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Axioms of Mathematical Immunology

Tibor Bakács[1], Tamás Szabados[2], László Varga[3], Gábor Tusnády[1]

[1] Alfréd Rényi Mathematical Institute of Hungarian Academy of Sciences, 1053 Budapest, Reáltanoda u. 13-15, Hungary.
e-mail: tusnady%math-inst.hu
[2] Technical University of Budapest, 1521 Budapest, Egry J. u. 20-22, Hungary.
e-mail: szabados%math.bme.hu
[3] Hungarian Power Companies Ltd., 1011 Budapest, Vám u. 5-7, Hungary.
e-mail: lvarga%mvm.hu

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Summary. Current wisdom describes the immune system as a defense against microbial pathogens. It is claimed that the virgin immune system has a capacity to produce antibodies against the entire antigenic universe. We assume, by contrast, that the responding capacity of the immune system is limited. Thus it cannot stand in readiness to deal with a practically endless diversity and abundance of microbes. Axioms and theorems are suggested for a mathematician audience delineating how the immune system could use its limited resources economically. It is suggested that the task of the immune system is twofold:

(i) It sustains homeostasis to preserve the genome by constant surveillance of the intracellular antigenic milieu. This is achieved by standardization of the T cell repertoire through a positive selection. The driving force of positive selection is immune cell survival. T cells must constantly seek contact with complementary MHC structures to survive. Such contact is based on molecular complementarity between immune cell receptors and MHC/self-peptide complexes. At the highest level of complementarity a local free energy minimum is achieved, thus a homeostatic system is created. Homeostatic interactions happen at intermediate affinity and are reversible. Alteration in the presented peptides typically decreases complementarity. That pushes the system away from the free energy minimum, which activates T cells. Complementarity is restored when cytotoxic T cells destroy altered (mutated/infected) host cells.

(ii) B cells carry out an immune response to foreign proteins what requires a change in the genome. B cells raised under the antigenic influence of the normal intestinal microflora, self-proteins and alimentary antigens must go through a hypermutation process to be able to produce specific antibodies. It has a certain probability that hypermutation will successfully change the genome in some clones to switch from low affinity IgM antibody production to high affinity IgG production. Interactions (typically antibody antigen reactions) in an immune

Correspondence to: L. Varga

response happen at high affinity and are irreversible. High affinity clones will be selected, stimulated and enriched by the invading microbes.

A complete account of the course of an infectious disease must also include a description of the ecology of the immune response. It is therefore suggested that during prolonged interaction between host and infectious organism, carried on across many generations, the adaptive antibody population may facilitate the evolution of the natural antibody repertoire, in accordance with the Baldwin effect in the evolution of instinct. (see Appendix 6)

Keywords. Complementarity – Homeostasis – Immune reaction – Hypermutation – Natural antibody – Complement distribution – Ecology – Axioms

1 Introduction

Throughout the life experience of a mammalian organism, in an ever-changing set of relationship, it adapts to its environment. In large measure it is the immune system that determines the overall success of this adaptability. As the immune system has an owesome destructive capacity the main concern of every theory of immune reactivity is how it distinguishes between friend (self) and foe (non-self)? Earlier theories agreed that such specificity must be learned during ontogenesis in order to remember what to attack later during the lifetime of the organism. They argued, however, whether the immune system should learn what is self (to avoid harm) or self-tolerance is ensured by eliminating self-reactive lymphocytes, creating holes in the repertoire.

Metchnikoff, for instance, assumed in the 1880s that the immune system is self-centered, as immunity was a form of physiological inflammation, which maintained organismic identity. In other words, immunity first defined the organism, then protected it. The clonal selection theory of Burnet, by contrast, defined the immune self in a negative definition of the host: those set of antigens that lead to the purging of their complementary (self-reactive) lymphocytes. Thus Burnet's immune system was able to recognize only non-self. The idiotypic network theory of Jerne was yet again self-centered, as it generated anti-idiotypic antibodies to its own antibodies. Indeed, he viewed the immune system as a functional network dominated by a mainly suppressive behaviour, which was open to stimuli from the outside [see in Podolsky and Tauber (1997)].

Later it became apparent, however, that specificity in itself was not sufficient to generate an immune response. Janeway suggested [Janeway (1989)] that immune response required both the presence of a suitable antigenic determinant to signal specific lymphocyte through its antigen receptor and the complementary activation of less specific responses of other nondiscriminatory cells (e.g. macrophages and antigen presenting cells APCs). In this context it was relevant what Varela et al. suggested that self is not a genetic constant, thus specificity cannot be learned forever during ontogenesis [Varela et al. (1988)]. They showed that self bears the genetic make-up of the individual and of its past history, while shaping itself along an unforeseen path. The global properties of the immune system cannot, therefore, be understood from analysis of component parts alone.

Recently Podolsky and Tauber synthesized from various theories and models [Varela et al. (1988), Cohen (1992), Grossman and Paul (1992), Fuchs (1992), Matzinger (1994)] a newer view of the immune function, what they call "contextual" theory: "Immunity can be defined only in particular contexts,and from the history of events in these contexts reactivity or immune silence ensues. The discriminating issue is that for any given element,x, the context becomes paramount and the importance of the intrinsic nature of x as an entity becomes minimal or even nonexistent. A truly contextual formulation must show that x cannot be dealt with as a separate entity but must be defined within an entire nexus. In this scheme, x becomes less definitive than its full context; it is only in this context that the meaning of x emerges." [Podolsky and Tauber (1997)] Here we follow this idea by building a system of mathematical relation shaping the base lines of immunology.

Physiological phenomena have usually physiological explanations: foot explains walking, in such cases there is no need for mathematics. Mathematical models might be helpful, however, when there is some puzzle in physiology: at first sight foot is not visible, yet the organism is able to walk. The relevant question is whether using a given number of elements, can a mathematical system be build which predict the existence of physiological function(s) not yet revealed by experiments? A mathematical system is a set of definitions and statements. Some objects are identified by definitions, when their identity is initialized, others by statements which describe their behavior and relations to each other. Statements may belong to a specified set of postulates or axioms in which case they are not proven. Other statements are classified as theorems, conjectures, which are consequences of definitions and axioms. To our knowledge no attempt was thus far made to formulate an immune theory in an axiomatic form. Our purpose therefore is to make the groundwork for an abstract model of the mammalian immune system that is built on axioms. We try to classify physiological evidences into axioms and theorems. Axioms that are incorporated into a model should explain theorems or conjectures. We start with a brief summary of the most important physiological evidences, which can be explained within the framework of current models of the immune system, and those paradoxes, which do not fit into these theories. For a more comprehensive view of the immune system [see Rowe (1994), Roitt (1994), Melchers (1998)].

Basic physiological evidences, as explained by current models

- It is commonly believed that the immune system is essentially a *defense* system against microbial pathogens, its main task is to *destroy* and eliminate pathogens, which threaten the integrity of the host. (This is the main point where we deviate from the standard theory.) The virgin immune system stands in readiness to deal with the entire antigenic universe.

- The immune system is a diffuse organ, composed of *non-specific* and *specific* (clonally distributed) cells. These are developed from a single stem cell during a differentiation process in the primary lymphoid organs (bone marrow and thymus). They circulate in the blood and lymph or taken up the secondary lymphoid organs (spleen and lymph nodes). Immune cells may act directly, via cell-cell contact but also via production of soluble molecules.

- Non-specific cells (phagocytes/antigen presenting cells, APCs) take up and inactivate foreign substances present in the internal environment. They are activated *uniformly* and *instantly* (in vast numbers) when foreign substances are tagged by antibodies and/or complement. Clonally distributed cells (T cells and B cells) react individually (thus specifically) by binding to structures which are sterically *complementary* to their cell surface receptors. Such binding may result in activation, e.g. cell division, differentiation, secretion of various molecules (e.g. antibodies) and lysis of other cells. As naive clone size is small when activation starts, specific reaction occurs only *after a time lag*.

- Although organisms may be macroscopically alike, no two individuals with identical composition exist, as the *genetically coded* amino acid sequences of their proteins may be different. Collection of enzymes of an individual forms the 'protein fingerprint'. This genetic diversity is expressed in the different shape of proteins (three-dimensional conformation). In general genetic diversity is proportional to the *phylogenetic remoteness* of species.

- The marker of individual uniqueness is the *major histocompatibility complex* (MHC), class I molecule, which is present on all cells (except erythrocytes). Its related structure, the MHC class II molecule, is present only on immune cells. MHC molecules are involved in mutual cell recognition; indeed, T cells can read information on other cells only if the communicating cells posses appropriate MHC structures. This syngeneic preference is called the *MHC-restriction* phenomenon. T cells must *learn* to recognize the MHC structures of the host (*self*) to distinguish from that of other individuals (*non-self*).

- It is the *affinity* of the T cell receptor (TCR) for MHC molecules, which decides between life and death for immature thymocytes. High-affinity recognition of the MHC/self-peptide complexes on the APC by the appropriate TCR provokes their programmed cell death. Those, which recognize MHC molecules with lower affinity, are positively selected from the remaining repertoire of cells. In this way, the repertoire of peripheral T cells are *standardized* and *programmed*.

- In contrast to T cells, the repertoire of antigen-recognizing receptors of B cells appears not to be standardized. Their repertoire is capable of binding the *three-dimensional conformations* of molecules of biological and non-biological origins. They have seemingly endless capacity to produce antibodies against an equally endless diversity of antigens.

- *Antigens* are substances, which are recognized as non-self based on a steric complementarity between the immune cell receptors and the antigen. Antigens and receptors may fit into each other as a key fits a single lock. The measure of complementarity (specificity) is characterized by the binding *affinity*. Antigens may be native proteins, but also parts of proteins processed and presented by host cells.

- Processed *intracellular* antigens (e.g. peptides from mutated proteins or viruses) are presented by class I MHC complexes. Altered cells are recognized and destroyed by cytotoxic T cells. Native antigens from the *extracellular* environment (e.g. bacteria and their products) are labeled for elimination by antibodies and removed from the host by phagocytes. B cells produce antibodies.

- One consequence of the above physiology is that destructive immune reaction against self (*autoimmunity*) is relatively rare.

- Another consequence is that *transplantation* of non-self tissues is impossible without immunosuppression.

- The immune system is not only able to accept information entry but also to process and store acquired information in its *memory*. The basis of such memory is the production of specific *antibodies* (complementary, soluble cell surface molecules) whose affinity to the inducing antigen may be increased during an immune response by *hypermutation* of antibody genes. The presence of specific antibodies makes a faster and more efficient *secondary* reaction possible, when the host is confronted again with the same antigen.

- Without vaccination the immune system responds poorly, many have to die for survivors to become immune.

Some unexplained evidences and paradoxes

- The "*thymic paradox*" remains to be solved: why T cells that must recognize self-peptide- MHC complexes to escape cell death in the thymus, do not respond to that same self-peptide-MHC in the periphery? (Appendix 2)

- If genetically coded amino acid sequence difference is the basis of foreignness (species remoteness), why do *allogeneic* tissues of the same species induce the strongest T cell response, where the difference between donor and recipient protein sequences might be only a single amino acid? (Appendix 2)

- How can the *fast replication* of viruses and bacteria be controlled with immune cell clones, whose initial size is small and division rate is slow? (Appendix 1)

- What is the driving force behind *immune surveillance*? (Appendix 2)

- If the T cell repertoire requires continuous interactions with self-MHC molecules for survival, can their *homeostasis* exert any feedback influence on the regeneration of host cells (e.g. liver cells or red cells)? (Appendix 2,8)

- *Phagocytes* can take up and inactivate foreign material, if they are *tagged* by specific antibodies and complement components. How are phagocytes directed to recognize foreign material in a naive host, *before* the production of specific antibodies? (Appendix 4)

- How can the relationship of the immune system to *bacterial symbionts* be explained in terms of destructive immunity? (Appendix 3)

There are certain parallels between models of the immune system and that of other biological systems, i.e., among others prey-predator systems are similar to immune networks, which in turn resemble large-scale evolution. The latter may be reiterating its dynamics in every-day immune reactions, which themselves were developed during evolutionary interactions of host and invading parasites. (Appendix 5)

2 Axioms

To avoid confusion between the new definitions we suggest and thoses that are not substantially different from current thinking, the former is designated as "our axiom or proposition" respectively at the end of each relevant paragraph.

I. *Elements.* Contacting parts of all elements are made of proteins and occur in either solid or soluble form (i.e. cell-surface or soluble proteins). The elements are as follows:

a) T cytotoxic cell (Tc),
b) T helper cell (Th),
c) B cell (B),
d) Phagocytic cell (P),
e) Antigen presenting cell (APC),
f) Non-immune cell (NI),
g) Foreign cell (F), under physiologic conditions it is a microbe,

h) Soluble molecules (s), e.g. antibodies, complement proteins, bacterial toxins;

Elements of a-e are the immune cells, a-f are the host (self) cells, whereas f-h make up the surrounding cells/molecules.

II. *Characteristics of elements.* Defined characteristics determine the specific interactions of all elements. These are organized at the protein level via complementary space structures of activated protein profiles. Coupling of proteins is not an 'all or nothing' phenomena, as complementarity (i.e. goodness of fit) is measured on a continuous scale. Protein binding is competitive and favors the best fit among available candidates. Coupling of proteins is reversible following the rules of statistical mechanics. All host cells, carry so-called Major Histo-Compatibility system I molecules (MHC I), while B and APC, in addition, carry a second Histo-Compatibility molecule (MHC II).

- *Tc* has cell surface receptors (TCRI) and is capable of binding to complementary MHC I molecule, which presents peptide of digested protein from *within* the cell. Complementarity of such binding may change (typically decrease) if peptides from mutated or viral proteins are presented. That activates the *cytotoxic* mechanism of Tc against mutated/infected cells.

- *Th* has cell surface receptors (TCRII) and is capable of binding to complementary MHC II molecule, which presents peptides of engulfed, digested substances from the *extracellular* space. Complementarity of such binding may change (typically decrease) when peptides from microbes are presented. That activates Th cells to secrete molecules to help B cell's hypermutation.

- *B* has cell surface receptors (BCR) and is capable of binding to complementary *native* (i.e. undigested) proteins, including to that of the microbes. The B cell cannot discriminate between the proteins of an antigen and antibody. High affinity binding between BCR and protein results in B cell multiplication and antibody production (each B cell clones produce one type of antibody). The consequence of low affinity binding may be different: in the *absence* of help of Th cells it will result in the production of germ line encoded (unmutated), *low* affinity (IgM) natural antibodies. In the *presence* of help, however, low affinity binding induces hypermutation, i.e. random changes in the characteristics of antibodies produced. Further to the binding affinity, the number of BCRs (on a given B cell surface) coupled to proteins also influences the B cell response. The dose-response curve between the density of occupied BCRs and B cells response is bell-shaped. The response will be strongest at an optimum of receptor occupancy, whereas deviation in both directions decreases the intensity of response. B cell will die by neglect if very low affinity makes contact of proteins impossible.

- *P* has cell surface receptors (FCR) for antibodies and is capable to *engulf* and digest extracellular substances (microbes and proteins respectively) provided antibodies tag them.

- *APC* has cell surface receptors (FCR or BCR) and is capable to engulf, digest and *present* extracellular substances (microbes and proteins respectively).

- *NI* lacks cell surface receptors (TCR, BCR, and FCR respectively).

- *F* under physiologic conditions has neither cell surface receptors, nor MHC I-II molecules.

- s may be secreted by any cells of the system, membrane bound molecules/ receptors are also secreted in a soluble form (sMHCI-II, sTCRI-II, sFCR, sBCR, this latter is the antibody).

III. *Life cycles of immune cells.* The life span of immune cells are short, thus they are produced constantly throughout life. Clonally distributed cell surface receptors (TCR and BCR) assembled by random combination of germline genes; these are actively engaged in the survival of the cell, which carry them. Only those Tc and Th will survive which have medium affinity receptors to contact complementary MHC I and II structures. Such contact provides stimulation for these cells. Similarly B cells, which have medium affinity receptors for complementary native proteins, which can stimulate them, will survive. Such stimulation is called positive selection, which enriches the non-immune repertoire with self-complementary cells. P and APC need no such stimulation to survive. (Appendix 2,3)

IV. *Life cycles of non-immune cells.* The life span of most NI cells is longer than the immune cells, but shorter than that of the organism; thus they must also be renewed throughout life. The stimulation for renewal comes partly from the surrounding NI cells but also from complementary immune cells via the MHC I-II complexes (our axiom). (Appendix 8)

V. *Infection.* The host may be invaded by pathogens in one of two ways. Viruses must enter directly into cells to use the cell's own protein machinery for replication. Thus virus peptides will be first presented as other cell proteins by the MHC I molecules. The newly synthesized virus particles are released into the extracellular space. By contrast to viruses, most bacteria can enter and live in the extracellular environment (some bacteria, however, are intracellular parasite). (Appendix 4)

VI. *Antigens.* Any molecule is an antigen whose peptide fragment, when presented by the MHC II, decreases the complementarity between Th and APC. Such a change results in release of molecules from Th cells, which help to activate hypermutation in B cells (our axiom). (Appendix 1,4)

VII. *Immune reaction.* It is the activation of B cells by complementary proteins in the presence of helper molecules. Such activation induces hypermutation, which in turn will generate specific, high affinity antibodies. During this process the genome of the activated B cell is permanently altered (our axiom). (Appendix 4)

VIII. *Information processing and storage.* Communication of immune and non immune cells may be direct, cell to cell contact, which requires cell surface receptors and MHC molecules, but it may also be indirect when cells of either source may contact soluble form of cell surface molecules. Storage of new information is possible in B cells (but not in T cells or other immune cells) as only B cells have a mechanism (hypermutation) to change their genome (our axiom). (Appendix 4)

3 Definitions and Theorems

What is molecular complementarity? Root-Bernstein and Dillon [Dillon and Root-Bernstein (1997)] define complementarity as non-random, reversible coupling of the components of a system, which refers to non-random, non-covalent interaction between molecules. Higher order levels of complementarity are also possible in living systems: cell organelles, cells, tissues, organs and organisms all couple non-randomly. Coupled systems are stabilized against change, they are buffered in time as well as thermodynamically, persistent and conservative in an evolutionary sense. Complementarity is what leads to the reduction in variance in an aggregate of components that defines their interactions as a system. Molecular complementarity, in a biological system, protects against death due to loss of homeostatic control or loss of sufficient free energy.

The immune system develops by self-organization. The chaotic condition produced by the random combination of germ line receptor genes becomes ordered following ontogenesis. The immune repertoire will contain mainly self-complementary cells, thus the local entropy of the system decreases. Complementarity depends on the temporal relationship of non-immune cells to the birth of the immune system. Any molecule or cell (irrespective of their genetic background) that is present in the developing host during a finite learning period will be adopted as part of self, as they will be able to positively select immune cells with complementary receptors.

By contrast, anything (including the host own cells) which was not present during this critical period will be rejected later as non-self, as they will lack complementary immune counterparts. As transplantation of allogeneic tissues creates much stronger perturbation of complementarity than any infection or mutation, it will induce the strongest reaction.

To survive immune cells constantly strive to contact complementary protein structures of their surroundings, including cell surface and soluble molecules. Thus, from a collection of isolated cells, the immune system becomes a network of cells undergoing an intricate series of interactions with each other as well as other host cells and molecules. Such a way a system is created whose elements may be short lived, but the essential characteristics of the system survives for decades. A clearcut presentation of technical problems is given by Gács [Gács (1986)] where a well-defined mathematical construction leads to similar activities as that of immune reaction (our proposition). (Appendix 2,3)

The immune system is a supersystem. According to Tada a supersystem is, which engenders itself by generation of its diverse components from a single progenitor, mostly by stochastic expression of receptors, followed by selection and adaptation to the environment. Cells that fail to adapt are excluded, and those that can will survive and proceed to the next differentiation process [Tada (1997)]. We include in this theory the colonization of the host by the intestinal flora, which also functions as a source of endogenous stimuli, crucial for the development of a fully competent intestinal immune system including the development of natural antibody producing B cells (our proposition). (Appendix 3)

Complementary systems are homeostatic. Kauffman claims that a deep theory of homeostasis is still missing [Kauffman (1993)]. He suggests that interacting proteins in a cell form a dynamical system. Dynamical systems stabilize and stabile states are called attractors. In complex organisms cell types are such attractors. Indeed, homeostatic return of a perturbated cell to its previous pattern of gene activities after many possible chemical perturbations seems likely to be a fundamental property of most cell types. The genome uses only a subset of cell types in the genomic repertoire what implies the possibility that some unused cell types might behave poorly. Such cells may undergo mitotic divisions without cessation and eventually became cancers. The question is whether homeostasis of cells can be explained by internal genetic regulatory system alone or is it also influenced by external regulatory factors?

Feedback and feedforward regulations are both controlled by coupling, and in almost every case, mediated by molecular complementarity [Root-Bernstein and Dillon (1997)]. The consequence of forming a coupled system between immune and host cells/molecules is that no significant alterations in replication rates, concentrations or structural stability of essential reactants are allowed. Such system has a tendency to return to a local free energy minimum, which is a state when complementarity between components is highest.

Tc cells carry out the constant surveillance of the intracellular antigenic milieu of host cells. Alteration in the peptides presented by the MHC I molecule (due to mutation or viral infection) typically decreases complementarity between Tc cells and host cells. In other words the system is being pushed away from the local free energy minimum, which activates contacting Tc cells. In such way activation does not depend on random encounter between infected/mutated host cells and specific receptor carrying Tc cells but occurs immediately. The number of activated Tc will be proportional to the concentration of MHC I molecules carrying altered peptides. As infected/mutated cells threaten the integrity of the host by spreading an infection to other cells or by unlimited growth, the ultimate goal of Tc cells is to restore homeostasis by destroying altered cells as fast as possible. Interactions during homeostatic regulation happen at intermediate affinity, thus they are reversible. Tc cell affinity does not increase as a result of interactions (there is no change in the Tc cell's genome). Homeostatic regulation by Tc cells does not require help from other immune cell (our proposition). (Appendix 8,9)

Homeostasis must be broken to generate an immune response. B cells carry out the immune response against foreign (non-self) proteins. The non-immune B cell repertoire, however, is centered on the intestinal flora, alimentary and self-proteins. An invading pathogen microbe is, therefore, first complexed by polyreactive natural antibodies, binding with low affinity to microbes but to some extent also to host proteins respectively. As the degree and order of antigen repetitiveness of microbes is higher than that of the host cells, a sensitization difference is created. It was demonstrated that *complement distribution* is very sensitive to small differences in sensitizing antibody concentrations among competing targets [(Bakács et al. (1994), Tusnády et al. (1992)]. Complement accumulates asymmetrically on microbes since they carry more antibodies, than host cells. Asymmetrical accumulation of complement in turn activates APCs to engulf microbes. The presented microbial peptides decrease complementarity between MHC II and Th cells, consequently Th cells become activated. Secretion of helper lymphokines induces hypermutation in a number of B cell clones complementary with low affinity binding to microbes. Hypermutation is not oriented but its speed or intensity depends on the goodness of fit between antigen and B cell receptor. There is a stochastic probability that some clones will successfully change their genome to switch from *low* affinity IgM antibody production to *high* affinity IgG production. Such clones will be selected and enriched by the invading microbes. Interactions during an immune response (typically antibody antigen reactions) happen at high affinity, thus they are (from a practical point a view) irreversible. Antibody affinity may increase upto 5-6 orders of magnitude as a result of hypermutation. Immune response by B cells requires help from other immune cells. Following the clearence of microbes the new high affinity B cell clones are kept stimulated for some time by anti-idiotypic antibody producing clones [see in Szabados et al. (1999)]. It is important to note in this context, that microbes of the normal microflora cannot invade the host, thus they will not be complexed by natural antibodies, neither will they be taken up by APCs. The normal microflora cannot therefore generate help to ignite an immune response (our proposition). (Appendix 4)

Memory has three levels. Positive selection produces a repertoire of immune cells carrying germ line coded receptors, which are complementary to self. This is the *primary* memory which 'knows only self'. The immune system may also generate a *secondary* memory by fine-tuning of its antibody repertoire to specific antigens by hypermutation (e.g. natural immunity to childhood infections). Secondary memory is engraved into the genetic material of B cells. We would include a *tertiary* memory, what concerns the integrated memory of a population residing in a given geographical location over a historical period of time. It is formed during several generations by the selection of individuals who are genetically best endowed to respond to characteristic microbes of the local environment. As the ecology of infections suggest that prolonged interaction between host and infectious organism - carried on across many generations and among suitably numerous populations on each side - creates a pattern of mutual adaptation, the tertiary memory is stabilizing the response of a population to drastic new infections (our proposition). (Appendix 5,6)

Slow changes may result in cancer. There are 10^{16} cell divisions in a human lifetime [Alberts et al. (1994)], which are bound to result in mutations, theoretically each of which may produce a cancer cell. Complementarity between host and immune cells inhibits such transformations from fast progression. As such a supersystem is described to exist at the *edge* of chaos, slight degrees of perturbations of initial conditions (which are insufficient to activate the immune system) may result in aggressive growth of some transformed somatic cells over a 20 to 30 years period (our proposition). (Appendix 10)

4 Conclusions

The suggested axioms and theorems may be used to build a new model of the immune system. Such a model would assume that the immune system has limited resources what must be used economically. Homeostasis is sustained by a standardized Tc cell repertoire, which constantly survey the intracellular antigenic milieu. They destroy host cells, which deviate from self-parameters, be such deviation due to mutation or infection respectively. Since they constantly seek contact with complementary host cells to survive, their activation occurs immediately following foreign peptide presentation by MHC I molecules. They need no help neither have they memory, other than that of the MHC.

B cells carry out immune reaction with the help of APCs and Th cells. By contrast to homeostatic reaction, immune reaction is based on high affinity interactions. To produce high affinity antibodies against invading microbes the genome of some B cell clones must be permanently altered by hypermutation. As the majority of bacteria and parasites can replicate independently of host cells in the fluid phase of the body, they are invisible to the naive immune system until engulfed by phagocytes and presented by MHC II molecules. Phagocytosis is, however, inefficient without antibodies and/or complement components. The polyreactive natural antibodies and the complement system, thus, play a critical role to 'turn the attention' of the immune system from homeostatic control of self-components to the production of specific antibodies against foreign proteins (see diagram in Figure 1).

There are two essential differences between B cell (immune) and T cell (homeostatic) reactions. We have demonstrated by computer simulations [see Szabados et al. (1999)] that an effective B cell-antibody reaction to a new pathogen affects usually only a minority of the B cell population and takes relatively long time (as it requires several divisions, hypermutation and formation of antibody producing plasma cells). A typical T cell response, by contrast, affects a significant part of the T cell population, as following viral infection they loose binding to infected host cell partners and are immediately activated. In other words, a standardized T cell repertoire reacts faster than a random one.

A prediction from the above theorems is that under physiological condition efficient immune response cannot be mounted against all microbes. Assuming that the germline encoded natural antibody repertoire was formed during coevolution with microbes from our natural habitat (including the intestinal microbiota) "new" microbes, which are not part of the local environment, may invade the organism without significant resistance. That seems to be the case with several "new" often-lethal virus infections. The Bolivian hemorrhagic fever epidemic, for instance, resulted from the disruption of the natural habitat of the *Calomys* field mouse, the natural reservoir of the virus [Johnson et al. (1966)]. The *Mastomys* rat caused Lassa fever epidemic when people drove out its natural competitor, the larger, more aggressive black rat, *Rattus rattus* [Monath et al. (1974)]. Ebola virus infection, the second most lethal disease of the twentieth century,is also suspected to be a zoonosis, although its natural reservoir is not known yet [Pattyn (1978)]. (Appendix 5,6,7)

The clinical experience and immunpathophysiology of acute graft-versus-host disease (GVHD) what develops after allogeneic bone marrow transplantation may also be interpreted in support of our axioms and theorems. It is caused by mature T cells in the marrow. The probability of developing acute GVHD is directly related to the degree of HLA (MHC) incompatibility. Perhaps more importantly, acute GVHD still develops in about 20-30% of patients transplanted from an HLA-identical sibling, indicating that even the slightest deviation from complementarity between T cells and host cells will activate an aggressive behaviour in T cells [Howell and Navarrete (1996)]. Furthermore, a prominent pathologic feature of acute GVHD - the disparity between the severity of tissue destruction and the paucity of the lymphocytic infiltrate - suggests the role of soluble mediators in target cell destruction, rather than the requirement of direct contact between host cell and T cell [Ferrara et al. (1996)].

Some further predictions following from our theorems may be testable experimentally: (i) regeneration of host cells is partly controlled by the immune system; (ii) natural antibody repertoire should contain cross-reactive antibodies to the most frequent pathogens in a given geographical area; (iii) the number of aborted malignant transformations is higher than that of the infections.

Appendix

To support the axioms and theorems, we present a selected list of literature, which is compatible with the suggested principles.

1. *The numerical abundance, antigenic variation and fast replication of microbial world cannot be controlled by clonally distributed, slowly dividing immune cells.*

Conventional wisdom claims that the immune system has to be capable of recognizing virtually any pathogen that has risen or might arise. The suggested theorems for a new model immune system by contrast are built on the assumption that the variety and variability of the antigen universe is unlimited, which cannot be matched with the limited variety/variability of clonally distributed immune cells. A possible simile is shooting sitting ducks versus running game. In theory (and to some extent in experiments) it is possible to cover the vastness of protein universe. In reality, however, a new highly virulent infection is often fatal.

20^{400} *potential proteins* of length 400 can be constructed from 20 amino acids [Benton (1996), Kardar (1996)]. We do not know, however, what fraction of the theoretically possible protein repertoire may exist in nature. An educated guess is that much more than the number proteins studied thus far. For instance, the number of prokaryotes on earth is estimated to be 4-6x10^{30} cells. Their large population size, rapid growth and enormous potential to accumulate mutations implies that events that are extremely rare in the laboratory could occur frequently in nature. Given the *numerical abundance of prokaryotes*, the absence of data on their diversity is a major omission in our knowledge of life on earth [Whitman et al. (1998)].

Constant *antigenic variation* is a hallmark of several RNA viruses, as their replication is an error-prone process. The quasi-species nature of such viruses provides a moving antigenic target for what the host immune system can never fully control [Farci et al. (1997), McMichael and Phillips (1997), Brown and Richman (1997), Bonn (1997), Feinberg (1996), Jack (1996)].

Viruses and bacteria replicate with *explosive speed*. For example, a single influenza virus produces 1000 progeny in ten hours, each capable of infecting another cell and producing 1000 progeny in each; if unchecked, this would cause death in two or three days [Paul (1993), Adams (1996), Boman (1996)].

Importantly, not all mammalian species have repertoires of the size predicted for mice and humans or attainable in synthetic libraries [Butler (1997)].

2. *Selection and survival of T cells depend on constant stimulation from host cells. T cells become activated when presented foreign peptides obstruct contact with self-cells.*

T cell repertoire, in the model, requires continuous interactions with self-MHC molecules. Since the extreme flexibility of the TCR-MHC interaction, does not allow precise antigen recognition, T cells become activated when presented foreign peptides obstruct contact with self-cells, thus they decrease the affinity of their interaction. Activation is proportional to the number of the infected cells, short lived and leads to the destruction of cells harboring pathogens but generates no long lasting memory.

Genetically, the immune self is encoded at the MHC locus. The only known physiological function of the MHC is the *control* of T-cells. The *affinities* of the various TCR/MHC class I+peptide interactions are *low*, indeed similar to those of the interaction between natural immunoglobulin M and antigen (10^{-4} to 10^{-7} M) [Margulies (1997)]. A TCR is selected because it learns the three-dimensional coordinates of self-MHC displaying one of a large array of self-peptide surfaces and then recognize non-self as a *deviation from the self*-coordinate, which in most cases might differ by only a few atoms. The critical interaction for positive selection between the TCR and the MHC molecule can be viewed as such that the peptide either allows or obstructs this contact. *Extreme flexibility* in TCR recognition was suggested when small changes in size, hydrophobicity, or conformation of a TCR contact residue resulted in a 1 million-fold range in activity for different ligands. Altered peptide ligands are therefore assumed to provide a decreased (and not increased) affinity interaction with the TCR. In the case of alloreactivity, by contrast, the coordinate differs at several sites, which make a large number of T cells respond to non-self MHC molecules [Ignatowicz et al. (1997), Vessey et al. (1997), Joyce and Nathenson (1996), Matsui et al. (1994), Allen (1994), Kersh and Allen (1996)]. In the absence of selecting MHC molecules, peripheral mature T cells are short lived and disappear, indicating that *continuous contact* of the TCR with selecting MHC molecules is *required* for survival of T cells. The same environment of self-MHC and self-peptides complexes, that initially drove the positive selection of T cells in the thymus, guarantees their survival in the periphery [Hemmer et al. (1998), Kilberg et al. (1997), Freitas and Rocha (1997)].

Substantial activation and expansion of CD8 T cells indeed often characterize viral infections. This is seen in humans during the acute phase of infection with viruses that replicate systemically. Thus, only a small number of the CD8+ T cells are actually specific for the infecting virus. The specificities of the remainder of the CD8+ T cells have not been determined. As the effector: target cell ratio would be *insufficient* to eradicate the infection exclusively by direct cell-mediated mechanism, secretion of lymphokines also help the host to control infections [Murali-Krishna et al. (1998), Butz and Bevan (1998), Guidotti and Chisari (1996), Kundig et al. (1996), Doherty et al. (1996), Tough and Sprent (1996)].

3. *The intestinal flora selects and stimulates the B cell repertoire in a naive host.*

In the current model B cells are fighting some but coopererating with other microbes.

All respiratory and photosynthetic capacity of eukaryotic cells was obtained from bacterial symbionts. Consistent with this, pathogenicity to humans is a rare trait among eukaryotes and bacteria [Boman (1996), Pace (1997)]. The average human contains 10^{13} eukaryotic cells but 10^{14} bacteria. Given the greater rate, at which bacteria divide, this ratio may, over a lifetime, reach thousands or even *millions to one*. Since these are in very close proximity to the intestinal immune system, it is believed that a "trialogue" between the *intestinal microbiota*, the self-renewing intestinal epithelium, and the diffuse gut-associated lymphoid tissue is critical in forming and maintaining a dynamic ecosystem, involving eukaryotic cytokines and prokaryotic cytokine-like molecules. The intestinal flora functions as a source of endogenous stimuli, which is crucial for the development of a fully competent intestinal immune system. Indeed, the normal intestinal microbial flora is quite similar to self antigens, as genetic factors influence selection of "self" flora during colonization (e.g. bacterial flora of monozygotic twins is more similar than that of dizygotic ones), furthermore its antigenic composition is permanent over life. Consistent with this there is a cross-tolerization between self-antigens and from the intestinal flora indicating that tolerance of an individual to his own intestinal flora may share aspects of self tolerance [Duchmann et al. (1997), Henderson et al. (1996), Duchmann et al. (1996)]. It is important in this context that the intestinal lining alone is estimated to contain more lymphoid cells and produce more antibodies than any other organ in the body [Feartherstone (1997)].

4. *Complement distribution between innocuous host cells and pathogens are directed by natural antibodies and are essential to ignite an immune reaction in a naive host.*

The model immune system suggests a mechanism to resolve the paradox that a specific immune response has to be started by non-specific phagocytosis.

The neonate responds to a restricted range of antigens, and generally makes low-affinity IgM antibody. The production of such *natural* Ig is believed to result from immunization and polyclonal B cell (B1, CD5+ subset) activation by microflora present on mucosal surfaces. Antibodies raised under the antigenic influence of the normal microflora might be effective in recognizing common antigenic structures shared by different micro-organisms including pathogenic ones [Sudo et al. (1997), Helgeland et al. (1996), Seledtsov and Seledtsova (1997)]. ABO histo-blood group antibodies are also formed as a result of trisaccharide-specific immune stimulation of the gut-associated lymphoid system by intestinal gram-negative bacteria [Friedli et al. (1996)]. *Pattern recognition* receptors, for conserved molecular structures of pathogenic microorganisms, allow for self/non-self discrimination [Stryhn et al. (1996), Medzhitov (1996)]. The degree and order of antigen repetitiveness is, for example, an immunological discriminator for mature B cells to react or to ignore antigens [Bachmann et al. (1996)]. Extracellular antigens (e.g. most bacteria) are first complexed by polyreactive natural antibodies and components of the *complement system*, and presented to B cells on antigen-presenting cells [Vidard et al. (1996), Rajewsky (1996), Reyes et al. (1997)]. As complement distribution has been shown to be very sensitive to the relative concentrations of sensitizing antibodies on competing targets, slight differences in sensitization between innocuous host cells and pathogens may be sufficient to direct initial, non-specific immune attack preferentially against pathogens [Bakács et al. (1994), Tusnády et al. (1992)]. Consistent with this suggestion that patients with hereditary deficiencies of classical pathway complement proteins have a dramatically high prevalence of autoimmune disease, typified by systemic lupus erythematosis (SLE), furthermore complement also plays an important role in the generation of antibody responses [Walport et al. (1996)].

The interface between cellular and humoral immunity was suggested to be the mandatory requirement for T cell help to generate substantial, high quality Ab responses [Topham et al. (1996)]. Th cells become activated as presented foreign peptides obstruct contact of the MHC II molecules on APCs. They help the process of *affinity maturation*, during which production of high affinity antibodies occurs by hypermutation. Although it was estimated that the *affinity ceiling* of antibodies produced in immune responses are not likely to exceed a limit of around $10^{10}M^{-1}$ [Foote and Eisen (1997)], it takes time until 5-6 orders of magnitude increase of affinity is reached. These high affinity antibodies are, therefore, to prevent the *reinfection* of the host by the same pathogen, but not to conquer primary infections.

5. *Prolonged interaction between host and infectious organism selects for individuals best adapted to local environment.*

Classical microbiological and immunological research is concerned with direct interactions between microbe and host. A complete account of the course of an infectious disease must, however, include a description of the ecology of the immune response [Levin et al. (1999)]. The current model assumes that full adaptation of the organism to the environment can only be achieved during several generations.

The ecology of infections suggests that prolonged interaction between host and infectious organism, carried on across many generations and among suitably numerous populations on each side, creates a pattern of mutual adaptation. At equilibrium, the microbe would be expected to replicate efficiently, cause minimal disease to the host, infect a high proportion of the host population, be perpetuated in host populations, and show increased genetic diversity with time. From an ecological point of view, the most lethal disease-causing organisms are poorly adjusted to their role as parasites. The first encounter of the Black Death, the bubonic plague, between 1346-1350 in Europe left about one third of the population dead. The situation was even worse when the Spaniards arrived to Mexico and Peru inaugurating free exchange of infections between the Old World and the New. Within fifty years the population had shrunk to about one tenth of what had been there when Cortez landed. The symptoms of syphilis at the beginning of the 16th century were peculiarly horrible in Europe, but by the end of century the more fulminant form of infection were dying out. The 'domestication' of many epidemic diseases occurred between 1300 and 1700, as an estimated 120 to 150 years are needed for human populations to stabilize their response to drastic new infections [McNeill (1998)].

The avian influenza viruses and their wild waterfowl hosts appear to provide a classic example of an optimally adapted system, as the viruses are ubiquitous in their hosts, infection is nearly always asymptomatic, and large amounts of virus are shed by infected birds. By contrast, human influenza A (but not B and C) viruses have been prevented from reaching an evolutionary equilibrium with their host by an irregular infusion of avian virus genes into the human gene pool. Evolution of influenza viruses is influenced by the physical barriers that prevent intermixing of their hosts. The domestication of pigs, however, changed fundamentally the ecology of human influenza viruses. Since the pig is the only domesticated mammalian species, which is reared in abundance, and is common hosts for human and avian influenza viruses, it became the intermediate host for reassortment, producing new genes with a selective advantage over the parent viruses. Such reassortments are the sources of emerging new human pandemic strains [Webster et al. (1992)].

A man made example of adaptation is the introduction of myxomatosis virus to the rabbit population of Australia. The initial impact was explosive: in a single season an area as great as all of western Europe was infected, with a death rate of 99.8 per cent. Next year, the death rate went down to 90 per cent and seven years later mortality was only 25 per cent." [McNeill (1998), Fenner and Ratcliffe (1965)].

6. *Acquired characteristics could become part of the genetic makeup of succeeding generations without Lamarckian inheritance. The Baldwin effects.*

It may be relevant in context of the current theorems that the adaptive antibody population was suggested to facilitate the evolution of the natural antibody repertoire, in accordance with the Baldwin effect in the evolution of instinct.

Around 1896, Baldwin proposed that learned or acquired characteristics could become part of the genetic makeup of succeeding generations without Lamarckian inheritance. Individuals that learn or acquire useful characteristics during their lifetimes tend to survive, and, Baldwin claimed, this would cause succeeding generations to have a higher probability of acquiring the same characteristics, even though the characteristics themselves were not genetically propagated. Indeed, in a model it was shown that there could be an interaction between evolution and somatic learning [Anderson (1996), Perelson et al. (1996)].

7. *Mutual adaptation between host and microbes results in increasing incidence of endemic infectious diseases.*

The outcome of confrontation between host and microbe cannot be described in extreme terms such as either immunity or death. An intact immune system is watertight against some but not against *all* infections. The long-term consequence of mutual adaptation is that a significant part of a population will live together (even if not harmoniously) with a number of microbes. To reflect this reality, the efficiency of a model immune system should be chosen to be limited.

Even if artificial immunization and extensive use of antibiotics support the immune system, it cannot cope with a large number of infectious diseases. When it comes to human health, therefore, the emergence and reemergence of microbes constitutes the greatest threat of all, infectious diseases continue to be a leading cause of morbidity and mortality worldwide. Recent outbreaks and epidemiological studies predict that their incidence will increase while the world's population continues to grow [Garrett (1994), Finlay and Cossart (1997), Culliton (1997)]. Human migrations have been the main source of epidemics throughout history. Trade caravans, religious pilgrimages, and military campaigns facilitated the spread of plague, smallpox, and cholera. Global travel is a fact of modern life, 10% of the world's population was registered at international terminals during just one year. Evolution of microorganisms; new infections will therefore continue to emerge, as known infections will change in distribution, frequency, and severity [Spier (1997), Colwell (1996)].

Approximately 5% of the world population (an estimated 350 million carriers) is infected by the hepatitis B virus (HBV) [West and Calandra (1996)], whereas hepatitis C virus (HCV) infection is becoming increasingly diffused worldwide currently involving 1-2% of humans (an estimated 170 million carriers) [Ferri et al. (1997)]. By the year 2000 it is forecasted a cumulative total of close 40 million HIV infections in men, women and children [Mertens and Lowbeer (1996)] and nearly 2 million people will die each year of AIDS [Adler (1997)]. The Epstein-Barr virus (EBV) has evolved a highly successful relationship with its human host as it initially infects almost the entire human population, subsequently remains latent lifelong in most individuals. Reactivation of the virus or uncontrolled proliferation of the latently infected cells may follow in persons who develop EBV-associated proliferative disorders and tumors (Spring et al. 1996). Recombinant avian influenza viruses, which may infect men, show rapid radiation while moving among human hosts resulting in the 1957 (Asian) and 1968 (Hong Kong) pandemics [Bonn (1997), Holland (1996)]. Influenza viruses infect approximately 120 million people in the world's richest countries each year, many more during flu pandemics [Glaser (1997)].

Tuberculosis (TB), is now the world's leading killer of adults; 30 million are expected to die from TB in the next 10 years. After an absence of more than 100 years cholera was reintroduced into Latin America in the nineties. Within two years the disease had spread from Peru to Mexico, and in the past six years there have been 1.4 million reported cases of cholera causing more than 10 000 deaths in the Americas [Sanchez and Taylor (1997), Colwell (1996)]. Food borne infection with *Esherichia coli* O157, unknown twenty years ago, has become a food safety concern in Japan, Europe, and the Americas. Lyme borreliosis, first indetified in North America in 1982, is now known to be endemic in North America and Europe, being transmitted to humans who come into contact with ticks which normally feed on rodents and deer, the reservoir of *Borrelia burgdorferi* in nature. The Hantavirus pulmonary syndrome, first recognized in 1993, is now known to occur sporadically throughout North America, and at least twenty other emerging infectious diseases have been identified during this same 20-year period [Heymann and Taylor (1997)]. Over millions of years parasites have developed sophisticated strategies to adapt to their hosts, parasite infections therefore tend to be chronic [Moll (1996)]. Approximately 270 million people are infected with Malaria at any given time and threatens the health and life of 2400 million people worldwide [Ryan et al. (1994), Culliton (1997)]. *Entamoeba histolytica*, an intestinal protozoan, infects 10% of the world's population. The estimated population involved in the most widespread parasitic infections, like *Trichuriasis*, *Schistosomiasis*, *Strongyloidiasis*, *Filariasis*, and *Cestodiasis* are 800, 200, 90, 90 and 65 million, totaling to more than 20% of the world's population [Ryan et al. (1994)].

8. *Putative role of homeostatic T cell control in the regulation of regeneration and programmed death of host cells.*

The current model predicts a regulatory role for T cells, for which assumption no experimental evidence is available yet. The selected homeostatic processes are poorly understood and could be (at least partly) under T cell control.

Most animal cell divisions depend on extracellular *growth factors*, which are mainly produced by neighboring cells. If the cells are deprived of such signals, they activate an intrinsic death program and kill themselves. In adult humans, billions of cells die every hour [Raff (1996)]. What, controls how many times a cell divide is not well understood. For example, the human immune system strives to maintain homeostasis of *T cell numbers* with a poorly understood gauge that senses total numbers (all CD3 T cells). This regulation has been called "blind homeostasis" since it does not discriminate between specific T cell subsets. In AIDS patients $2x10^9$ cells (about 5% of the total body CD4 T-cell population) are being destroyed each day, thus an equal number of T cells must therefore be produced [Feinberg (1996)]. It is tempting to speculate that the dramatic weight loss in African AIDS "slim disease" cases [Serwadda et al. (1985)] has something to do with the collapse of homeostatic regulation exerted by T cells. A further example is the liver, which has an almost unlimited capacity to regenerate. A single hepatocyte gives rise to $1.7x10^{10}$ cells. Hepatic resections in dogs, primates and humans demonstrated that the regenerative response is *proportional* to the amount of liver removed. The size of liver from large dogs transplanted into small ones, gradually decreased until its size became proportional to the new body size. Conversely, the transplanted baboon liver in humans grew in size within a week until it reached the size of human liver. Thus liver mass is precisely regulated by signals from the body. When rats are joined in pairs through parabiotic circulation, hepatectomy of one member of the pair causes regeneration of the intact liver of the other member providing evidence that a *mitogenic signal* for hepatocytes appear in the blood during liver regeneration [Michalopoulos and DeFrances (1997)]. Red cell mass is also controlled within a narrow range. When their number decreases, production is increased via erythropoietin release, which also prevents apoptosis of early erythroid precursors. The current thinking is that no physiological mechanisms can shorten red cell survival; it is regulated entirely by cell production. In adapting to acute plethora in microgravity, however, astronauts' red-cell mass falls too rapidly to be explained by diminished red-cell production. Consistent with this, during this time little change in red-cell production can be demonstrated. *Neocytolysis*, the selective destruction of the youngest circulating red cells, would reconcile the observations on spaceflight and descent from altitude, which is limited to reducing red-cell mass by 10% over a few days [Alfrey et al. (1997)].

9. *T cell control of self may be more efficient by participation of soluble receptors.*

The homeostatic regulatory role of immune cells cannot be carried out exclusively by cell to cell contact, since only 2% of immune cells are circulating at any one time. The theorems suggest, therefore, that soluble receptors of both host and immune cells may participate in homeostatic control.

Soluble forms of human leukocyte class I antigens (sHLA I) were first reported about 20 years ago to be present in the plasma or serum of healthy individuals. T and B lymphocytes *secrete* considerable amounts of sHLA I to cell culture supernatants in a variety of *in vitro* and *in vivo* activation systems [Tambutti et al. (1996)]. Serum levels of sHLA I and II molecules *increase* during acute rejection episodes following organ transplant and acute graft-versus-host disease as well as during infectious and autoimmune diseases. It has also been reported that sHLA I and II may *downregulate* activated immune cells [Inostroza et al. (1997), Filaci et al. (1997)]. Multimeric soluble MHC class II molecules stably occupied with covalently attached peptides bind with appropriate specificity to T cell hybridomas and T cells from T cell receptor transgenic mice [Crawford et al. (1998)]. There is also a growing number of soluble agonistic (IL-6, ciliary neurotropic factor, IL-11, and glia-derived neutrotropic factor receptors) and antagonistic (IL-1 and TNF receptors) receptor proteins, modulating the biological functions of their cognate ligands [Peters et al. (1997)].

10. *Limits of homeostatic control: overall incidence of cancer in humans increases exponentially with age above 30 years.*

The homeostatic function may be 'exhausted' over a long period of time, which could eventually result in malignant diseases.

There are at least two reasons to suggest that the immune system is of importance to defend against malignancies. Firstly, persons undergoing maintenance immunosuppressive treatment (MIST) were shown to be at increased risk for the development of early malignancies [Radl et al. (1996)]. Furthermore, HIV-infected persons with a compromised immune system have an estimated 530-fold increased risk of Kaposi sarcoma and an 81-fold increased risk of non-Hodgkin's lymphoma, according to the National Cancer Institute studies of hemophiliacs [McNeil (1997)]. Secondly, viruses, including HPV3, EBV, hepatitis B virus, and human T-cell leukemia/lymphoma virus type I, are associated with approximately 20% of all human cancers worldwide [Evans et al. (1997)]. Consistent with this that at present between one-fourth and one-fifth of cancers worldwide are attributable to infection [Parsonnet (1997)]. Particularly chronic infections are associated with cancer incidence, latter in humans increases exponentially with age beginning at about 30 years. It is assumed that multiple genetic changes are related to destabilization of cells with the age of the organism [Rubin et al. (1996)]. The dimension of time, a latency period often 20 years or more between the initiation of carcinogenesis and the terminal, metastatic phase of the disease, is therefore critical in carcinogenesis. There is only a stochastic probability that an early stage will progress to a later one, as the natural history of many forms of epithelial carcinogenesis indicates that many, if not most, early lesions disappear spontaneously [Sporn (1991)]. A single cell can establish fatal disease in several mammalian species with a number of different neoplastic cell types [Schabel (1975)]. It was shown that selection is more important than an increased mutation rate in the growth of a tumor [Tomlinson et al. (1996)]. Tiny tumors lie dormant and undetected until an unknown mechanism triggers them to secrete growth factors that will induce angiogenesis [Saphir (1997)]. Dissemination of tumor cells probably occurs at a very early stage, perhaps when 10^6 or fewer tumor cells are present. The disseminated cells can die quickly, grow progressively or become dormant (similarly to microbial latency) latter may last for a lifetime [Uhr et al. (1997)].

Carcinoma is therefore not a disease of an individual cell, rather a complex failure of homeostasis in which epithelium and mesenchyme fail to communicate, resulting eventually in invasion and metastasis. It has taken millions of years of evolution to organize group of cells as functional tissues. When driven by mutagenesis, this organization unravels, resulting in carcinogenesis, and eventually leading to the chaos that is cancer [Sporn (1996)]. Such complex system is exquisitely sensitive to initial conditions as defined by chaos theory. Trivial degrees of perturbation can contribute to either the death or cure of the patient [Schipper et al. (1996)].

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Figure legend

Figure 1.

Diagram of a model. The large square (delineated by a dotted line) represents intracellular space, which includes three smaller rectangles, that of the non-immune cells (NI), T helper + T cytotoxic cells (Th + Tc) and antigen presenting cells (APC) respectively. The small black square, on the top of the large one, represents B cells. The intracellular space is surrounded by the extracellular space, which contains the soluble molecules and the microbes (only natural antibodies and viruses are shown). The intestinal flora, located in the extracellular space, is drawn as an elongated rectangle partly overlapping the square of B cells. There are two complementary interfaces: (i) between the MHC I of NI and Tc cells; and (ii) MHC II of APC and Th cells respectively.

A virus must enter NI cells to start replication. Presentation of viral peptide by MHC I perturbs (typically decreases) complementarity with Tc cells, which evokes a homeostatic response against infected cells. Newly released viral particles may be tagged by natural antibodies and complement (latter not shown) to be engulfed by APC. Presentation of viral peptide by MHC II perturbs (typically decreases) complementarity with Th cells. That will result in lyphokine release, polyclonal B cell activation, and hypermutation and eventually in high affinity antibody production, the trademark of a specific immune response (not shown).

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