infection: HLA-DR4 as a possible genetic resistance factor for dengue hemorrhagic fever. *Hum. Immunol.*, 63, 1039-44.

- 394 Lerner, S.P. and Finch, C.E. (1991). The major histocompatibility complex and reproductive functions.  
395 *Endocr. Rev.*, 12, 78-90.
- 396 Lozano, G.A. (2010). Evolutionary explanations in medicine: how do they differ and how to benefit from  
397 them. *Med. Hypotheses.*, 74, 746-9.
- 398 Mangalam, A.K., Taneja, V. and David, C.S. (2013). HLA class II molecules influence susceptibility versus  
399 protection in inflammatory diseases by determining the cytokine profile. *Journal of Immunology*,  
400 190, 513-8.
- 401 Mathews, J.D., Whittingham, S., Hooper, B.M., Mackay, I.R. and Stenhouse, N.S. (1973). Association of  
402 autoantibodies with smoking, cardiovascular morbidity, and death in the Busselton population.  
403 *Lancet.*, 2, 754-8.
- 404 Mayr, E. (1961). Cause and effect in biology. *Science*, 134, 1501-6.
- 405 Murphy, K.M., Travers, P. and Walport, M. (2011). *Janeway's Immunobiology*. Taylor & Francis, Oxford.
- 406 Nesse, R.M. (2013). Tinbergen's four questions, organized: a response to Bateson and Laland. *Trends in*  
407 *Ecology & Evolution*, 28, 681-2.
- 408 Nesse, R.M., Ganten, D., Gregory, T.R. and Omenn, G.S. (2012). Evolutionary molecular medicine. *J Mol.*  
409 *Med. (Berl.)*, 90, 509-22.
- 410 Neufeld, K.M., Karunanayake, C.P., Maenz, L.Y. and Rosenberg, A.M. (2013). Stressful life events  
411 antedating chronic childhood arthritis. *J Rheumatol.*, 40, 1756-65.
- 412 Patterson, K.B. and Runge, T. (2002). Smallpox and the Native American. *Am. J Med. Sci.*, 323, 216-22.
- 413 Perlman, R.L. (2013). *Evolution & Medicine*. Oxford University Press, Oxford.
- 414 Pollard, K.M. (2016). Silica, Silicosis, and Autoimmunity. *Front Immunol.*, 7, 97.
- 415 Quirke, A.M., Fisher, B.A., Kinloch, A.J. and Venables, P.J. (2011). Citrullination of autoantigens: upstream  
416 of TNFalpha in the pathogenesis of rheumatoid arthritis. *FEBS Lett.*, 585, 3681-8.
- 417 Schlosstein, L., Terasaki, P.I., Bluestone, R. and Pearson, C.M. (1973). High association of an HL-A antigen,  
418 W27, with ankylosing spondylitis. *N. Engl. J Med.*, 288, 704-6.
- 419 Schmid-Hempel, P. (2011). *Evolutionary parasitology*. Oxford University Press, Oxford.
- 420 Shanks, N., Larocque, S. and Meaney, M.J. (1995). Neonatal endotoxin exposure alters the development of  
421 the hypothalamic-pituitary-adrenal axis: early illness and later responsivity to stress. *J Neurosci.*, 15,  
422 376-84.
- 423 Shanks, N., Windle, R.J., Perks, P.A., Harbuz, M.S., Jessop, D.S., Ingram, C.D. and Lightman, S.L. (2000).  
424 Early-life exposure to endotoxin alters hypothalamic-pituitary-adrenal function and predisposition to  
425 inflammation. *Proc. Natl. Acad. Sci. U. S. A.*, 97, 5645-50.
- 426 Spitzer, C., Wegert, S., Wollenhaupt, J., Wingenfeld, K., Barnow, S. and Grabe, H.J. (2013). Gender-specific  
427 association between childhood trauma and rheumatoid arthritis: a case-control study. *J Psychosom.*  
428 *Res.*, 74, 296-300.
- 429 Stearns, S.C. and Medzhitov, R. (2016). *Evolutionary medicine*. Sinauer Associates, Inc., Sunderland, MA.
- 430 Straub, R.H. (2014). Insulin resistance, selfish brain, and selfish immune system: an evolutionarily positively  
431 selected program used in chronic inflammatory diseases. *Arthritis Res. Ther.*, 16(Suppl 2), S4 (pages  
432 1-15).
- 433 Straub, R.H. (2015). *The origin of chronic inflammatory systemic diseases and their sequelae*. Academic  
434 Press, San Diego.

- 435 Straub, R.H., Bijlsma, J.W., Masi, A. and Cutolo, M. (2013). Role of neuroendocrine and neuroimmune  
436 mechanisms in chronic inflammatory rheumatic diseases-The 10-year update. *Semin. Arthritis*  
437 *Rheum.*, 43, 392-404.
- 438 Straub, R.H., Cutolo, M., Buttgerit, F. and Pongratz, G. (2010). Energy regulation and neuroendocrine-  
439 immune control in chronic inflammatory diseases. *J Intern. Med.*, 267, 543-60.
- 440 Straub, R.H. and Schradin, C. (2016). Chronic inflammatory systemic diseases: An evolutionary trade-off  
441 between acutely beneficial but chronically harmful programs. *Evol Med. Public Health.*, 2016, 37-  
442 51.
- 443 Tinbergen, N. (1963). On aims and methods of ethology. *Zeitschrift für Tierpsychologie*, 20, 410-33.
- 444 Wang, L., Zou, Z.Q. and Wang, K. (2016). Clinical Relevance of HLA Gene Variants in HBV Infection. *J*  
445 *Immunol. Res.*, 2016, 9069375.
- 446 Wikelski, M. and Ricklefs, R.E. (2001). The physiology of life histories. *Trends in Ecology & Evolution*, 16,  
447 479-81.
- 448 Williams, G.C. (1957). Pleiotropy, natural selection, and the evolution of senescence. *Evolution*, 11, 398-411.
- 449 Wilson, E.O. (1975). *Sociobiology: The new Synthesis*. Harvard University Press, Cambridge, MA.
- 450 Wingfield, J.C. (2008). Comparative endocrinology, environment and global change. *Gen. Comp*  
451 *Endocrinol.*, 157, 207-16.  
452  
453