CHAPTER 5

Disabled defences

The adaptive immune system derives its functional characteristics from the self-organising properties of the developing lymphoid cells as they relate to the world. It is especially sensitive to initial conditions, and the imprintings being made during early life are constricting for later reactivity. The process of assembling the integrated and well-functioning immune system is a complex undertaking, and several developmental trajectories may lead the system towards a well-functioning state. The immune system is thus multiply realisable.

But while there are multiple ways to build a functional system, even more paths are available for the assembly of a malfunctional system. Since each organism self-organises its immune system in the light of a unique immune history, the malfunctional immune system may differ amongst individuals with similar phenotypic diseases. This idea suggests that immune system diseases are not natural kind entities; there are no unique ways to classify them, there are many plausible and defensible ways of doing so, and the best way will depend on both the purposes of the classification and the peculiarities of the disease in question.

Despite being fitness reducing, immune system malfunctions increase in prevalence. This is partly owing to the increasing prevalence of elderly people in the Western world. But there are also malfunctions of the immune system that increasingly occur in younger individuals. It is the purpose of this chapter to explain immunosenescence and diseases of the immune system by first giving an explanation of how the concepts of function and malfunction apply to the issues at hand, and thereafter to disentangle these concepts as they relate to the immune system’s being-in-the-world. It will emerge that immune system aberrations occur owing to evolutionary contingencies, and that they are proximally caused by spatio-temporal mismatches between the immune system and the world.

5.1. Failure to perform

GOAL-DIRECTEDNESS

With the demise of vitalism and the emergence of Darwinism, the Aristotelian concept of teleology was replaced by naturalistic explanations of life’s directedness. But instead of purging the notion of goal-directedness from biology, as Newton did for physics, Darwin provided an alternative explanation that preserved goal-directedness. His evolutionary metaphysics effectively split the teleological explanation into two varieties – the functional and the intentional. The two can be differentiated on the basis of characteristics related to the agents that perform the
The evolutionary view of functions holds that the function of something is the effect it has and so explains why it is there (Wright 1973). Functions in the evolutionary sense are based on origin and are as such closely related to the concept of adaptation. Hence, the reason why a trait has been retained and modified throughout evolutionary time is explained by the adaptive role the trait had in organisms that possessed it. The seemingly goal directed behaviour of the trait is explained as being caused by the process of natural selection, a strictly \textit{a posteriori} process that never sets up future goals but, in contrast, rewards past events.

The second usage of function, which depicts a proximate real-time explanatory concept, appeals to the workings of the component parts of the system (Cummins 1975). When biochemists, physiologists or immunologists explain how a complex system manages to perform some capacity, they often explain the capacity as being the function of the system. By appealing to the causal capacities of the component parts, biologists need not refer to overall systemic goals or purposes when providing a functional explanation (Amundson and Lauder 1994). When immunologists claim that the function of the immune system is to eradicate antigen, they do not claim that the immune system anticipates the future. Rather, their explanation is wholly mechanistic. The immune system is, like any other biological system, regulated by causal mechanisms, and derives its goal-directedness from a set of subsystems whose non-teleological behaviour simulates overall goal-directedness. Antigen eradication is explained by the fact that antigen triggers receptors of the innate and adaptive immune systems that in turn activate a plethora of molecular mechanisms. These evolutionary selected mechanisms are active as long as the triggering antigen is sensed by the receptors. After eradication of the antigenic stimulus there is no further activation going on and, hence, the immune response is brought to an end.

While functional explanations pertain to all living entities, intentional explanations have traditionally been reserved for rational man (Elster 1979). The explanatory scopes of the two types of explanations are often contrasted by claiming that intentional agents are capable of using indirect strategies to realise their goals while non-intentional functional agents, who do not set themselves goals, are not. Nevertheless, the demarcation between the intentional and the functional is not
always easy to draw in practice. Results from research on adaptive systems demon-
strate that discriminatory assessment of environmental signs as well as proper
responding to the signs can be performed without mental operations being invoked.
Such meaning-making is, for example, characteristic for the adaptive immune
system, which performs a differentiated response to a given sign on the basis of
context (Neuman 2004). Even the smallest organisms, the bacteria, have developed
intricate channels of communication to co-operatively self-organise into highly
structured adaptively plastic colonies. Some authors even go so far as to equate this
behaviour with social intelligence and to claim that adaptive plasticity in bacteria
simulates intentional behaviour (Ben Jacob et al. 2004).

Despite there being a fuzzy border between intentional and functional explana-
tions, Mohan Matthen and Edwin Levy (1984, p. 353) were definitively on the
wrong track when they claimed that the immune system is goal-directed, and that
“some of the things that the immune system does can be described and understood
as being errors made in trying to achieve these goals”. Although they acknowledged
that the utilisation of teleological explanations is a precarious and anthropomorphic
undertaking, they still claimed that “the immune system is capable of arriving
at justified false beliefs” (1984, p. 365). Since errors can only be meaningfully
ascribed to a system if the system is directed towards a goal that is known by the
system beforehand, their explanation endows the immune system with intentionality.
Invocation of “justified false beliefs”, which is on par with Plato’s maintenance in
Theaetetus (1989, 201d) that knowledge is “justified true belief”\(^1\) make perfect
sense when truth and falsity are measured in terms of a correspondence between
a statement and the world to which it applies. But where scientific explanations
are concerned with correspondence and theoretical truth, the immune system has
evolved to care for survival, reproduction and practical truth. Whether the immune
system reaches “justified false beliefs” or not, is therefore irrelevant. It is fitness that
is of essence, and in biology it may sometimes pay to act on “untrue” representations
of the world if this acting promotes fitness.

MALFUNCTIONING

A distinctive part of the concept of function is that where there is function there
may be malfunction – a failure of a system to perform the explanatory activity.
A variety of causes, including genetic, developmental and environmental, can be
amassed to explain proximate malfunctions. The immune system can, for example,
be proximally caused to malfunction by malignancy, lack of resources, or infectious
agents. Historical malfunctions are, on the other hand, more intricate to explain.
Since traits retained in a lineage are the results of the trait’s previous successes,

\(^1\) The actual sentence reads “true belief with the addition of an account was knowledge, while belief
without an account was outside its range.”
Paul Sheldon Davies (2000) has argued that selected malfunctions cannot possibly occur. This was also the view of Charles Darwin:

No organ will be formed, as Paley has remarked, for the purpose of causing pain or for doing injury to its possessor. If a fair balance be struck between the good and the evil caused by each part, each will be found on the whole advantageous. After the lapse of time, under changing conditions of life, if any part comes to be injurious, it will be modified; or if it be not so, the being will become extinct, as myriads have become extinct (Darwin 1859, p. 229).

But even though malfunctions cannot be selected for, they can still increase in frequency owing to the process of natural selection. This may occur if the malfunctional trait is coupled to a beneficial trait under strong selective pressure. Since different traits are coupled at the organismal level, the outcome of selection for any individual trait depends upon the other traits that the organism comes equipped with. In addition, the selection for a trait depends upon the level at which the trait is selected, and whether there are counter-selective forces at work on other levels. Traits can be selected for or against at several levels simultaneously and there is a real possibility that fitter traits may decrease in frequency while less fit traits increase. The result depends on the relative strengths of the selective pressures that are at work at each level.

Co-selection of traits may occur because of linkage, which occurs when the genes are close together on a chromosome, or because of pleiotropy which occurs when a single gene has two phenotypic effects. The effect of linkage in the evolution of malfunctional traits is well exemplified by the mammalian MHC complex. Since the genes that encode the MHC molecules are located close together on the same chromosome, they are usually inherited en bloc. One MHC gene in the cluster may thus confer protection against infectious disease, while a closely linked gene may confer susceptibility to disease.

The MHC genes also exemplify pleiotropy, but the classic example of this phenomenon is sickle-cell disease, which results from a point mutation in the gene that produces haemoglobin. The bearers of the mutation, who develop malformed blood cells, are simultaneously protected against malaria. Individuals that are homozygous for the mutated gene develop a severe haematological disease whereas heterozygous individuals are better off. Since both hetero- and homozygous individuals are protected against malaria, the best combination is to be heterozygous in malaria infested regions. In this case the optimal phenotype, normal blood cells and resistance to malaria, is not attainable owing to antagonistic pleiotropy; the same cause leads to two opposing effects – sickling and resistance.

Besides co-selection, malfunctioning can also increase owing to inevitable outcomes of the evolutionary process itself. During natural selection average fitness should increase with regards to the environment that existed previously, i.e. the selective environment. But the environment, which includes other members of the population as well as biotic and abiotic factors, changes all the time. And since fitness is always fitness relative to the environment, a trait that is at a local optimum
in one environment may be rendered malfunctional if environmental change induces the trait’s movement away from the local optimum. If environmental change leads to changes in developmental outcome, environmental change may even lead to novel phenotypes. Hence, organisms or lineages can grow unfit simply by virtue of standing still in a changing world.

THE DISPOSABLE ORGANISM

In stark contrast to the assertion that malfunctions are never evolutionary selected stands the common observation that organisms increasingly experience deterioration and malfunctional diseases as they age. For example, the relative increase in death rates for people over 65 compared to the rates for people aged 25–44 are 43-fold for cancer and 89-fold for pneumonia and influenza (Troen 2003). The unfavourable and near-universal phenomenon of senescence is perplexing for at least two reasons. First, cumulative natural selection should ordinarily proceed towards lengthening life, not shortening it. And second, it is truly remarkable that organisms which produce and maintain themselves during development should be unable to perform the much simpler task of merely maintaining what is already formed.

Still, the observation that the maximum lifespan of organisms is species specific suggests that some form of selection should be involved in senescence. To understand how this may come about, consider a trade-off that occurred when unicellular life gave rise to multicellularity. While single-celled individuals had to embody capacities for both reproduction and survival, cells in multicellular ensembles were offered the opportunity to specialise in one component or the other. This opportunity was seized by the ancestors of extant metazoans as they evolved a germ line that specialised in reproduction and a soma that specialised in vegetative functions. It is in this sense that the germ line, which has been reproducing for more than three billion years, owes its immortality to a vehicle, the ephemeral soma. Since reproductive costs can be lowered to the degree that the soma acquires mates, evolutionary theory predicts that the soma should evolve characteristics that would further enhance the reproductive component of fitness. This also implies that the soma should be maintained at least so far that it contributes to the germ line’s reproduction.

But this line of reasoning does not account for why the soma deteriorates beyond the reproductive ages. To explain this, we have to take development of the soma into consideration. Selection for ageing can then be explained as an antagonistically pleiotropic phenomenon. This process may come about if a particular constellation of genes affects individual fitness in opposite ways at different ages, and if the beneficial effects become manifest at younger ages while the detrimental effects manifest at older ages (Williams 1957). The genes responsible for ageing would thus be kept in the gene pool by selection on their beneficial effects to the young that possess them and not owing to their detrimental effects in senescence. Natural selection can thus give rise to mechanisms that both create and destroy the organism.
Because organisms have a large capacity to maintain themselves in response to external perturbations, it is evident that ageing cannot be likened to a passive “wear and tear” process. Metchnikoff was well aware of this when in 1904 he envisioned old age as an infectious chronic disease which is manifested by a degeneration, or an enfeebling of the noble elements, and by the excessive activity of the macrophages. These modifications cause a disturbance of the equilibrium of the cells composing our body and set up a struggle within our organism which ends in a precocious ageing and in premature death, contrary to nature. (Citation from Bibel 1988).

While Metchnikoff speculated that old age is caused by cells of the innate immune system, Roy Walford (1969) further claimed that the adaptive immune system has a causal role in the ageing of vertebrates. He believed that the immune system incited the pathogenesis of ageing by bringing about “the unleashing of self-destroying processes of the nature of auto-immunity or transplantation disease.” (Walford 1969, pp. 203–4).

In his theoretical outlook Walford distinguished between ultimate and proximate explanations of ageing. He held that proximate causes would differ amongst different species, but that the ultimate causes should be the same. These causes were postulated to reside within the dividing cell populations, but he did not elaborate further upon the mechanisms involved.

Building upon the works of Buss (1987) and Maynard-Smith and Szathmáry (1995), Bruce Charlton (1996) took Walford’s idea one step further when he suggested that ageing was ultimately caused by “endogenous parasites”. Charlton claimed that replicating lineages within an organism should inevitably evolve to elude surveillance, resist suppression and subvert organismal integration. Such lineages, which include malignant cells and clonally proliferating lymphocytes, should gradually adapt to the internal environment. The cells that elude the control mechanisms may then evolve in a, for the organism, maladaptive direction. In this perspective, ageing is the progressive deterioration of the soma owing to the exploitative behaviour of its component parts.

Little is still known about the cellular and molecular bases for longevity differences between species, and the immunologic hypotheses of Metchnikoff, Walford and others have so far not been vindicated. Still, several observations support the statement that the risk of suffering chronic diseases during senescence depends on influences acting early in life, and thus that ageing has a developmental origin. One mechanism that may promote ageing, and which fits nicely into the theoretical framework of Williams, is inflammation following organismal insults. Several observations support the view that while a strong proinflammatory immune response is necessary to resist otherwise fatal infections in early life, the overproduction of inflammatory molecules may cause inflammatory diseases and even death later in life (Licastro et al. 2005).
And in accordance with the views of Metchnikoff, Walford and Charlton, the factors that contribute to inflammation are mostly infectious agents, especially the chronic ones. For example, several viruses have been connected to an altered response pattern of the adaptive immune system. This is probably owing to their induction of a reconfiguration of T cell immunity, manifesting as the accumulation of senescent and dysfunctional cells (Pawelec et al. 2004), a shift in subpopulation frequency and expressed repertoire of antibodies and T cell receptors (Miller 1996), and a concomitant increase in regulatory T cells (Gregg et al. 2005).

These observations, combined with some general characteristics of senescence, including the decreased resistance to infectious disease and a decreased protection against cancer, are compatible with a view stating that higher demands are imposed on the regulatory elements of multicellular organisms during ageing. Deterioration occurs when these demands are exhausted in one way or other. Since the human organism was set to live 40 to 50 years during the course of evolution, it is perhaps little wonder that life beyond that point is marked by chronic diseases that slowly but inexorably damage all the organs, including Alzheimer’s disease, atherosclerosis, and type II diabetes.

5.2. The re-enacting of ancient conflicts

THE EVOLUTION AND DISRUPTION OF INDIVIDUALITY

The concept of individuality, which is derived from the Latin word for non-divisible, *individuus*, has fared a tortuous road. Several attempts at determining necessary and sufficient conditions for individuality have been proposed (Santelices 1999; Wilson 1999), but the concept is still ambiguous. The properties most typically associated with biological individuality include genetic homogeneity, physiological autonomy, spatio-temporal continuity, rejection of grafts from non-self, and demarcation from other members of the same or different species. In the context of the current discussion, individuality is to be understood as an evolutionary concept that denotes entities that possess heritable variation in fitness and who have a complex structure with an internal organisation that develops through time.

Evolutionary individuals have appeared several times during evolutionary history. When for example prokaryotic cells joined to form the eukaryotic cell and when eukaryotic cells joined to form multicellular organisms, new evolutionary individuals emerged as a result of evolutionary transitions (Figure 5.1). Once two individuals joined to form a higher level individual, the two had to relinquish their individuality in favour of the higher level group of cells. The fitness of the previously independent entities were thus transferred to the higher level entity, and survival and reproduction came to depend upon their ability to cooperate for the good of the new individual (Michod 1999).

The multilevel selection approach to evolutionary transitions seeks to understand how a group of pre-existing individuals becomes a new evolutionary individual – how independent entities unite to form a multicellular adapted unit. For the entity
to emerge as an individual, the new evolutionary unit must have found ways to modify the selfish tendency of competing entities while promoting their cooperative interactions for common benefit. In addition, the properties of the new entity must be made heritable to continue the evolutionary race. Given enough time this would lead to well-integrated and well-functioning organisms. What has been termed the paradox of the organism; that it is not torn apart by its conflicting constituents (Dawkins 1990), has thus been solved by evolution through the orchestration of appropriate developmental sequences and the hierarchical imposition of conflict-modifying mechanisms.

The sequestration of germ cells in early development, which in vertebrates takes place at the three or four cell stage (Soriano and Jaenisch 1986), has been proposed as one example of conflict-mediation between cells at the new organismal level (Buss 1987). Sequestration of germ cells implies that the genome of the somatic cells cannot be propagated unless they cooperate to enhance the reproductive potential of the germ. Since cooperation between the germ and the soma delimits the opportunity for cheating and thus disintegration of the new unit, a group consisting of specialised germ and somatic cells is thus no longer divisible – it has become an individual.

While evolutionary individuals are identified by the processes that have generated them, each evolutionary individual has to maintain its organismal integrity throughout life. The word integrity, which is derived from the Latin word *integer*, means the quality of being complete or undivided, and depicts the state of having an intact and uncorrupted self despite continuous conflicting motivations. Integrity thus entails individuality. If integrity is disrupted, evolutionary individuals may be let loose. Zlatko Dembic (2000, p. 563) has naturalised the concept of tissue integrity to be “a measure of all-possible adhesive and signalling contributions that a single cell accepts and sends in its normal, resting state.” According to this outlook, the disruption of tissue integrity – not the experience of non-self or danger, is seen as the prime stimulus for immune system activation.

The maintenance of the integrity of evolutionary individuals is a precarious undertaking, and multiple defence mechanisms against disrupting challenges have evolved. The fact that vertebrate organisms develop from single cells means that, barring mutation, cells in these multicellular organisms are clones. This high level
of relatedness is invoked to explain the high degrees of developmental coordination and extreme altruism observed in extant organisms, for example the relinquishing of reproductive capability by somatic cells. But even though kinship among members of the group tilts selection in favour of the group of cells and away from the entities that make up the group, germ-line sequestration is apparently not sufficient to oblige cooperation.

Several other means of directly suppressing the selfish tendencies of cheating entities have evolved. Such adaptations, which restrict the opportunity for conflict between the levels, are termed conflict modifiers (Michod and Nedelcu 2003). The uniparental inheritance of mitochondria, which ensures that there is no conflict between the mitochondria from the two parents, is one type of evolved conflict modifier. Others include the programmed cell death that occurs during development of the lymphocytes in the thymus, and the production of modifier cells, which are termed regulatory cells when they serve to modify immune system reactivity.

The most important disrupters of integrity are entities that are experienced as foreign to the individual. In the context of the present discussion there are three types of foreignness to consider; infection, chimerism and mosaicism. The parasitic entities that give rise to these phenotypic states display different degrees of disparity as compared to the host individual and thus elicit different degrees of host defence. Some characteristics of these inducers of proximate malfunctions are depicted in Figure 5.2 and summarised in the next section.

**INTRAORGANISMAL PARASITISM**

**Infection**

Infectious agents invade the tissues and cells of the host organism and sometimes even integrate their nucleic acids into the host’s DNA. This generates intercellular heterogeneity and disruption of tissue integrity. While the immune system often manages to rid the exogenous agents before too much damage develops, several agents have evolved mechanisms to evade the immune system and thus to survive

![Figure 5.2](image_url)

*Figure 5.2. The three types of parasitism as delineated by gradations of danger and self. Infectious agents are more non-self than chimeric cells, which in turn are less self than mosaic cells. All three agents may signal danger to the immune system.*
and sometimes even reproduce during the entire life of the host. The agent that causes tuberculosis, *Mycobacterium tuberculosis*, has for example evolved mechanisms to maintain persistence, as have several viruses, including Epstein-Barr virus, HIV and hepatitis C virus.

It has recently become clear that infecting agents that proliferate within a host often display features typical of genetic heterogeneous populations, and that these populations may be in conflict with each other and with other infecting agents as well. The complicated population dynamics that emanate from such interactions has been well described in HIV infection, during which the massive overproduction of mutant viral particles becomes adjusted by the selective pressure exerted by the immune system. The result is a complex distribution of non-identical but closely related genomes that are sometimes termed quasispecies (Eigen 1996; Domingo 1998). The evolution of quasispecies is frequently observed during antiretroviral therapy when strains containing drug-resistance mutations emerge as a result of the selective pressure set off by the drugs.

Another characteristic of viral quasispecies is their frequent compartmentalisation in different cells and tissues of the same patient. This phenomenon, which has been observed during infections with both HIV (Itescu et al. 1994) and hepatitis C virus (Ducoulombier et al. 2004), probably occurs as a consequence of competition and differential survival of the different strains. The multi-strain phenomenon and differential predilection for specific tissues has also been observed in patients infected with Epstein-Barr virus, but in this case it appears that the patients become infected with multiple strains of the virus (Sitki-Green et al. 2004).

It has repeatedly been observed that infections with the Epstein-Barr virus lead to a dysregulated immune response. This is in part owing to the virus’ peculiar capacity to induce transcriptional activation of genes from endogenous retroviruses that are able to stimulate or delete T cells with specific T cell receptors (Sutkowski et al. 2001). There is evidence that also other substances may activate endogenous retroviruses and thus induce poorly regulated immune responses. Since the human genome contains at least 22 retroviral families, some with virtually intact genomes (Bromham 2002), such transcriptional activation may lead to intraorganismal competition and probably also to inflammatory, autoimmune and malignant diseases (Goldberg et al. 2000).

### Chimerism

Owing to the potent defence mechanisms elicited when attempting to transplant cells from one individual to another, the second type of parasitism, chimerism was, with

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2 In Greek mythology, the chimera was a monstrous creature with the head of a lion, the body of a goat and the tail of a serpent. Today, chimeras are routinely created in laboratories – mice and other animals with humanised immune systems are, for example, created for the purpose of better understanding health and disease.
one major exception, long believed to be a rare event in vertebrates. The exception to the rule was pregnancy, during which the mammalian foetus manages to survive despite being located within the uterus. But observations made in the late 1990s demonstrated that vertebrate chimerism may come naturally also in other settings.

The cells of the foetus have invasive potential and may establish themselves within the mother for life (Bianchi et al. 1996), and conversely, maternal cells can be detected in adult offspring up to 28 years of age (Maloney et al. 1999). In addition, as many as 8% of non-identical human twin pairs have chimerical blood (van Dijk et al. 1996). Establishment of microchimerism, which refers to the stable presence of a small number of non-host cells, usually stem cells or their progeny, is apparently only possible during the maturation of the immune system and during pregnancy-related immunosuppression (Anderson and Matzinger 2001). Hence, in contrast to infectious agents which establish themselves despite active host defences, chimerism is a result of host tolerance to foreignness.

Since haematopoietic stem cells may cross the placenta to establish in the mother and child, there is a possibility that the offspring’s lymphocytes may attack the mother’s tissue, and vice versa. Another possibility is that cells that cross the placenta may transdifferentiate into other types of cells, including hepatocytes, myocytes, keratinocytes and neural cells (Forbes et al. 2002). They may then become targets for attack by host lymphocytes, or alternatively, the chimeric lymphocytes may attack the host cells. Both scenarios will result in phenotypic autoimmune disease.

Several autoimmune diseases, including systemic sclerosis, primary biliary cirrhosis and Sjögren’s syndrome, have been associated with microchimerism. These diseases have much in common with chronic graft-versus-host disease which occurs following transplantation. Since graft-versus-host disease is caused by mismatches between the MHC genes of the two individuals, and since autoimmunity associated with microchimerism appears to be linked to MHC molecules, it has been hypothesised that foetal microchimerism may induce autoimmunity in the mother (Nelson 2002). Since there is cellular migration from mother to child as well, and since maternal cells can be detected in adult offspring up to 28 years of age (Maloney et al. 1999), a similar argument may be used to explain autoimmunity in offspring.

Selection pressure exerted by parasites is believed to be the major cause of the polymorphism observed in the HLA, but direct evidence for this supposition is limited (Hughes and Yeager 1998). The diversity may also be owing to mating preferences in some species (Klein 2000). By extending these speculations, one may wonder whether interference with mate selection can have any influence on the prevalence of autoimmune disease. Several investigations have confirmed that MHC molecules are associated with women’s choice of male odour, and that women prefer MHC-disparate males (Penn and Potts 1999; Jacob et al. 2002). When women are taking oral contraceptives, they seem to prefer the odour of MHC-similar men (Wedekind et al. 1995). Since contraceptives mimic the effects of pregnancy, these women may be attracted to MHC-similar men. Accordingly, females that choose mates while using contraceptives and later conceive a child with the same man,
may be at increased risk of harbouring MHC-similar microchimeric cells. Whether or not there is an association between having MHC-similar microchimeric cells and autoimmune disease has, however, never been ascertained.

The chimerism discussed so far originates during the development of the individual organism. But chimerism can also be understood as being the result of evolutionary processes. In the evolutionary sense, all multicellular organisms are chimeric. The nucleus consists of molecules that are phylogenetically related to endogenous retroviruses (Li et al. 2001) as well as to archaeabacterial and eubacterial ancestors (Staub et al. 2004). Quite analogously, the ribosomes (Staub et al. 2004) and mitochondria (Andersson and Kurland 1998) have an endosymbiotic origin. The endogenous retroviruses are able to encode and express proteins that may be targets of autoimmune attack (Krieg et al. 1992), and so are mitochondria (Baum 1995) and ribosomes (Stafford et al. 1998).

Mosaicism

Somatic mosaicism, which designates the presence of distinct populations of somatic cells in a given organism, results as a consequence of developmental processes. Somatic mosaicism is often caused by mutations of DNA, but may also occur owing to changes of the genome that do not affect the DNA sequence. Such changes, termed epigenetic, refer to modifications in gene expression that are controlled by heritable but potentially reversible changes in DNA transcription. The best known epigenetic signal is DNA methylation, in which cytosine, one of the four chemical bases that make up the genetic code, is tagged by a methyl group. DNA methylation is generally associated with silencing of gene expression, whereas active genes are usually unmethylated. But cytosine methylation is also important for genome stabilization, as made evident in people who suffer from immune system deficiencies owing to mutant genes for the DNA-methylation enzyme (Xu et al. 1999).

By metaphorical analogy to mosaics created by artists, Shoenfeld and Isenberg (1989) pictured the different phenotypic expressions that autoimmune diseases may take in different individuals as being the outcome of differential rearrangements of identical or nearly identical biological starting material. For example, the phenotypic expression of systemic lupus erythematosus and multiple sclerosis in monozygotic twins that are discordant for the disease may be owing to epigenetic alterations (Petronis 2001). Such ideas have led several researchers to emphasise the potential role of dysregulated epigenetics as being a susceptibility factor for the development of complex diseases. Epigenetic alterations have also been invoked to explain the age of onset, the phenotypic fluctuations and the differential susceptibility of males and females for disease manifestations. Interestingly, these ideas on development are concordant with Kirschner and Gerhart’s (1998) view on evolvability, according to which evolution may take place without there being alterations in the genetic system.
Mosaicism is a characteristic feature of malignant diseases. Genetic alterations in malignant cells lead to profound changes, including immortalisation, blocking of terminal differentiation, invasiveness and potential for metastasising. Most antigens expressed by cancers are non-mutated self-antigens, and are thus ineffective at triggering immune responses. Hence, malignant cells also have the ability to evade the immune defences; the cells with the highest evasive potential are the ones that are selected for further proliferation. But mosaicism can also take clinical importance if it occurs at the level of haematopoietic progenitor cells in which case it may lead to increased susceptibility for disease, generation of immune diversity and phenotypic variability among monozygotic twins (Youssoufian and Pyeritz 2002).

A special type of mosaicism occurs in women. Early in female development cells randomly inactivate either the maternal or the paternal X chromosome. Each of these cells gives rise to a patch of cells in the adult female that maintains the same X chromosome in the inactive state. Thus, some regions of her body uses the X she inherited from her father, while the rest utilise the X inherited from her mother. A woman is thus a mosaic of two cell populations. Not all the genes in the inactivated X chromosome are inactive, though. About 15% of the genes in the inactivated X chromosome escape inactivation and are thus expressed at higher levels in females as compared to males (Carrel and Willard 2005).

Although not experimentally verified, the phenotypic differences that follow from random inactivation of X chromosomes could theoretically lead to internal conflicts between the two lineages during embryonic development. In line with this reasoning, Jeffrey Stewart has argued that the higher prevalence of autoimmune diseases in females as compared to males could be owing to their pattern of X inactivation mosaicism (Stewart 1998). He argued that if the dendritic cells of the thymus, which are derived from a small number of progenitor cells present at the time of X inactivation, all have the same X inactivation profile, there is a risk that maturing T cells that are reactive against self-molecules encoded by the inactivated X chromosome will not be negatively selected. These T cells will then emerge from the biased thymus as mature T cells. If they encounter peripheral cells using the X chromosome that was inactivated in the thymus, there is a chance that they will interpret the products of that other X chromosome as foreign and thus attack the cells. Thus, autoimmune disease in females is an internal conflict between the two fractions that make up a mosaic woman, much like the chronic graft-versus-host response that follows transplantation and chimerism.

Although the three types of parasitism – infection, chimerism and mosaicism – have traditionally been held to be distinct, some recent observations of transmissible tumours challenge this view. The first suggestive example comes from individuals that belong to the Australian marsupial, The Tasmanian devil. They develop facial-tumour disease following bites by conspecifics in the mouth regions. The disease, which is of high pathogenicity, eventually leads to the death of the animal. Evidence now indicates that the cancerous cells, which are karyotypically similar in the afflicted animals, are derived from a clone capable of being transmitted amongst different members of the species (Pearse and Swift 2006).
The second example comes from a tumour that grows in dogs of all breeds, and which can be transplanted into immunocompetent animals of other canine species, including foxes, coyotes and jackals. While the spread of cancerous cells amongst Tasmanian devils may be owing to a high degree of kinship amongst the members of the species, which reduces their immune responses to the implanted cancers, this is definitely not the case with the venereal tumour disease caused by transmission of cancerous cells between dogs. After coitus, the tumour cells firstly grow rapidly, after which they eventually regress spontaneously three to nine months later. The regression is apparently caused by the immune response as the afflicted animals are immune to rechallenge of the cancer, and since passive transfer of immunoglobulins from recovered dogs also confers immunity. The tumour, which probably arose from a common ancestral neoplastic cell originating in a wolf or a dog between 200 and 2500 years ago (Murgia et al. 2006), has reached a worldwide distribution. It is thus a successful parasite that harbours characteristics of infectious agents, chimeric transplanted cells and malignant mosaic cells.

**AUTOIMMUNITY – A CONFLICT AMONGST EVOLUTIONARY INDIVIDUALS**

Associations to be explained

The term autoimmune disease comprises a fairly heterogeneous group of diseases that are characterised by the occurrence of autoreactive T cells and autoantibodies in the sera and tissues of afflicted patients. The rich variety of autoreactive lymphocytes and antibodies are expressed to a limited degree in healthy individuals, while they are found at high concentrations and in distinct patterns in patients with specific diseases. Since there are few qualitative differences between naturally occurring autoreactive receptors and receptors that are involved in autoimmune disease, and since not all patients with autoimmune disease express autoreactive receptors, autoreactivity is neither necessary nor sufficient for the diagnosis autoimmune disease.

The autoimmune diseases are traditionally recognised as being systemic if the autoantigens are widely distributed, and organ-specific if they are restricted to a single type of tissue. The former group includes systemic lupus erythematosus, rheumatoid arthritis and many more, while the latter group comprises autoimmune thyroiditis and multiple sclerosis amongst others. The relationship between the autoreactive cells and disease etiopathogenesis is circumstantial in most cases. Hence, the term autoimmune disease depicts a nosological, not an etiological entity. There are exceptions to this, though. The autoimmune haemolytic anaemias, which are characterised by autoantibodies that react with membranous antigens, are etiologically defined.

Each autoimmune disease is a heterogeneous entity, and patients diagnosed with the same disease may exhibit a wide variety of symptoms and signs. These features
are well displayed in systemic lupus erythematosus and multiple sclerosis. Systemic lupus erythematosus, which afflicts nearly every organ in the body, is associated with a characteristic pattern of autoantibodies reactive with nuclear, ribosomal, mitochondrial and membranous antigens. Like many other autoimmune diseases, including multiple sclerosis, it has a disproportionate preponderance in that it affects females several fold more often than males. The disease is also typical in that it seldom manifests before puberty but typically shows itself during early adult life (Beeson 1994).

Multiple sclerosis, an autoimmune disease that afflicts the central nervous system, displays similar age and sex-associations to lupus. Like lupus, patients with multiple sclerosis also express a variety of antibodies against intracellular autoantigens (Lu and Kalman 1999), and exhibit strong associations with genetic components, especially genes that encode certain MHC antigens. The increased disease concordance rate in monozygotic as compared to dizygotic twins, 30% versus 5%, is also similar to lupus. The prevalence of the two diseases, which is different at different locations of the Earth, is connected not only with the genetics of the populations who inhabit different regions, but also with environmental stimuli in the different regions (Keegan and Noseworthy 2002).

The unfolding of some infectious diseases is regularly accompanied by expansion of distinct autoantibodies and T cells (Ray et al. 1996). Quite analogously, the immune responses towards malignant cells are accompanied by autoreactive lymphocytes that are generated against antigens that need not even be expressed on the malignant cells (Lang et al. 2003). Also chimerism, for example following liver transplantation, is sometimes accompanied by autoreactive lymphocytes (Vergani and Mieli-Vergani 2002). A most peculiar observation, which contests the view that autoimmunity is a direct consequence of autoreactivity, is the observation that a variety of immunodeficiencies, both of the inborn and the acquired types, are accompanied by increased susceptibility to autoimmune manifestations (Etzioni 2003).

While several successful therapies that specifically target the disease-inducing mechanisms have been described for autoimmune disorders in animal studies, these have so far not been approved for the treatment of human disease. The fact that non-specific treatment, like corticosteroids, interferons and blockade of tumour necrosis factor, is successful while specific treatment is not, suggests that we do not understand the etiopathogenesis of the autoimmune diseases well. Despite claims to the contrary, we remain ignorant of what drives the chronicity of these diseases, and because “we do not understand the differences between the chronic and acute response, we cannot be sure which, if any, animal models of disease provide good reflections of the key processes that occur in human disease.” (Feldmann and Steinmann 2005, p. 612).

When viewed from a biosemiotic angle, according to which sustained survival requires continuous monitoring of environmental signs followed by precise adaptive responses to the encountered stimuli, the relevance of animal models for human autoimmune disease becomes especially problematic. Whether the immune system
of an animal detects a sign or not depends upon the evolutionary history of the species to which it belongs. Hence, there is a possibility that organisms of different species interpret the world differently, and that they in a sense inhabit different antigenic Umwelts. Differing Umwelts combined with multiply realised immune systems and conventional classification of immune system diseases suggest that proximate explanations of malfunctions may not generalise well.

Proximate explanations

In *The clonal selection theory* and in *Self and not-self* Burnet (1959, 1969) explained autoimmunity as an occurrence that followed failures of inactivation mechanisms for self-reactive T and B cells in the central lymphoid organs. The mechanisms that lead to central tolerance have now been worked out in detail, and several experimental investigations in animals testify to their importance. It is clear that self-reactive B and T cells normally escape the central inactivating mechanisms, but that they are rendered non-pathogenic by several mechanisms that lead to peripheral tolerance. These include failures at co-stimulation by accessory molecules, B cell receptor editing and several others. Hence, autoimmunity should occur when the suppressive mechanisms, be they central or peripheral, fail to perform.

Much recent work has been put into investigations of the regulatory aspects of the immune response, and many autoimmune diseases are now considered to be the result of a dysregulated immune system. Skewed functionality of regulatory T cells and the cytokines they produce has been amongst the strongest candidates to explain diseases like lupus and multiple sclerosis. Failures at regulation are connected to genetic factors in the afflicted individuals, but environmental factors are also important.

The association between autoimmune diseases and certain MHC molecules is for example believed to be owing to the ability of these MHC molecules to present disease-inducing peptides to autoreactive T cells. The peptides may be derived from self or from non-self that mimic self. Among the best characterised environmental factors that lead to autoimmune disease are infectious agents. For example, both lupus (McClain et al. 2005) and multiple sclerosis (Lang et al. 2002) express autoreactive receptors that cross-react with molecules of the Epstein-Barr virus. While some autoreactive responses may be explained by molecular mimicry, in which the pathogen exhibits molecules that are very similar to the molecules of the host, this is not always the case (Rose 1998). There are also convincing observations which suggest that the activation of endogenous retroviruses may be the proximate cause of multiple sclerosis (Fujinami and Libbey 1999) and lupus (Adelman and Marchalonis 2002).

While lupus is characterised by major disturbances in the B cell system, the major disturbances in multiple sclerosis are within the T cell system (Williams et al. 1994). And whereas treatment with interferon-α alleviates the symptoms of multiple sclerosis, interferon-α appears to have a pathogenic role in lupus. This
phenomenon may be owing to the differential effect that interferon has on accessory cells and on the differentiation of T cells into T helper 1 or T helper 2 cells (Lohoff and Mak 2005).

Several mechanisms may account for the associations between autoreactivity and infection. These include release of sequestered auto-antigens following tissue damage, induction of inflammatory cytokines and costimulatory molecules, as well as trade-offs between the beneficial and deleterious effects of the regulatory T cells. The mechanisms can all lead to the expansion of autoreactive cells. Nevertheless, direct links between any cause and specific autoimmune diseases has rarely if ever been established. While infectious diseases have been associated with a variety of chronic autoimmune diseases, a true causal pattern between infectious agents and a specific disease has rarely been revealed in humans. The interactions are complex, and the causal chain goes in both directions; in some cases infections trigger autoimmunity, while infections may protect against autoimmunity in other cases.

In their discussion of self tolerance and autoimmunity John Rioux and Abul Abbas (2005, p. 584) summarised the contemporary status of proximate explanations in the three postulates

i) autoimmune disease develops when self-reactive lymphocytes escape from tolerance and are activated.
ii) the failure of self tolerance is the fundamental cause of autoimmunity
iii) autoimmunity is thought to result from a combination of genetic variants, acquired environmental triggers such as infections and stochastic events.

While the three postulates cogently summarise the received view on autoimmunity, a deeper analysis of the postulates discloses that they are better at revealing lack of knowledge than of explaining. As will become clear in the following sections, postulate i) has low explanatory value because activated self-reactive lymphocytes are prevalent also in healthy individuals; postulate ii) is tautological in that failure of self-tolerance is but another expression for autoimmunity and so cannot be its cause; and postulate iii) is too general to be of any explanatory value. Still, postulate iii), or so I will argue, parses the investigation in the right direction as it hints to the evolutionary genesis of the predisposition for autoimmunity.

An ultimate explanation

Contesting the explanandum

The paradoxical notion that the immune system serves as a vehicle for self-destroying capacities is currently regarded as the main explanandum of autoimmunity. It dates back to the 1950s when Ernest Witebsky, in an attempt to circumscribe the inconsistent concept of autoimmunity, designated etiological criteria for
human autoimmune disease. The criteria, which were later revised to accommodate new knowledge derived from molecular and cellular biology, were graded into three evidential categories: direct, indirect and circumstantial (Rose and Bona 1993).

**Direct evidence** for autoimmune disease comes from transfer studies in which a disease is reproduced in a healthy individual following direct transfer of antibody, for example from mother to child during pregnancy. **Indirect evidence** is obtained if the disease can be reproduced in experimental animals or if autoantibodies or self-reactive T cells can be isolated from the afflicted organs, while **circumstantial evidence** includes statistical associations with autoimmune phenomena or susceptibility genes as well as favourable response to immunosuppression.

Fundamental to the revised criteria is the belief that “the disease is caused by an autoimmune response of the host without regard to the origin of that response.” (Rose and Afanasyeva 2003, p. 136). This way of framing the problem has encouraged a wide range of investigations, but although much information has been collected concerning the detailed immunopathology of autoimmune diseases, most evidence for autoimmune disease remains indirect and circumstantial. It is therefore relevant to ask whether diseases subsumed by the two latter criteria really are on par with disease as identified by the first criterion, and whether exclusion of the origin of the autoimmune response from the explanandum is wise or not.

To give an example, the rheumatic diseases systemic lupus erythematosus, Sjögren’s syndrome and rheumatoid arthritis are believed to be autoimmune, but the evidence for this is largely indirect and circumstantial. As is made evident from investigations demonstrating that the probability of disease given observed antibody is low, the autoantibodies that characterise the diseases are neither necessary nor sufficient constituents of the disease (Ulvestad et al. 2000). On the other hand, when combinations of several autoantibodies are tested by likelihood ratio testing, it is clear that patients with rheumatic disease have distinct immune system aberrations that are not manifest in control patients (Ulvestad 2003). The results of such investigations point out a major explanatory problem in autoimmunity research; the fact that autoreactivity is common and occurs naturally (Avrameas 1991), and that pathogenic autoantibodies are routinely generated during the response to foreign antigen (Ray et al. 1996). It even appears that autoreactivity may be beneficial for organ restitution and elimination of waste products (Masloréns 2000; Schwartz 2002), and it has been postulated that autoreactivity is a special case of immunity – while immunity removes threats from without, autoreactivity removes threats from within (Nevo et al. 2003).

Observations that autoreactivity comes naturally, both following infections, malignancies and chimerism, and that autoimmune disease may occur in immunodeficient individuals, are not easily reconciled with the view that all diseases currently categorised as autoimmune diseases are caused by the immune system. On the other hand, the observations would be likely under a hypothesis stating that autoreactivity in some diseases is merely an epiphenomenon that occurs as a result of some other cause. As demonstrated in the next section, this idea allows
us to discriminate between inflammatory epiphenomenal autoreactivity and true autoimmunity. The difference is dependent upon whether the disease emanates in the innate or the adaptive immune system.

*Organismal integrity – a precarious undertaking*

Since the concept of immunity signifies the idea that independent organisms stand against each other, the addition of the prefix auto- should designate the paradoxical conception that the competing organisms were integrated within one and the same organism. This view, which makes sense if the cells of the host fight an invading infectious agent, is not as straightforward if there are no foreigners to contend. However, if organism is understood as laid out in this book, as a composite entity made up from lower level individuals that once coalesced to form higher level individuals, autoimmunity can be put on par with immunity, the difference being that immunity designates contemporary conflicts whereas autoimmunity is the re-enacting of ancient conflicts between lower level evolutionary individuals.

This theoretical outlook entails that anything that has or gains heritable variation in fitness, including infectious agents, mitochondria, transopsons, malignant cells, chimeric cells and lymphocytes, should be able to precipitate autoimmune disease. Furthermore, it serves to explain a wide variety of perplexing phenomena in autoimmunity without having to invoke one type of reactivity for immunity and another for autoimmunity. And since maintenance of both integrity and identity are explained through a unified hypothesis, explanatory coherence is conserved. The view does, nevertheless, necessitate that we reconceptualise and disunify our ideas of what autoimmune diseases are.

The re-enacting of ancient conflicts is owing to the embodied drive inherent in any organism that is or once was an individual. Organisms are designed by natural selection to transmit their genes to future generations. Each composite organism consists of a variety of evolutionary individuals that are harmonised to enhance fitness. It is central to the hypothesis that when any of the evolutionary individuals undergo reproduction, there is a chance of conflict because not all genes, be they in mitochondria, somatic cells or lymphocytes, have equal opportunities to be transmitted to the offspring. Reproduction thus provides a chance for evolutionary individuals to exploit the organismal resources at some cost to the rest.

To ensure fairness in reproduction, countermeasures against exploitation have evolved. For example, most genomes contain suppressors that limit the activity of endogenous retroviruses; most cells have mechanisms that suppress the mitochondria; and most organisms have suppressors that regulate the activity of their immune system. Malfunction of any of these conflict modifying systems should lead to a reactivation of the selfish tendencies of the evolutionary individuals involved. If for example ancient retroviruses are left unchecked, there is a real chance that the internal workings of the cells involved would malfunction and that disease would ensue. And if tumour suppressor genes are malfunctional, malignancy may ensue.
In an analogous manner, the regulatory context becomes disarrayed when a conflict between hosts and pathogens occurs.

It is an interesting but largely unexplored possibility that activation of the immune system may be caused not only by non-self or danger, but also by the relaxation of control mechanisms. It is a common observation that cells grown in vitro take on an activated profile. This phenomenon is usually assumed to be owing to the fact that the cells become activated by the novel surroundings. While this is probably true in many cases, it is conceivable that some cells take on the activated profile because suppressive mechanisms that kept them silenced when in situ have been relaxed. To the extent that this is correct, the result obtained from in vitro studies need to be given a cautious interpretation as to their relevance for the in vivo situation.

There are several mechanisms that could deregulate the conflict modifying systems, but infectious disease is probably the most prevalent. This is made evident by the high proportion of autoimmune disease that are associated with infectious agents and by the observation that 15–20% of all cancers are related to infection. Infections may impinge on systemic, intercellular, cytoplasmic and nuclear suppressor systems, and the same infectious agent may thus impinge on many suppressor systems simultaneously. The outcome of the various competitive interactions will probably depend on the number of cells involved, and chronic disease is probably a chance occurrence that occurs if the dose is high, the struggle is intense, the different agents are mismatched, and the duration of the conflict is beyond a point of no return.

In accordance with this perspective, disease is the result of malrestricted competition between evolutionary individuals. The conflicts are seen as being the result of failures at conflict-modification. Deregulation of conflict modifiers would allow the suppressed individuals to regain their embodied drive and thus to partake in conflicts within. The three kinds of parasites previously discussed may themselves deregulate the regulators and thus induce conflicts. Continued activation of the immune response, either through chronic infections, chimerism or malignancy, should be able to modulate the embodied drive of evolutionary individuals. If these are the lymphocytes, it should lead to autoimmune disease. Autoimmune disease is, accordingly, a proximate manifestation of ultimate and unresolved conflicts.

While dysregulated conflict modification is the common feature of autoimmune disease, the variegated symptoms and immunophenotypic changes that accompany the various diseases are probably consequential to the level at which conflict modification is disrupted. Since the levels are entwined, it is conceivable that a disruption of conflict modifiers at one level should afflict the conflict modifiers at other levels. The stratified defence system, in which the adaptive immune system has been built upon the innate immune system, would imply that malfunctions of the innate system should have a readout in the adaptive system. But since this readout occurs as a consequence of innate dysregulation, it should not be designated autoimmunity; inflammatory activity would be a better term. Hence, in this case the expanded autoreactive T and B cells are only epiphenomena to the underlying unresolved conflict.
The common explanation for associations between immune system derangements and disease. The immune system has been evolutionarily selected to function optimally. Malfunctions are not selected but occur owing to deregulation of regulators in either the innate or the adaptive immune systems. Any deregulation may lead to diseases and immune system derangements. The deranged response may thereafter influence the signal and thus establish a vicious circle.

Figure 5.3. The associations between parasitism and disease as well as the difference between inflammatory and autoimmune diseases are depicted in Figure 5.3. If the conflicts emanate at the level of the innate immune system, the adaptive immune system derangements are but epiphenomena to the true conflict at the lower level. If, on the other hand, the conflict modifiers are severed at the level of the adaptive immune system, as occurs when central or peripheral tolerance-inducing mechanisms are disrupted, the ensuing disease is truly autoimmune as it is caused by the autoreactive receptors. Thus, of three evidential categories summarised by Rose and Bona (1993), direct evidence for autoimmunity emanates in the second lens, while the indirect and circumstantial evidence may as well be located to the first as to the second lens.

Stocktaking

The hypothesis stating that chronic diseases are caused by the re-enacting of ancient conflicts between evolutionary individuals emphasises the role of conflict modification and deregulation of conflict modifiers throughout development, and is built on three major assumptions. The first assumption is that conflict modifying mechanisms emerged and evolved as a consequence of evolutionary transitions, especially the transitions from prokaryotes to eukaryotes and from eukaryotes to multicellular animals, and that harmonising of the layered and entwined conflict modifying mechanisms was necessary at the higher transitory level. The second assumption is that some conflict modifiers, owing to their central function for cellular life,
should have been retained throughout phylogeny. A third major assumption is that deregulation of the conflict modifiers should lead to malfunctioning.

There is much evidence to support the hypothesis, but since it was abducted from observations already at hand, its fit with observations can not by itself be used to evaluate its credentials. After all, evolutionary explanations are in many ways akin to “just-so” stories in that they may provide justified accounts that fit any observation whatsoever (Gould and Lewontin 1979). Hence, as any other evolutionary hypotheses, the conflict hypothesis needs to be tested by investigating the accuracy of its predicted observations and by comparing these predictions to predictions made by alternative hypotheses. In the following, several mechanisms and molecules involved in some sort of conflict modification that provide differential support for the hypothesis are enlisted. The record is not intended to give a comprehensive treatment of the subject, but is merely intended to hint at directions for further investigation.

The first group of defence-related conflict-modifying molecules to be considered, the cyclophilins, have been demonstrated in a wide variety of organisms, from prokaryotes to metazoans and plants (Romano et al. 2004). The cyclophilins are found in all tissue types and in all subcellular compartments of multicellular organisms, where they take part in the folding of proteins as well as in other cellular processes. Although much remains to be learned about the regulation of cyclophilins and their role in protective responses, they have been associated with the protection of cells from apoptosis (Lin and Lechleiter 2002), from retroviral infections (Towers et al. 2003), and from overreaction to bacterial endotoxins (Trahey and Weissman 1999).

When the immunosuppressive drug cyclosporine A, which binds to and inhibits the activity of cyclophilins, is administered to patients with transplanted tissues, the pronounced immunosuppressive effect induces acceptance of the graft. The drug can also induce remission of autoimmune diseases like lupus (Dammacco et al. 2000) and multiple sclerosis (Pette et al. 1997), while it enhances the development of cancer (Andre et al. 2004). Thus, cyclophilins seem to be involved in the inflammation or autoimmunity induced by infectious agents, chimeric cells and mosaic cells, although their exact role in these processes is not known.

Another group of widely distributed conflict modifying molecules, the heat shock proteins, is present in prokaryotes and in different subcellular compartments of eukaryotes, including the nucleus, mitochondria, endoplasmic reticulum and cytosol. Their synthesis is upregulated during infection, transplantation and cancer, and it has been suggested that they have become specialised to modify stressful events through their impact on cytokine production, triggering of Toll like receptors and deliverance of maturation signals to antigen presenting cells (Pockley 2003).

The heat shock proteins also facilitate protein folding of many important signal transduction elements; they influence morphogenetic responses to environmental cues, and buffer normal development from the destabilizing effects of perturbation processes. They are thus important for the ability of organisms to mount plastic responses to environmental signals. They may also buffer the impact of mutations,
as proteins with amino acid changes become unstable unless heat shock proteins help their folding. In *Drosophila melanogaster* the importance of heat shock proteins is made evident by observations that flies with mutations in the heat shock proteins exhibit various phenotypic variations that are not observed in flies without these mutations (Rutherford and Lindquist 1998). While the effects of various amino acid changes are masked in flies with normal heat shock proteins, flies that are heterozygous for mutant heat shock proteins show unusual morphological abnormalities because their heat shock protein activity is insufficient. Hence, mutations that are masked in normal flies reveal themselves as morphological anomalies in heterozygous flies. An even more pronounced buffering effect of heat shock proteins has been observed in the plant *Arabidopsis thaliana* (Queitsch et al. 2002).

Heat shock proteins, which are upregulated at sites of inflammation, are strong inducers of the innate immune system (Prohaszka and Fust 2004), but are also involved in regulation of the adaptive immune system. The proteins are immunodominant, and a substantial amount of the T cell response to infectious agents is directed towards peptides derived from these proteins. It has been speculated that this response towards heat shock proteins from infectious agents leads to an anti-self response owing to molecular mimicry, and that this response precipitates autoimmune disease. Recent evidence does, nevertheless, indicate that T cells reactive with own heat shock proteins are regulatory T cells that serve to suppress autoimmunity (Van Eden et al. 2002; Pockley 2003). Upon this scenario, the heat shock proteins function as conflict modifiers of both the innate and the adaptive immune system.

Conflict mediation occurs also at the level of the nucleic acids. For example, the stability of RNA is regulated by small interfering RNAs whose nucleotide sequence can pair with messenger RNA, thus targeting this mRNA for destruction before it can be translated into protein. The small interfering RNA mechanism appears to be an evolutionary ancient mode of genome defence that has important regulatory roles in both prokaryote and eukaryote genomes (Gottesman 2005). It serves to protect the germline of *C. elegans* against retroviral elements (Vastenhouw and Plasterk 2004), and there are also indications that the system protects against viral infections (Carmichael 2002). The degree to which it has any role in malignancy is still not clarified.

While cyclophilins, heat shock proteins and interfering RNAs are present in all organisms, some conflict modifying molecules apparently made their phylogenetic appearance with the multicellular organisms. This includes the molecule 2-5A synthetase, which is expressed in sponges as well as in vertebrates, but not in bacteria and yeast (Cayley et al. 1982; Grebenjuk et al. 2002). In human cells, the enzyme is localised to the nucleus, the nucleolus, the ribosomes and the mitochondria (Besse et al. 1998). The enzyme, which induces the cleavage of single-stranded RNA, has a functional role in intracellular homeostasis and defence against infecting agents. The function of the enzyme is best characterised in antiviral host defences, but the enzyme also functions in the regulation of the stability of RNAs that control host cell division, differentiation and apoptosis. It thus regulates the survival and
reproductive ability of both self and non-self. The dual role of the enzyme requires that it should be tightly regulated; otherwise it might lead to disenchanting consequences. Too strong expression would lead to elimination of infectious agents but also to self-harm, while too low expression would lead to increased reproduction of the infectious agent at a cost to the host’s reproduction and survival.

While the deleterious consequences of 2-5A synthetase are tolerable in organisms like sponges, in which cells are disposable to a higher degree than cells of vertebrates, higher metazoans with specialised organ systems would require either the disappearance of the enzyme, as has happened in insects, or it could become regulated by a higher level system, as took place in vertebrates where the genes for 2-5A synthetase came to be strongly regulated by interferon-α (Der et al. 1998).

Interferon-α has a multitude of effects, but only some of these are mediated through 2-5A synthetase. Interferon-α regulates the activity of a wide variety of genes, and it provides an important linkage between the innate and the adaptive immune systems, for example by acting as an adjuvant through the stimulation of dendritic cells (Le Bon and Tough 2002). Owing to potent anti-viral and antiproliferative effects, interferon-α has been used with success for the treatment of chronic hepatitis C viral infections, for leukaemia, and for autoimmune diseases such as multiple sclerosis. The exact mechanisms by which interferon-α treatment reduces disease activity in multiple sclerosis are largely unknown, but they may be mediated through receptors for interferon-α on microglial cells in the brain (Yamada and Yamanaka 1995). Microglia are macrophage-like cells that are able to stimulate and be stimulated by T cells, and who effectuate the degradation of myelin in multiple sclerosis brains (Ulvestad et al. 1994). But there may also be other mechanisms involved as interferon-α treatment of patients with multiple sclerosis increases the concentration of IgG and complement components and decreases the concentration of lymphocytes (Ulvestad et al. 2004).

Patients with lupus have serum levels of interferon-α that are sometimes as high as in patients with acute viral infections and in patients on treatment with interferon-α. Interestingly, a prominent side-effect of interferon-α treatment in patients with cancer and infectious disease is the development of autoantibodies against nuclear antigens and the development of autoimmune-like disease. Since the diseases are characterised by dysregulation of apoptosis, it has been hypothesised that the autoreactive antibodies are generated against material from apoptotic cells, and that these autoantibodies are rendered pathogenic in genetically predisposed individuals because of the adjuvant effects of interferon-α. This then leads to the formation of immune complexes that act as endogenous inducers of interferon-α, which again sustains the autoimmune process, thus establishing a vicious circle (Ronnblom and Alm 2001).

In a similar manner to the molecules involved in the innate immune response, the receptors of the adaptive immune system have a role in conflict modification. The evolutionary precursors of the receptors were probably non-rearranging molecules engaged in signalling and adhesion that became co-opted for defence-related functions in the vertebrate lineage (van den Berg et al. 2004). Their descendants are
expressed on the so-called innate B and T lymphocytes, a subset of phylogenetically old lymphocytes that express germ-line encoded autoreactive antigen receptors.
The cells, which recognise inducible self-ligands in conditions of tissue damage, cellular injury and stress, have probably been evolutionary selected to carry out a set of regulatory functions that involves cell-to-cell communication (Bendelac et al. 2001).

The precursors of the adaptive immune receptors, who very likely were mediators of conflicts amongst cells within the organism, evolved to become mediators of conflicts between the host and the parasitic world. This imposed a novel selection pressure on the receptors, and the adaptive immune system thereafter evolved largely as a result of the selective pressure imposed by infectious agents. But since the genes encoding the variable parts of the immunoglobulin and T cell receptors were anciently involved in mediating conflicts within, there were structural constraints on the molecules that restricted their future evolution. It is likely that the ancient function of the co-opted immune receptors could not be eliminated in vertebrates, and that this is why they have a relatively high affinity for endogenous evolutionary individuals, many of which needed to be controlled by a policing mechanism during the evolutionary transitions.

The autoreactive receptors that expand during infectious disease in current vertebrates may therefore be triggered, not by the disease-inducing agent, but by the danger experienced by the cells. The receptors are, in a sense, re-enacting their role as mediators of conflict between evolutionary individuals. This readily explains why the most common autoantigens are phylogenetically conserved molecules localised to distinct compartments within the cell, amongst others the nucleus, the nucleolus, the ribosomes and the mitochondria. The autoantigens in lupus are for example evolutionary conserved intracellular molecules that are involved in important functions such as DNA replication, chromosome segregation, DNA transcription and protein translation (Tan 1996). When viewed from an evolutionary angle it further emerges that the targeted antigens possess a common characteristic in addition to that of being evolutionary conserved; they are associated with ancient endosymbionts.

But if immunoglobulins were re-enacting ancient conflicts one would expect that the various antibodies against each autoantigen, say against double stranded DNA, should display some conserved characteristics in their antigen-binding sequences; that their usage of variable fragments should be restricted. This is not the case, and even though there are abnormalities in the B cell functioning of the systemic autoimmune diseases, there is little common variable-region gene usage (Dorner and Lipsky 2001). The heterogeneous repertoire of T cell and B cell receptors even suggests that there is an antigen-driven immune response in many of these diseases (Capra and Natvig 1993). This may, however, be owing to the fact that the receptors analysed were derived from diseased patients. Whether the pre-disease autoreactive receptors were similarly mutated is not known.

The heterogeneity of receptors observed may also be owing to the fact that each germline encoded antibody can bind to a large variety of unrelated antigenic
determinants. While this ensures that the primary antibody response is composed of antibodies with a high degree of evolvability (Manivel et al. 2002), in some cases these antibodies can recognise epitopes both on infectious agents and self-molecules (Quinn et al. 1995). If the antibodies are triggered by the infectious agent, this may further explain the absence of observed gene-restriction of autoimmune receptors.

5.3. Environmental challenges

The resources of innate and adaptive immunity, which include the molecules and cells that constitute the immune system, are memory traces that have been shaped during previous immune responses, both in evolutionary and developmental time. While the memory traces of the innate immune system are engraved entirely in the genes, the memory traces of the adaptive immune system are in addition engraved in the variable antigen receptors and in the relative concentrations and distribution of cells and molecules that make up the system.

Deficiency of resources need not lead to malfunction since immunocompetence is multiply realisable. And although deficiency and malfunctioning are tightly associated within the innate immune system, the two do not have the same ontological status within the adaptive immune system. Malfunctions or deletions of the resources that make up the innate immune system are seldom encountered. This is partly owing to their deleterious consequences when absent and, hence, their fitness reducing effects. But it is also owing to the way that deleterious effects are buffered during development. For example, if specific resources of the innate immune system are absent from birth, as in gene knock-outs of certain cytokines, the consequences are often less serious than if the same deficiencies develop in adults. This is probably because the immune system self-organises to perform its function without them.

While total deficiencies of the innate immune system are rare, several variant molecules that are differentially associated with resistance to infectious agents exist. These include amongst others CD14, which is a receptor for bacterial lipopolysaccharide and probably also has a role in immune deviation towards allergic disorders (Baldini et al. 2002); a transcription factor for IL4, which is of importance for allergy deviation (Rockman et al. 2003); CCR5, which is a co-receptor for HIV and thus protects against HIV infection when absent (Paxton and Kang 1998); and caspase-12 which is associated with differential susceptibility to serious infectious disease (Saleh et al. 2004). Certain variants of the polymorphic defence molecules have also been associated with malfunctions of the adaptive immune system. The polymorphisms of these genes have a decisive effect on the response patterns of the adaptive immune system and are therefore closely associated with its functioning.

Within the adaptive immune system malfunctioning signifies a relational property that needs not become manifest until the organism encounters an unfavourable environment. Deletions of components of the adaptive immune system are quite
frequent. They often go unnoticed, and their fitness reducing effects are not of the same magnitude as failures of the innate immune system. For example, deficiency of secretory IgA, which is the most common of the primary immunodeficiencies as it afflicts one in seven hundred individuals, is a heterogeneous condition with symptoms ranging from none to recurrent respiratory or gastrointestinal diseases (Edwards et al. 2004). While secretory IgA has a defined biological role, most individuals deficient for IgA are healthy owing to compensating defence mechanisms. There are alternative pathways to reach the same functional result, and IgA deficient individuals therefore seldom experience serious symptoms. While these alternative pathways may not be as efficient for protecting the mucosal membranes as IgA, they may still perform the feat as required.

Allergic, autoimmune and other chronic inflammatory diseases are sometimes said to be caused by an imbalance between the various types of T helper cells. This claim is unfortunate because the balance metaphor, which is derived from the ancient Hippocratic teachings, signifies a passive system in which the basic cure of any malfunction is to restore the balance between the elements. A better metaphor would be to envision the adaptive immune system as a decision-maker. Decisions involve recognition, regulation and thresholds, and signify activity as opposed to passivity. In addition, a decision-making system is compatible with the bearings of the embodied drive hypothesis. Deficiency of resources is seldom encountered in patients with allergic and autoimmune diseases, but biased decisions amount. Hence, the adaptive immune system may be responding in a functional or malfunctional manner according to how the decisions are effectuated.

ALLERGY – THE SPATIO-TEMPORAL MISMATCH HYPOTHESIS

Immunologists have characterised the proximate causal interactions of allergic disease in detail. But while they have been successful at explaining the mechanisms that lead to specific symptoms, including mast cell release of histamines upon triggering with allergens and IgE, they are less able to explain why the prevalence and severity of allergic disease have increased during the 20th century (Jackson 2001). It is clear that neither the human population nor the allergens that are the proximate causes of allergic symptoms have undergone any radical evolutionary process during this short time, and the role played by natural selection should therefore be negligible.

Nevertheless, if one acknowledges that the functionality of selected traits are spatio-temporally restricted, the increasing prevalence of allergic disease can still be understood and explained within an evolutionary framework. Since natural selection favours different genes in different places, organisms that are adapted to one environment and then move to a different environment may produce less adapted offspring in the new environment. The classical case of this is sickle cell anaemia, but the argument goes as well for temporally separated environments; if
the current environment differs from previous selective environments that gave rise to the trait, there is a real chance that adapted traits may be rendered malfunctional in contemporaneous surroundings.

In contrast to genetic resistance to malaria, which is unrelated to the developmental age of the individual, a growing body of evidence suggests that resistance to allergic, autoimmune and infectious disease is laid down in utero and during early childhood. Resistance is governed via a series of control mechanisms associated with the functional transition of the relatively quiescent foetal immune system to the more competent state required to survive in the extrauterine environment. For example, the capacity of the immune system to produce Th1 cytokines is selectively constrained during foetal life, probably owing to the cytokines’ toxicity towards the placenta (Chaouat et al. 2002). This cytokine deviation is achieved in part via the secretion of Th1-inhibitory mediators by the placenta.

After birth, recognition of microbial signals from the extrauterine environment, particularly via stimulation from the intestinal microflora, progressively induces maturation of the immune system towards the adult-equivalent range. The kinetics of this developmental process is highly variable, and slow or deviated maturation appears to be associated with reduced microbial stimulation. The belief that absence of microbial stimulation during early life events leads to immune system malfunctions has been epitomised as the hygiene hypothesis (Strachan 1989). One of it’s current versions holds that the Western world’s preoccupation with cleanliness has led to an altered intestinal microbial colonisation (Kim and Drake-Lee 2003). The microbes in the gut, which have coevolved with humans throughout evolutionary time, provide important signs to the developing immune system. And when the evolutionary selected interactions are altered, it alters the development of the immune system as well. This induces a lack of tolerance to otherwise harmless food proteins and inhaled antigens, as well as towards self-antigens. Immune system diseases like allergy are thus induced because the adjuvancy of our society has changed.

Traditionally, infectious agents are thought to precipitate disease because they compete with the host for resources. But those who take the Heideggerian view of the world seriously would argue that it is equally evident that microbes may do as much harm when absent. According to this view, only agents that are already being-with-others in the world can experience a loss; or stated differently, one cannot loose something that does not belong to oneself. And when individuals loose their evolutionary selected microflora, they simultaneously loose a part of themselves. This loss is proximally owing to the stimulating activity of microbial factors on the developing immune system. Because the microbes set up the network properties and response dispositions of the immune system, they perform a formative rather than, or in addition to, an efficient causal role.

The original hygiene hypothesis centred on the role that Th1-inducing microbial infections had on inhibiting Th2 mediated allergies. The balancing metaphor was often utilised to explain the effects of the different Th subsets, and disease was thought to be an imbalance between Th1 and Th2 responses. However, it has recently become clear that regulatory T cells are able to control the effector mechanisms of both Th1
and Th2 cells, and so the hygiene hypothesis has taken the form of a regulatory, not a balancing hypothesis (Maizels 2005). For example, multicellular worm helminth parasites have exerted a major influence on the evolution of the vertebrates. Worm-infection, which is highly prevalent in non-Western societies, is often asymptomatic, suggesting that the helminths have evolved sophisticated methods of immune evasion. Infection with helminths leads to a predominant Th2 response with production of high levels of IgE, but nevertheless, the infected individuals are protected from allergic manifestations. This, according to the regulatory hygiene hypothesis, is owing to the activity of T regulatory cells, which suppress effector mechanisms of both Th1 and Th2 cells (Wilson and Maizels 2006).

But individuals also differ in their genetic predisposition towards allergy. A recent observation in humans has intriguing bearings on the possibility of natural selection working on the Th1/Th2 network (Rockman et al. 2003). A single nucleotide polymorphism in the promoter of the cytokine IL4 was found to affect the binding of a transcriptional activator of IL4 in T cells. The allele, which leads to a threefold increase in IL4 production compared with the other allele, is common in some populations. Although the allele is currently associated with increased risk of allergic disease as it shifts T cells towards the allergic Th2 type, it might have conferred resistance against disease caused by infectious agents at some point in the evolution of the human species. This interpretation is supported by results that indicate that natural selection, and not genetic drift, drove the differentiation of the alleles. Selection on the IL4 promoter, which alters the cytokine pattern within the immune system, illustrates the importance of regulatory variation as well as the ease with which new beneficial regulatory interactions can occur by point mutation (Rockman et al. 2003).

The increasing prevalence of allergy has been characterised both as “the modern plague” and “epidemic”. Thus, in a sense the epidemic has become more virulent. That Westernisation of the world leads to more hygienic environments is well supported by data, but epidemiological data further indicate that cleanliness is not a sufficient cause for allergy to increase. The critical factor appears to be the interaction between relevant patterns of the environment and critical developmental stages of the individual organism. If the intersection between the two is uncoordinated in some way or other, if there is a spatio-temporal mismatch, allergic disease may develop (Figure 5.4).

The spatiotemporal mismatch hypothesis is able to explain both autoimmunity and allergy as being the results of evolutionary contingencies. There is much evidence that the increased incidence of autoimmunity and allergy that emerged during the twentieth century is directly associated with altered relations between hosts and parasites. The proximate causes involved in the two types of disease are thus similar, as both are caused by dysregulated conflict modifiers and because infectious agents are the main offenders of the conflict modifying mechanisms. While the roles of chimerism and mosaicism have been much explored in autoimmunity, their role in allergy is still largely uncharted, and the studies that have been performed are permeated with inconsistent findings (Turner et al. 2006).
**Figure 5.4.** According to the time-space model of organismal interactions with the environment, environmental change can change developmental outcome, thus leading to novel phenotypes. The life course of individual organisms are depicted as arrows, the length of each arrow stipulates relative length of individual life. The meandering line stipulates important environmental signals that impinge on the developing organism. Each individual encounters environmental stimuli at different periods of their life cycle, as marked by the intersection between arrow and environmental meandering. The figure depicts the narrowing diversity of environmental stimuli, the Westernisation of society, and indicates at least one individual (upper right) that does not receive the appropriate developmental triggers.

**CROSSING BARRIERS**

The most dramatic effect of host-pathogen interactions occurs when the spread of pathogenic microbes reaches epidemic proportions, in case of which an entire group of individuals or even a whole species may become extinct. This may happen if host organisms encounter infectious agents not previously present in their environment. The defence systems will then not be properly adapted to the new agent and catastrophic consequences may ensue. With the arrival of Christopher Columbus to America in 1492 the Indians, who had remained largely isolated from people on other continents for more than 30,000 years, experienced a mortality from infectious disease of more than 90% in many places (Naranjo 1992). The Indians had developed free from the epidemics that had been attacking Europe, Asia and Africa, and were therefore defenceless against infections caused by influenza, smallpox, measles, yellow fever, malaria, diphtheria and typhus.

Extensive human travelling all over the globe, increased contacts between previously separated species, increases in population sizes and changes in ecology are believed to be responsible for the emergence of new infectious disease and their rapid spread throughout the world, leaving few populations naive for long periods of time. An illustrious case was the outbreak of severe acute respiratory syndrome (SARS) in Southeast Asia in the spring of 2003 caused by a new type of coronavirus.
The virus, which passed over from an animal host to people, infected about 8000 individuals of which 10% died. The economic costs of SARS were estimated to nearly US$100 billion, mostly as a result of cancelled travel and decreased investment in the afflicted areas (Pearson et al. 2003).

The SARS epidemic was an astounding example of how quickly international collaborative efforts can identify causal infectious agents and provide diagnostic tests to identify infected but not yet diseased patients. The World Health Organisation (WHO) issued its first global warning on March 12th, and about a month later a detailed paper about SARS and the coronavirus responsible for the syndrome was published (Peiris et al. 2003). Solid background information helped the researchers to select workable hypotheses and methods to identify the infectious agent, and within three months methods for diagnosing of SARS were established around the world. Knowledge of the causative agent and its mode of spread established that isolation of infected patients would limit the dissemination of SARS. This measure was a success and by early July 2003 the WHO declared that the human chains of SARS virus transmission had been broken everywhere in the world.

Epidemic diseases of humans and their agricultural products may come to threaten the entire human enterprise if not proper measures are instantiated to limit their spread. About 40 new infectious agents responsible for human disease have been identified during the last 30 years (Desselberger 2000). The recurrence of old infectious agents and the emergence of novel diseases are cause for concern. When vaccines or specific treatment are unavailable, one has to rely on preventive measures or on the capability of the immune system to clear the infectious agent. That this is not always feasible has been shown repeatedly. A better understanding of the tactics used by novel pathogens as well as of the immune system’s defensive strategies is thus needed to handle the threats from without.

Ignorance of evolutionary and ecological aspects of host-parasite relations is a hindrance to the invention of alternative explanations for immune phenomena. For example, the explaining of host-pathogen interactions as a combat between the immune system and the microbe has severely biased the explanatory focal point. This is because the war-metaphor, which emphasises organismal survival, fails to take notice of the reproductive aspects of fitness. Since trade-offs involved in optimising one or the other fitness component may lead functional systems to evolve in quite opposite directions to the ones predicted, both kinds of fitness should be investigated.

A science that is comfortable with studying nature’s entities, the \textit{natura naturata}, without aiming to understand the processes that generate them, the \textit{natura naturans}, is in-comprehensive and runs the risk of seeing but aspects of the phenomena it aims to understand. In biology essentially new events continuously take place, events that defy prediction by virtue of inductive methodology. Based on previous observations and inductive methodology it is, for example, relatively straightforward to predict the likely occurrence of a new influenza epidemic next year. But the same methodology is not suitable to predict the novelties which are of practical concern – the antigenic characteristics of next years’ influenza virus. Such prediction would
require a more fine-grained understanding of evolutionary and ecological premises as well as better surveillance strategies.

The entities we observe have already happened and can therefore happen again – they are determinate possible. In biological evolution, however, novel phenomena may take place that were not immanent in those phenomena that preceded them. These are emergent phenomena – they are thus indeterminate possible (Østerberg 1988). The distinction between the determinate and indeterminate possible is important both epistemologically and ontologically. For the researcher that wants to predict novelty it is of essence to transcend the determinate possible that belongs to the *natura naturata*. Knowledge of the indeterminate possible can hardly be realised by studying *natura naturata* in isolation, but by investigating mechanisms, *natura naturans*, he may hope to be able to predict the indeterminate possible. The researcher that tries to outsmart the influenza virus by making a vaccine is in the business of predicting the virus’ next move up the evolutionary ladder. By getting a grip of *natura naturans*, his hopes of predicting the evolution of the virus and thus to produce a vaccine before the virus has finished its evolution, may come within reach.

To get an idea of the complexities involved, a comparison with a game of chess between a computer and a human opponent is appropriate. Because of the strict and unchanging rules of chess, computer scientists have managed to create successful computer programs that outperform their human competitors by their ability to predict the biological opponent’s next move. But while chess is performed according to fixed rules that generate determinate possible outcomes, the rules of host-pathogen interactions are constantly changing, thus making the outcomes indeterminate possible. These outcomes are still far too complex to simulate in a computer model.

The virus that tries to outsmart the host’s immune system by evolving novel antigenic structures is acting out the game of life, in which the only reward is paid in the currency of fitness. Like the researcher who needs a theory with predictive power, the host organism needs a defence system that is capable of acting in accordance with the same principles. While it is clear that the immune system is empowered with this capability when it encounters infectious agents with evolutionary conserved structures, several observations indicate that the predictive powers of the adaptive immune system are restrained. The fact that infecting agents manage to seclude themselves from the host’s defence systems and thus induce chronic inflammatory diseases attests to this (Lorber 1996; Zimmer 2001).

The post-SARS warning by the director general of WHO, that the global population could expect to face a new infectious disease every year, underscores the need to be alert to and continuously survey for emerging diseases. The burdens of health and the economic costs involved when infectious disease reaches epidemic proportions automatically launch questions like: What type of infectious agent causes the disease? By which mechanisms does the agent inflict disease? Why is the agent pathogenic? Are there any behavioural alterations that can limit the spread of the disease? Is specific therapy available? When will a vaccine be provided?
Clarification of the queries requires extensive interdisciplinary and international collaboration between scientists trained in a variety of biological and medical specialities, including specialists trained in immunology, microbiology, evolutionary biology, ecology, molecular biology, epidemiology, pharmacology and vaccinology. The specialists should investigate the co-evolution of man and specific microbes as well as ecological interactions between man and a variety of other species, and all these observations should be related to the developmental stage of the individual. Investigation of the genetics of the interacting species will not suffice; the spatio-temporal appearance of reciprocal signals should also be evaluated. These signals may for example be developmentally shaped, and two infectious agents with the same genetic architecture may thus differ in pathogenicity even in identical twins. Semiosis and phenotypic plasticity are thus of essence.

Evolutionary theory in its contemporary form is not the kind of theory that can reveal the necessity of what happens or what will happen. A fundamental question that needs to be asked is whether it can become such a theory. Based on results from empirical and conceptual investigations outlined several places in this book, I think not. The basic arguments upon which I base this belief were outlined already in the 19th century, with Darwin’s theory of natural selection and Hegel’s conceptualisation of history. Kierkegaard (1849, p. 59), who adapted many of Hegel’s insights, gave a precise formulation of these when claiming that “freedom is the dialectical element in the categories of possibility and necessity”. In our discussions of the immune self it became clear that the self is a kind of being that eludes attempts at objectivation; it cannot be caught in the act, so to say. The self is thus elusive and transcendental. And so is life, both of parasites and hosts. Since both the self and life itself are essentially free, they are transcendental in nature, always ready to cross barriers.

Freedom is mediated between semiosis (possibility) and law (necessity). The dialectic taking place between the two is extremely difficult to investigate and conceptualise. Whether or not science, even if it manages to grip the natura naturans through the natura naturata, will be capable of crossing the epistemological barrier between the determinate and the indeterminate possible is therefore an open question. Perhaps the most we can hope for is to be able to cope adaptively with the challenges of infectious agents and the malfunctioning immune system on a short term basis. But even this achievement, which will require outstanding research efforts of both empirical and conceptual sorts, will keep scientists occupied for decades.

As long as life continuously transcends its boundary conditions, the philosophical void that Orosz (2000) would like to see filled, between the satisfying accumulation of immunologic facts and their unsatisfactory understanding, can in principle not be fulfilled until the history of life has reached its completion. Hence, contrary to Jerne’s 1969-statement, the scientific era does not draw to an end (unless the same goes for life); the most we can say as of today is that the end of immunology might have begun.
These ideas on the course of history, which I have adopted to answer Orosz’ query for new perspectives on reality as well as to explain the ongoing history of host-parasite relations, were eloquently formulated by Hegel in his preface to the *Philosophy of right*:

Philosophy, as the thought of the world, does not appear until reality has completed its formative process, and made itself ready. History thus corroborates the teaching of the conception that only in the maturity of reality does the ideal appear as counterpart to the real, apprehends the real world in its substance, and shapes it into an intellectual kingdom. When philosophy paints its grey in grey, one form of life has become old, and by means of grey it cannot be rejuvenated, but only known. The owl of Minerva takes its flight only when the shades of night are gathering. (Hegel 1821, p. xxx).