

## THE DEVELOPMENT OF THE DEFENCE SYSTEM DURING EVOLUTION

PETR SÍMA

Institute of Microbiology, Czech Academy of Sciences,  
Department of Immunology and Gnotobiology, Prague, Czech Republic

### SUMMARY

A progressively growing bulk of evidence has shown that the immunity is an integral part of a general homeostatic system maintaining the integrity of the internal environment of an organism. Eumetazoan animals respond to the pathogens invasion with a cascade of adaptive reactions involving neuroendocrine and immune co-operations. In all living animals today the immune mechanisms evolved into an effective device which enabled their successful survival, and above all, their adaptive radiation in the biosphere. The immune strategy common to every natural assemblage of animals (a phylum) represents an appropriate fundamental morphofunctional pattern according to evolutionary history, and is determined by the natural forces of the environment in which these animals have radiated. The important animal assemblages in their order of increasing complexity comparing their basic body plans in relation to their immune potential are depicted in this survey.

### INTRODUCTION

There is no function without a structure, and there is no structure without a history. The history has always two faces, an ontogenetical and a phylogenetical one. The immunity is one of the basic attributes of all living creatures. The aim of this short overview is the reconstruction of its emergence from various points of view, and its evolutionary history. For this purpose we can theoretically admit the existence of major superassemblages of more interrelated, natural groups of animals. Within these groups, the immune capabilities of their representatives in the relation and dependence on their morphofunctional endowment will be determined.

### GENERAL REMARKS

#### **Evolution of homeostatic systems**

Homeostasis is a major attribute of all living matter, which is realised by a row of orchestrated autoregulative processes, including immunity (Austin, 1978). All living creatures from the

protists upward behave as open systems (Bertalanffy, 1953). We may accept them within the definition made by Orgel (1973) as "Complex - Information - Transforming - Reproducing - Objects - that - Evolved - by - Natural -

Selection". This definition can, from immunological point of view, be modified by adding - "and maintaining their integrity".

Even the most primitive ancient organisms had to integrate their simple processes into a harmoniously balanced form, and more than one function had to co-ordinate at the same time. Fulfilment of this condition is the basis for transition from inorganic matter to a living organism regulating its metabolism. The emergence of regulatory mechanisms was fundamental for establishment of the homeostatic control (Bernard, 1877; Lahav, 1985).

#### **A role of hierarchisation in evolution of homeostatic systems**

Obviously, the more complex an organism is, the more stratified is the organisation of its homeostatic devices ("the stratified stability"). The capacity to maintain stability increases with greater stratification of the biological system.

The genetic code, and the biochemical and physiological processes are virtually constant among both the lowest and highest animal phyla. More than 90% of total enzyme activities is common in both the prokaryotes and eukaryotes. Similarly, the cells as structural entities (tissues and organs as well) are constructed with the same uniformity. Thus the only evolutionary way of achieving the greater complexity is by increasing the structural and functional hierarchisation (Bronowski, 1970; Bonner, 1988).

#### **Homeostasis has adaptive advantages**

Each higher level of homeostasis ensures better adaptation capability of species (Huxley, 1953). The adaptive advantages of homeostasis have been obviously functioning in periods of evolutionary stasigenesis, when ensured

a relatively long-lasting stage of stable survival of the species (Rensch, 1966). Qualitative changes of homeostatic mechanisms have passed during evolutionary dysbalance, within stages of anagenesis (progressive evolution) and cladogenesis (diversification).

#### **Evolution of neuroendocrine regulation**

The changes in the metazoan way of life from the sessile way to the active seeking of food were accompanied by the origination of new structures and organs that would ensure more developed locomotory functions. The increasing morphofunctional complexity required a considerable increase in energy supply. The ancestral metabolic system was not sufficient any more, but the new, more efficient mechanisms for obtaining energy from the food did not evolve as a consequence of this transition. It was precisely the evolving and consolidating of the system of hormonal hierarchical regulations that assured the more efficient stimulation of these traditional metabolic pathways to manufacture energy more effectively (Czaba, 1980; Pertseva, 1991).

#### **Co-evolution of immune and neuroendocrine systems**

Up to the present, the highest level of homeostasis has been reached by the mutual functional interconnection of highly hierarchised systems, the neuroendocrine and immune (Ader, 1981). Almost all hormones secreted in the organism have been shown to significantly influence the immunological reactions and humoral immune vectors like cytokines may affect their neuroendocrine targets. Moreover, many kinds of hormones are manufactured by immunocompetent tissues and cells. Immune and neuroendocrine systems are similarly organised and phylogenetically emerged in a similar way: from dispers-

edly localised cells and tissues towards highly structurally hierarchised organs.

### **Immune mechanisms have evolved as a defence of individuality**

The existence of living organisms on the Earth is conditioned by their ability to maintain their own individuality, which means the ability to keep genetic self-stability. Every organism either extinct or extant is a product of a never ending co-evolution with other organisms, from microbial to multicellular, in the form of symbiosis, commensalism, or parasitism. The principle to maintain individuality of all eukaryotic multicellular animals, from the sponges upward, lies in the prevention of any other alien form of living system into the internal milieu.

From this point of view, immunity must be considered as a fundamental attribute of living organisms, similar to metabolism, irritability, or reproduction. All of the following eventualities could caused the emergence of the first immune phenomena among ancestral organisms.

### **Factors threatening the integrity**

#### *Parasitism*

It was already mentioned that the uniqueness of an individual is ensured by the functional co-operation of neuroendocrine and immune systems. However, only immune system is able to neutralise and to destroy pathogens penetrating from external environment. Diseases accompany all living creatures from the very beginning of their lives and the faculty of falling ill (the pathibility) belongs to the general characteristics of life. Under the evolutionary pressures of pathogenic vectors, the immune mechanisms have been more precisely formed with the primary aim

to increase the possibility of the individual to survive (*Doberstein, 1951*).

#### *Fusion*

The fusion of genetically different individuals or their parts means the threat of somatic parasitism and it can result in the lost of individuality. The transplantation reaction may be a phyletic consequence of the adaptations to the risk of that parasitism (*Buss and Green, 1985*).

### **Internal processes requiring homeostatic regulation**

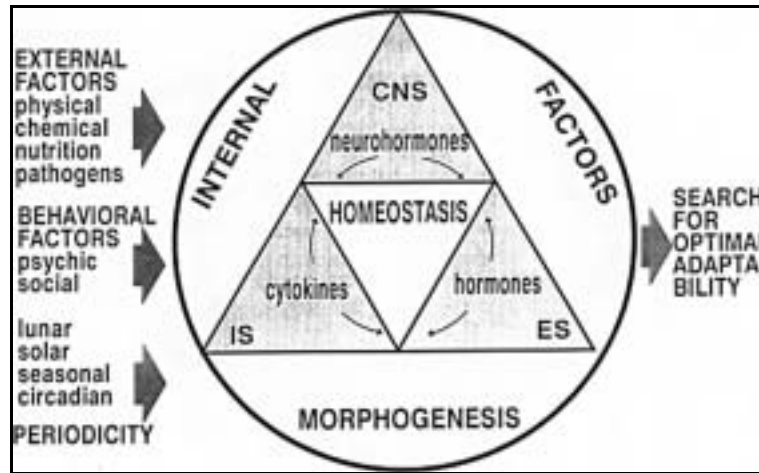
#### *Growth, morphogenesis, ageing*

Whereas the neuroendocrine system monitors the chemical characteristics of internal environment, the immunity perceives the antigenic expression on the cell surfaces throughout the body. The synchronisation of the processes of histogenesis (histolysis) during embryogeny requires a regulation by a system capable of both the recognition and elimination of disturbances (*Moscona, 1974; Stewart, 1992*). The same is valid for the surveillance and elimination of potential harmful changes during postembryonal stages of life (*Goya, 1991*).

#### *Neoplasia*

Mutant cells, which do not fulfil their functional role and may represent a potential danger for a steady-state within the internal milieu are recognised and eliminated by immune mechanisms. The molluscs, arthropods, and vertebrates are the only animal groups with clear-cut cases of neoplasia. In spite of that, all animals with at least cell-mediated immune system can be expected to have neoplasms (*Balls and Ruben, 1976*).

The complex role of homeostasis is shown in Figure 1.



**Figure 1:** The complex role of homeostasis.

## EVOLUTION OF IMMUNITY

### Basic mechanisms of immunity

Two fundamental patterns of internal defence strategies evolved in the remote past: the constitutive (non-anticipatory) and adaptive (anticipatory) immunity (Klein, 1989). The constitutive immunity involves innate mechanisms utilising predominantly the phagocytic cells, killer cells, and non-specific humoral substances. To be endowed by the adaptive type of immunity means to possess the specific receptors recognising and binding a vast number of antigenic epitopes, and as a consequence of these events to manufacture a row of cellular and humoral reactions realising the specific response.

All main taxa of eumetazoan animals have developed proper immune strategies constricted by their morphofunctional possibilities only. However, three basic immune phenomena are common for all animal assemblages: the capability of recognition (of self or nonself), processing of immunogenic material, and response to it.

### Recognition

Recognition should be understood as an affectory phase of the immune reaction. Generally, it means a type of communication of an individual with the surrounding environment. All organisms, even the unicellular ones, are capable of recognition *via* their cellular surface receptors. The protostomians do not possess variable-region molecules, e.g. immunoglobulins or TCR. Emergence of these molecules among ancestral vertebrates was a crucial novelty for the evolution of adaptive immunity (Cooper, 1992).

### Processing

The processing can be understood as the transport of the signal received from the receptor to other molecules, and subsequent analysis of the information from the signal (Werdelin and Mouritsen, 1992). The endocytosis is generally regarded as the first stage of immune processing. All eukaryans are capable of phagocytosis. In more ad-

vanced animals with more hierarchised immune system, various types of specialised populations of accessory and effector cells evolved to meet the needs of efficient effector parts of the immunity (Síma and Větvicka, 1992).

#### *Response*

The effector phase of the immune reaction is the response. As a large diversity of animals exists, it is not surprising that various forms of immunological response can be found. These forms differ from each other in several respects: specificity, rapidity, efficiency, and existence of immunological memory.

#### *Analogy and homology*

The elucidation of questions concerning the evolution of immune systems is connected with the problems of origin and relationships between the metazoan phyla. Different ancestry resulted in different consequences even under the same selective pressures. The research of the analogy and homology of immunity should generally be subordinated to the following considerations (Síma and Větvicka, 1990):

1. The emergence of qualitatively new immune properties occurs at all phylogenetical levels, and many properties are passed on vertically from ancestral taxon to another as apomorphies.
2. The principal variations in immune characters cannot be presupposed within a single natural group of animals (a monophyletic taxon).
3. The more evolutionary remote natural groups of animals (sister groups), and the more remote animals are from their ancestors, the greater the differences will be found in their more complex immunity.
4. The more evolved (or younger in

evolutionary terms) such natural assemblage is, the more complex may the immune pattern be. This is not valid for some specialised groups, e.g. the parasites. These animals did not evolve a more progressive types of immunity, but rather conserved the ancestral type, or even partially lost some of its functions.

#### **The basic body plan**

Multicellular organisms with whatever body arrangement, shape, and size had to ensure the availability of chemical substances for life of every cell, and the removal of the wastes. The larger organisms evolved networks of channels directly connecting their internal tissues with the exterior (water channels in sponges), or replacing of external environment by fluids or "blood" circulating within the systems of body spaces, channels or vascular system.

All animals belonging to the main phyla are built on the same fundamental body plan, which represents the most convenient evolutionary compromise between the morphofunctional possibilities determined by the genome and selective pressures coming from the environment. Larger steps in the phylogeny of homeostatic systems always began with the appearance of the new basic body plans in the main animal phyla, especially with the emergence of the first coelomate and metamerised metazoans, further with the onset of chordate-vertebrate basic body plan and endothermy (Clark, 1964; Romer, 1971). Similarly, all variations of immune apparatuses within a phylum are the variations of one ancestral scheme, more or less specialised according to developmental changes associated with the major morphological novelties accumulated during the evolution (Conway Morris, 1993; Valentine et. al., 1996).

## THE OVERVIEW OF IMMUNE PHENOMENA AMONG MAIN ANIMAL TAXA

### DIBLASTIC PHYLA

#### **I. Irregular or radial, cell-aggregate basic body plan**

##### *The poriferans*

The sponges are most primitive multicellular creatures. Neither true tissues nor organs are present, and the cells display a considerable degree of independence. To summarise the immune pattern of the sponges they have a highly discriminative and, in the same extent, co-operative cellular defence system. Phagocytosis is the major defence reaction, and the free-wandering amoeboid cells, the archaeocytes, are the main effector cell population. They are active also in quasi-immune recognition, cytotoxic reaction, and graft rejection. The various lectins are involved in aggregation phenomena allowing cell to cell contacts (Vasta, 1991). The histoincompatibility and cytotoxicity may seem to be correlated with the presence of inducible specific alloimmune memory (Hildemann et al., 1980; Van de Vyver and Barbieux, 1983).

#### **II. Radially symmetrical sac-like basic body plan at the tissue grade of construction**

##### *The coelenterates and the ctenophorans*

The functional specialisation of cells

can be seen for the first time in phylogeny. The gastrovascular cavity is in larger species transformed into a series of narrow canals functioning similarly to a circulation system. The simple general body plan of coelenterates was not sufficiently plastic, thus the more complex immune structures or organs could not develop. Therefore, the immunological defence of these animals remained limited only on phagocytosis and histoincompatible reaction accompanied by certain alloimmune memory (Bigger and Hildemann, 1982; Buss et al., 1985). A humoral component of the coelenterate immunity could be represented by an external mucus secreted by most of these animals. It may play a role in the protection against pathogens (Burkholder, 1973), recognition processes, as well as in cytotoxic reactions (Muscatine, 1989). It is possible that the coelenterates avoid other more complex evolutionary solution of their immune potential by developing a very effective capability of regeneration which is regarded to be the most powerful in the entire animal kingdom. The speed of healing following a damage may significantly reduce the possibility of pathogen invasion (Sparks, 1972).

### TRIBLASTIC ACOELOMATE PROTOSTOMIAN PHYLA

#### **III. Bilateral sac-like basic body plan at the triploblastic grade of construction**

##### *The platyhelminths*

The platyhelminths are endowed with a third layer, the mesoderm, which represent an important advance in phylogeny: it forms an evolutionary background for later emergence of various organs including those devoted to immunity.

Mesodermal parenchyma contains free wandering cells, the neoblasts, which have features resembling some vertebrate haemocytoblasts. Planarians are still devoid of a definitive blood-vascular system and no specialised structures for the immune functions are known. Immune capability of these mostly minute animals are scarce, and only phagocytosis and graft rejection have

been described. Most species of flatworms have also considerable powers of regeneration (*Valembois, 1982*).

#### **IV. A tube-within-a-tube basic body plans**

##### *The nemerteans*

In comparison to flatworms, there are two evolutionary progressive features in nemerteans: Their digestive tract has a second opening (the anus) situated at the posterior part of their body; Secondly,

even more important, they are the first animals in phylogeny possessing a true closed circulatory system. Their vessels are lined by an epithelium, which is exceptional among the invertebrates. Cells resembling vertebrate macrophages and small lymphocyte-like cells can be found among several categories of blood cells. The nemerteans are able to reject xenografts with some sort of short immunological memory (*Langlet and Bierne, 1977*).

### **PSEUDOCOELOMATE PHYLA**

##### *The aschelminths*

The common feature of these animals is the possession of a body cavity derived from a persistent blastocoel - the pseudocoel. These animals are devoid of any circulatory system. The role of

free-wandering amoeboid cells inside the mesenchymatous tissue is unknown. Practically, no information is available about their immune patterns (*Van de Vyver, 1981*).

### **EUCOELOMATE SCHIZOCOELIC PHYLA**

#### **Origin and importance of the coelom**

The acquisition of the secondary body cavity (the coelom), in eumotazoic body pattern conferred further progress upon the hierarchised control of homeostatic processes. The originally pluripotent mesodermic cells composing parietal or splanchnic layers of coelomic linings may differentiate under the inductive influence of ectoderm or endoderm into various functionally specialised tissues or organs. The development of organs within the sufficient space and their stratification along the alimentary tract could secure better effectivity of digestion and better utilisation of nutritions, and by that way it allowed higher income of the energy for more active life. These new conditions, together with growing body size, made the previous mechanisms of transportation of nutrient or waste less effective (by diffusion or cellular distribution) or fully inefficient, and could concomi-

tantly induce the development of independent transport system. A well-established circulatory system is therefore obligatory for almost all eucoelomate phyla.

The representatives of annelids, arthropods, and molluscs forming an artificial superassemblage, the "annelid superphylum", are regarded with a build-up of their secondary body cavity according to the schizocoelic mechanism. The echinoderms, hemichordates, and chordates ("echinoderm superphylum") form their coelom in enterocoelic way (*Kerkut, 1960; Clark, 1964*).

In eucoelomate animals the first defence structures evolved in connection with rostral part of the digestive tube, where the exposition to the environmental antigens induced development of such organs like typhlosole, a common organ present not only in invertebrates but also in some less advanced vertebrates.

### *The sipunculans*

The sipunculans possess a well developed coelom but no real vascular system has been formed. No haemopoietic structure has been discovered in the sipunculans, so that the differentiation of free coelomocytes probably occurred from the peritoneal epithelia (Dybas, 1981). These cells are vectors of the immune phenomena like recognition, phagocytosis, and elimination of particles from the coelomic

space. Moreover, they possess enzymes used in vertebrate cells for killing the bacteria. From the humoral defence factors, lysins and agglutinins have been determined in the coelomic fluid. Some signs of spontaneous cytotoxic activity of sipunculid leucocytes against various allogeneic and xenogeneic cells has been found, in contrast with previous acoelomate or pseudocoelomate animals.

## EUCOELOMATE SCHIZOCOELIC METAMERISED PHYLA

### **Origin and importance of metamerism**

The second key event in phylogeny, comparable in its importance to the evolutionary emergence of the coelom, is segmentation or metamerism. At this crucial event, the branching into two main directions of evolution within the animal kingdom established the differentiation of the annelid and the echinoderm superassemblages. All eumetazoic animals above this evolutionary level are segmented and have a coelom. It is important to realize the evolutionary importance of metamerism for the immune phenomena: the sophisticated defence systems in both members of annelid or echinoderm superphyla could evolve only in coelomatic segmented animals in which the regional specialisation of their body patterns has been the *conditio sine qua non* for functional specialisation

(Clark, 1964).

### *The echiurans*

The spoonworms represent the last evolutionary solution of the body construction antecedent the splitting of eucoelomic body plans into the modifications seen among representatives of annelid and echinoderm superassemblages. For the first time in phylogeny, segmentation appears to be a transitional phase during ontogenesis. Moreover, most of adult forms possess a closed simple blood-vascular system. No data are available about the immune pattern of these animals nor about the defence role of their free cells with exception of a clumping-like reaction in presence of bacteria (but no accompanying phagocytic reaction was observed). Only some bactericidal activity in the coelomic fluid has been described (Dybas, 1981).

## THE "ANNELIDE SUPERPHYLUM"

### *The annelids*

Generally, all structural novelties emergency of which we have followed and which are unambiguously considered to be fundamental, (i.e., the coelom, the closed blood vascular system and the metamerism), together with all major organs and organ systems are present. A relatively high number of

free-wandering cells can be found both in the coelomic fluid and inside the vascular system. They arise from specialised parts of coelomic or blood vessel epithelia, or from the distinctive structures described as "lymph glands" (Dales and Dixon, 1981). The main cell types involved in the defence processes (recognition, phagocytosis, encapsula-



tion, and histoincompatibility reaction) are various categories of amoebocytes (Cooper and Stein, 1981). With regard to the humoral immunity, substances with haemolytic, haemagglutinating, antibacterial, and antiviral properties have been detected in coelomic fluid. Moreover, the molecules of nonimmunoglobulin nature with enhancing effect on the phagocytosis, amounts of which can be increased by antigenic stimulation, and the primitive cytokine activity (IL-1 and IL-2-like) have also been found. It may be concluded that at least some representatives of annelids have evolved a highly sophisticated system of mutually collaborating cellular and humoral defence components, in many respects comparable to those of vertebrates *per analogiam*. Earthworms can be considered to be the first invertebrate animals having a specific anamnestic immune response (for review see Větvíčka, et al., 1994)

#### *The arthropods*

The arthropod's body plan has been proved to be enormously plastic and its modifications paved the way for the immense number of various species. The real coelomic cavity exists only in very early ontogeny. In later stages it gradually fuses and forms a mixocoel. The blood circulation system can be considered practically as open. The immune system of arthropods is capable of specific recognition of a wide range of antigenic material, and mounting of a vigorous response against it. Haemopoietic organs were found in larger species, and many morphologically distinct types of free or sessile cells manufacturing a wide range of the immune functions like phagocytosis, encapsulation, or rejection of transplants were described. In addition, an advanced system of humoral defence factors collaborating with the cells can be found. Bacterial agglutinins, the prophenolox-

dase, and lectins could serve as examples of defence factors naturally present in the haemolymph. The lysozyme, cecropins, attacins, dipteridins, defensins, and other molecules are among the inducible factors (Sherman, 1981; Bauchau, 1981; Gupta, 1991). It may be concluded that in this enormous and varied animal superassemblage, the very effective immune mechanisms based upon the proper design of co-operating components have been created.

#### *The molluscs*

The molluscs represent a sister group to the common stock of true coelomate groups, resembling them in few synapomorphic characters. They have rather mesenchymate organisation of their body design with very limited coelom due to the enormous development of the primary body cavity which has been transformed into a large vascular system, the haemocoel. All molluscs have this open system, with the only exception of cephalopods. These animals reached a maximal level of complexity of their blood vessel system which cannot be found in any invertebrate phyla. A steady state of renewal of haemocytes inside the vascular system, the epithelia and connective tissue, takes place. In case of emergency, the recruitment of haemocytes from connective tissue occurs. This phenomenon is analogical to that in the murine peritoneal cavity. Some haemocytes display macrophage-like properties. These cells produce a number of defence humoral substances with strong lytic, cytotoxic, agglutinating, and opsonising activities. Moreover, the presence of cytokine-like molecules (IL-1, IL-2, IL-6, TNF- $\alpha$ , and TNF- $\beta$ ) in the molluscan haemocytes has been observed (Franceschi et al., 1994). The existence of two effective phagocytic systems, the free cells and fixed cells, approximate the molluscs in analogy to that of vertebrates.

All molluscs recognise and respond to foreign materials, and in some species a surprisingly high degree of specificity occurs. On the other hand, the molluscs seem to lack the recognition of allograft tissue as non-self, but xenografts were always rejected. The majority of humoral substances and cell-surface factors manifest a lectin character (*Suzuki and Mori, 1990*) which may attach to or

agglutinate microbes and parasites, facilitate the processes of phagocytosis and encapsulation, or possess opsonising capabilities. In conclusion, with the exception of the above-mentioned analogies, nothing permits speculation about the homology of the mollusc immune pattern with that of vertebrate or any other invertebrate phyla (*Fletcher, 1982*).

## ENTEROCOELIC DEUTEROSTOMIAN PHyla

### The "echinoderm superphylum"

#### *The echinoderms*

The echinoderms represent a sister group with the chordate-vertebrate lineage. A number of crucial developmental characteristics are common to both assemblages. The coelom of echinoderms is well-developed and structurally specialised in the functions of vascular and haemocoelic systems. The echinoderms have developed the distinct organs with coelomocyte-poietic activity from which the axial organ appears to be ancient "lymphoid" organ. This organ is often considered to be a homologue of the vertebrate spleen. The axial organ cells were shown to be heterogeneous and its adherent cell subpopulation is regarded to express B cell-like characters. These cells were shown to produce a lytic protein factor having antibody-like properties. Another protein, the IL-1-like factor, was isolated from coelomic fluid (*Beck et al., 1990*). The echinoderms are able to reject allografts in a manner similar to that of vertebrates (*Karp and Coffaro, 1982*). Second-set allografts are destroyed in an accelerated manner. These phenomena indicate a clear-cut evidence for a specific memory which may represent an ancestral discriminative type of vertebrate transplantation immunity. The killing reaction against both allogeneic and xenogeneic echinoderm cells, as well as against normal and tumour vertebrate cells, can

be regarded as an analogue of the spontaneous cytotoxic reaction of vertebrate NK cells. Conclusively, the basic cellular defence reactions of echinoderms are still phagocytosis and encapsulation (*Smith and Davidson, 1981*). On the other hand, they possess remarkable immunological features that cannot be found in any other invertebrate phylum.

#### *The cephalochordates*

The cephalochordates are considered to be the true transitory group on the evolutionary pathway to vertebrates. The free coelomocytes seem to play no role in the defence except phagocytosis. Natural lectins of the invertebrate type have been demonstrated, but neither their recognition role nor co-operative role with phagocytes has been elucidated (*Millar and Ratcliffe, 1990*). Despite the apparent lack of any immunocompetence, these animals possess the ability to amplify their population of free cells by a mechanism common lately to all vertebrates, i.e. the proliferative multiplication of lymphoid cells. Moreover, cells morphologically similar to vertebrate lymphoid cells have been documented in the pharyngeal region (*Rowley et al. 1984*).

#### *The urochordates*

The haemocoelic vascular system of urochordates contains more types of

free cells capable of co-operation during a very specialised phagocytosis and encapsulation (*Wright and Ermak, 1982*). The histopathology of encapsulation resembles the formation of vertebrate granulomas. The urochordate lymphocyte is often regarded to be the homologue predecessor of all vertebrate lymphoid cells. The haematogenic tissue is organised in discrete structures (called "lymph nodules") localised in the vicinity of branchial region and digestive tract. A homology between those structures and haemopoietic tissues of vertebrates is supposed. The blood cells are involved in allogeneic rejection associated with a colony specificity and programmed senescence. It was suggested that the transplantation reaction is

governed by a MHC-like gene locus (*Weissman et al. 1990*). The lectins and other natural factors with an antibacterial activity in body fluid, together with the presence of some molecules of Ig superfamily (Thy-1 or a disulfide-linked heterodimer surface protein resembling mammalian lymphocyte receptors) has been described. Interleukin-like molecules also have been identified (*Raftos, 1994*). In summary, the urochordates possess main features of adaptive immunity: a structural basis resembling both the haemopoietic and the macrophage-phagocytic systems of vertebrates, and a capability for continual renewal of immunocompetent cell populations co-operating with humoral cytokine-like factors.

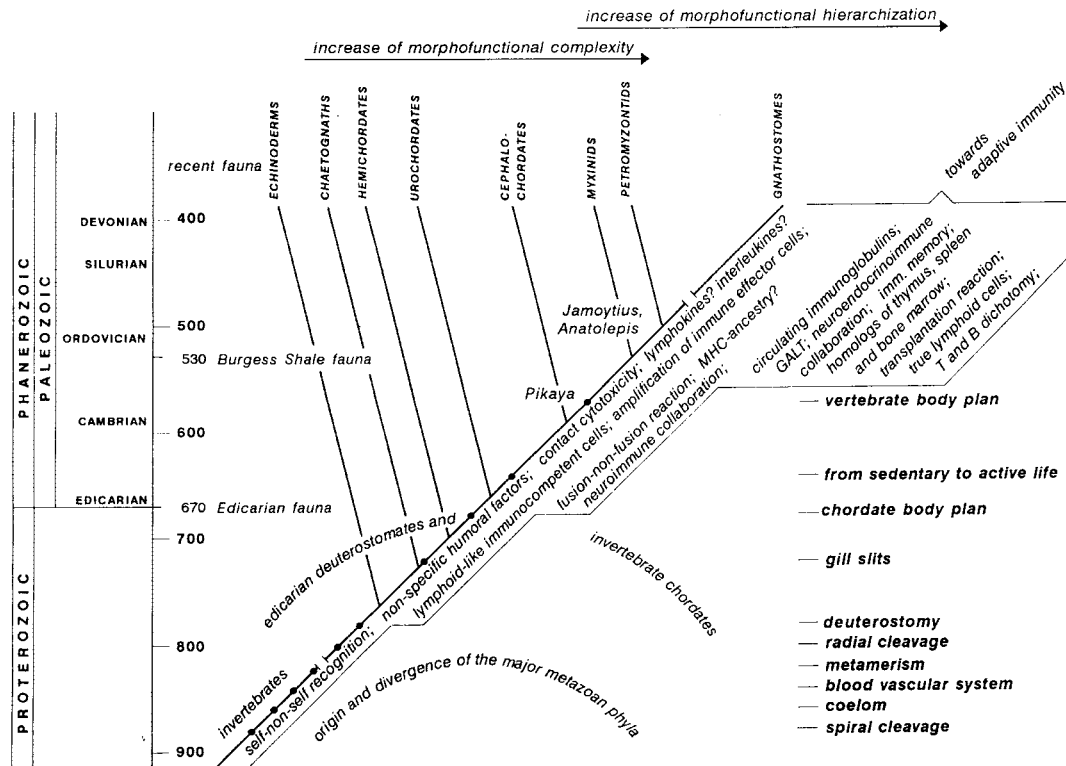
## THE VERTEBRATES

### *The agnathans*

Jawless fish are considered to be first true vertebrates. No final separation of the primary and secondary lymphoid organs exist, even if the presence of true plasma cells was revealed. Agnathans are the first animals able to react to an antigenic challenge by the production of "antibodies" with some degree of homology to mammalian Ig molecule. According to the new molecular analytic studies, the agnathan "antibodies" appeared to be rather the C3 complement component than true immunoglobulin (*Nonaka and Takahashi, 1992*). Nevertheless, these creatures express for the first time in immunophylogeny many progressive immunological features which cannot be found in any previous animal assemblage, indicating the similarity of their defence capacity to that of a common adaptive type of advanced vertebrates (*Fujii et al., 1992; Zapata et al., 1981; Zapata et al., 1984*).

### *The chondrichthyans*

The cartilaginous fish, regardless of their rather archaic and simple vertebrate body pattern, are first vertebrates characterised by well-developed cellular and humoral immune mechanisms. They possess distinct spleen (white and red pulp) and thymus, and important lymphohaemopoietic organs (Leydig's organ, spiral valve, epigonal organ). Besides the antibodies of the IgM isotype which molecular complexity is comparable to that of mammals, the skates evolved proper immunoglobulin class, the IgR isotype, which is not found anywhere else (*Kobayashi et al., 1984; Rast et al., 1994*). The question of the T and B lineage divergence remains unresolved similarly to the agnathans. The chondrichthyans can be considered as evolutionary critical animals. From chondrichthyans up, on the evolutionary scale, all basic molecular and cellular vectors of immunity, and all main immunocompetent structures can be



**Figure 2:** The comparison of the mutual evolutionary relationship of morphofunctional and immune phenomena.

found. Among chondrichthyan ancestors, in the deep past, started the immune strategy that we are accustomed to call the adaptive, anamnestic, inducible, and anticipatory immunity.

The comparison of the mutual evolutionary relationship of morphofunctional and immune phenomena is shown in Figure 2.

## CONCLUSION

When thinking about evolution of immunity, it must be kept in mind that all types of defence reactions of the present-day animals are optimal for them as these reactions made possible their phylogenetic survival and adaptive radiation.

The invertebrates do not show as a high degree of defence specificity as vertebrates, the discrimination may generally be so poor that allografts and sometimes even xenografts are not re-

jected. This may be an advantage as long as a reaction against self is avoided, or may be disadvantageous, e.g. in the case of autoimmunity or allergy. Those species whose bodies evolved to be minutes had reduced their structural organisation and also necessarily simplified their immune strategy. They have been looking for other evolutionary solutions to this problem and found them in the shortening of their life spans or in rapid changeover of

generations. In more advanced invertebrate taxa both the cellular and the humoral components are co-operative and highly specialised. The only missing component is the immunoglobulin molecule.

Besides elucidating how evolution built up the immune mechanisms piece by piece, the effort spent on the research of non-traditional models may be of extreme importance with even a practical use at least in two branches of biomedical science: "Once we comprehend the strategies used by primitive

animals, we hope to apply our understanding to mammalian host defences" (*Habicht*, 1993); secondly, it may be quoted *Sir F. M. Burnet* (1960): "As long as there are useful invertebrates like earthworms, oysters, or honey bees to be protected, and others like tapeworms, slugs, and mosquitoes to be destroyed, there will be a utilitarian justification for studying invertebrate pathology and whatever is equivalent in them to what we study in vertebrates as immunology".

## LITERATURE

- Ader, R. (Ed.): Psychoneuroimmunology. Academic Press, New York (1981).
- Austin, K.F.: Homeostasis of effector systems which can also be recruited for immunologic reactions. *J. Immunol.* 121, 793-805 (1978).
- Balls, M., and Ruben, L.N.: Phylogeny of neoplasia and immune reactions of tumors. In: Comparative immunology (Marchalonis, J.J., Ed.). Blackwell, Oxford, 167-208 (1976).
- Bauchau, A.G.: Crustaceans. In: Invertebrate blood cells 2. (Ratcliffe, N.A., and Rowley, A.F., Eds.). Academic Press, London, 385-420 (1981).
- Beck, G., O'Brien, R.F., and Habicht, G.S.: Characterization of interleukin 1 from invertebrates. In: Defense molecules (Marchalonis, J.J., and Reinisch, C., Eds.). Alan R. Liss, New York, 125-132 (1990).
- Bernard, C.: Lecons sur les phenomenes de la vie communs aux animaux et aux vegetaux. J.B. Ballière et fils, Paris (1877).
- Bertalanffy, V.L.: Biophysik des Fliessgleichgewichts, Einführung in die Physik offener Systeme und ihre Anwendung in der Biologie. Braunschweig (1953).
- Bonner, J.T.: The evolution of complexity by means of natural selection. Princeton University Press, Princeton (1988).
- Bigger, C.H., and Hildemann, W.H.: Cellular defense systems of *Coelenterata*. In: The reticuloendothelial system 3. (Cohen, N., and Sigel, M.M., Eds.). Plenum Press, New York and London, 59-87 (1982).
- Bronowski, J.: New concepts in the evolution of complexity. *Synthese* 21, 228-246 (1970).
- Burkholder, P.R.: The ecology of marine antibiotics and coral reefs. In: Biology and geology of coral reefs 2, Biology 1, (Jones, O.A., and Endean, R., Eds.). Academic Press, New York, 117-182 (1973).
- Burnet, F.M.: Invertebrate precursors to immune responses. In: Aspects of developmental and comparative immunology (Solomon, J.B., Ed.). Pergamon Press, Oxford, 13 (1981).
- Buss, L.W., and Green, D.R.: Histocompatibility in vertebrates: The relict hypothesis. *Dev. Comp. Immunol.* 9, 191-201 (1985).
- Buss, L.W., Moore, J.L., and Green, D.R.: Autoreactivity and self tolerance in an invertebrate. *Nature* 313, 400-402 (1985).
- Clark, R.B.: Dynamics in metazoan evolution. The origin of the coelom and segments. Clarendon Press, Oxford (1964).
- Conway Morris, S.: The fossil record and the early evolution of the metazoa. *Nature* 361, 219-225 (1993).
- Cooper, E. L.: Overview of immunoevolution. *Boll. Zool.* 59, 119-128 (1992).
- Cooper, E.L., and Stein, E.A.: Oligochaetes. In: Invertebrate blood cells 1. (Ratcliffe, N.A., and Rowley, A.F., Eds.). Academic Press, London, 75-140 (1981).
- Czaba, B.: Phylogeny and ontogeny of hormone receptors. *Biol. Rev.* 55, 47-63

- (1980).
- Dales, R.P., and Dixon, L.R.J.: Polychaets. In: Invertebrate blood cells 1. (Ratcliffe, N.A., and Rowley, A.F., Eds.). Academic Press, London, 35-74 (1981).
- Doberstein, J.: Wesen und Aufgaben einer vergleichenden Pathologie. Akademie-Verlag, Berlin (1951).
- Dybas, L.: Sipunculans and echiuroids. In: Invertebrate blood cells 1. (Ratcliffe, N.A., and Rowley, A.F., Eds.). Academic Press, London, 161-188 (1981).
- Fletcher, T.C., and Cooper-Willis, C.A., Cellular defense system of the *Mollusca*. In: The reticuloendothelial system 3. (Cohen, N., and Sigel, M.M., Eds.). Plenum Press, New York and London, 141-166 (1982).
- Franceschi, C., Paganelli, R., Fagiolo, U., and Ottaviani, E.: Cytokines, aging and evolution: The problem of promiscuity. *Int. J. Immunopathol. Pharmacol.* 7, 227-233 (1994).
- Fujii, T., Nakamura, T., Sekiyawa, A., and Tomonaga, S.: Isolation and characterization of a protein from hagfish serum that is homologous to the third component of the mammalian complement system. *J. Immunol.* 148, 117-123 (1992).
- Goya, R. G.: The immune-neurocrine homeostatic network and aging. *Gerontology* 37, 208-213 (1991).
- Gupta, A.P.: Insect immunocytes and other hemocytes: Roles in cellular and humoral immunity. In: Immunology of insects and other arthropods (Gupta, A.P., Ed.). CRC Press, Inc., Boca Raton, 19-118 (1991).
- Habicht, G.S., quot. in Travis, J.: Tracing the immune system's evolutionary history. *Science* 261, 164-165 (1993).
- Hildemann, W.H., Jokiel, P.L., Bigger, C.H., and Johnston, I.S.: Allogeneic polymorphism and alloimmune memory in the coral, *Montipora verrucosa*. *Transplantation*, 30, 292-302 (1980).
- Huxley, J.S.: Evolution in action. Chatto and Windus, London (1953).
- Karp, R.D., and Coffaro, K.A., Cellular defense systems of the *Echinodermata*. In: The reticuloendothelial system 3. (Cohen, N., and Sigel, M.M., Eds.). Plenum Press, New York and London, 257-282 (1982).
- Kerkut, G. A: The implications of evolution. Pergamon, New York (1960).
- Klein, J.: Are invertebrates capable of anticipatory immune responses? *Scand. J. Immunol.* 29, 499-505 (1989).
- Kobayashi, K., Tomonaga, S., and Kajii, T.: A second class of immunoglobulin other than IgM present in the serum of a cartilaginous fish, the skate, *Raja kenoei*: Isolation and characterization. *Mol. Immunol.* 21, 397-404 (1984).
- Lahav, N.: The synthesis of primitive "living" forms: Definition goals, strategies and evolution synthesizers. *Origin of Life* 16, 129-149 (1985).
- Langlet, C., and Bierne J.: The immune response to xenografts in nemertines of the genus *Lineus*. In: Developmental immunobiology (Solomon, J.B., and Norton, J.D., Eds.). Elsevier/North-Holland Biomedical Press, London, 17-26 (1977).
- Millar, D.A., and Ratcliffe, N.A., Activity and preliminary characterization of *Branchiostoma lanceolatum* agglutinin. *Dev. Comp. Immunol.* 14, 405-414 (1990).
- Moscona, A.A.: Surface specification of embryonic cells: Lectin receptors, cell recognition and specific ligands. In: The cell surface in development (Moscona, A.A., Ed.). John Wiley and Sons, New York, 67-99 (1974).
- Muscatine, L.: Endosymbiosis in *Hydra* and the evolution of internal defense systems. *Amer. Zool.* 29, 371-386 (1989).
- Orgel, L.E.: The origins of life, molecules and natural selection. Chapman and Hall, London (1973).
- Nonaka, M., and Takahashi, M.: Complementary DNA sequence of the 3rd component of complement of lamprey: Implication for the evolution of thioester containing proteins. *J. Immunol.* 148, 3290-3295 (1992).
- Pertseva, M.: The evolution of hormonal signalling systems. *Comp. Biochem. Physiol.* 100A, 775-787 (1991).
- Raftos, D.A.: Allorecognition and humoral immunity in tunicates. *Ann. N. Y. Acad. Sci.* 712, 227-244 (1994).
- Rast, J.P., Anderson, M.K., Ota, T., Litman, R.T., Margittai, M., Shablott, J.M., and Litman, G.W.: Immunoglobulin light chain class multiplicity and alternative organizational forms in early vertebrate phylogeny. *Immunogenetics* 40, 83-99 (1994).
- Rensch, B.: Evolution above the species level. Willey, New York (1966).
- Romer, A.S.: The vertebrate body. W.B. Saun-

- ders, Philadelphia (1971).
- Rowley, A.F., Rhodes, C.P., and Ratcliffe, N.A.: Protochordate leucocytes: A review. *Zool. J. Linn. Soc.* 80, 283-295 (1984).
- Sherman, R.G.: Chelicerates. In: *Invertebrate blood cells 2.* (Ratcliffe, N.A., and Rowley, A.F., Eds.). Academic Press, London, 355-384 (1981).
- Síma, P., and Větvička, V.: Evolution of immune reactions. CRC Press, Boca Raton (1990).
- Síma, P., and Větvička, V.: Evolution of immune accessory functions. In: *Immune system accessory cells* (Fornusek, L. and Větvička, V., Eds.). CRC Press, Boca Raton, 1-55 (1992).
- Smith, L.C., and Davidson, E.H.: The echinoderm immune system. *Ann. N.Y. Acad. Sci.* 712, 213-226 (1994).
- Sparks, A.K.: *Invertebrate pathology.* Academic Press, New York (1972).
- Suzuki, T., and Mori, K.: Hemolymph lectin of the pearl oyster, *Pinctada fucata martensii*: a possible non-self recognition system. *Dev. Comp. Immunol.* 14, 161-173 (1990).
- Stewart, J.: Immunoglobulins did not arise in evolution to fight infection. *Immunol. Today* 13, 396-399 (1992).
- Valembois, P., Roch, P., and Boildieu, D.: Cellular defense system of *Platyhelminthes*, *Nemertea*, *Sipunculida*, and *Annelida*. In: *The reticuloendothelial system 3.* (Cohen, N., and Sigel, M.M., Eds.). Plenum Press, New York and London, 89-139 (1982).
- Valentine, J.W., Erwin, D.H., and Jablonski, D.: Developmental evolution of metazoan bodyplans: The fossil evidence. *Dev. Biol.* 173, 373-381 (1996).
- Van de Vyver, G.: Organisms without special circulatory systems. In: *Invertebrate blood cells 2.* (Ratcliffe, N.A., and Rowley, A.F., Eds.). Academic Press, London, 19-32 (1981).
- Van de Vyver, G., and Barbieux, B.: Cellular aspects of allograft rejection in marine sponges of the genus *Polymastia*. *J. Exp. Zool.* 227, 1-7 (1983).
- Vasta, G.R.: The multiple biological roles of invertebrate lectins: Their participation in nonself recognition mechanisms, In: *Phylogenesis of immune functions* (Warr, W.G., and Cohen N., Eds.). CRC Press, Boca Raton, 73-101 (1991).
- Větvička, V., Síma, P., Cooper E.L., Bilej, M., and Roch, P.: *Immunology of annelids.* CRC Press, Boca Raton (1994).
- Weissman, I., Saito, Y., and Rinkevich, B.: Allorecognition histocompatibility in a protochordate species: Is the relationship to MHC somatic or structural? *Immunol. Rev.* 113, 227-241 (1990).
- Werdelin, O., and Mouritsen, S.: Antigen processing. In: *Immune system accessory cells* (Fornusek, L., and Větvička, V., Eds.). CRC Press, Boca Raton, 81-93 (1992).
- Wright, R.K., and Ermak, T.H.: Cellular defence systems of the protochordata. In: *The reticuloendothelial system 3.* (Cohen, N., and Sigel, M.M., Eds.). Plenum Press, New York and London, 283-320 (1982).
- Zapata, A., Ardavin, C.F., Gomariz, R.P., and Leceta, J.: Plasma cells in the ammocoete of *Petromyzon marinus*. *Cell Tissue Res.* 221, 203-208, (1981).
- Zapata, A., Fänge, R., Mattison, A., and Villena, A.: Plasma cells in adult atlantic hagfish, *Myxine glutinosa*. *Cell Tissue Res.* 235, 691-693 (1984).