From rejection to symbiosis. Human-infectious agents relations : a general theory of physiology and pathology. The contribution of tropical medicine.

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Abstract

In this paper, the word symbiosis (from the Greek *Sumbiōsis*) is used in its original sense and refers to all organisms which interact with each other, whether this association is beneficial, neutral or harmful to the host (mutualism, commensalism and parasitism). Symbiosis is found in every aspect of the living world. It is seen between infectious agents, in tropical disease vectors, in the human body and in illnesses. Immune-dependent symbiosis between infectious agents and the host is an opposite and complementary mechanism to defense and rejection immunity. This duality is found in many biological functions. Our comprehensive, compelling theory provides an overview of the different sites and mechanisms where symbiosis may occur. These symbioses are ongoing, four-dimensional evolutionary processes. They are gradually shifting away from phenotypic symbioses, including exosymbioses (metazoans, protozoa, yeasts, bacteria, viruses), tissular endosymbioses (metazoans, yeast), toward cytoplasmic and nuclear endosymbioses (protozoa, yeasts, bacteria, RNA viruses), before finally arriving at genomic endosymbioses (mitochondrial DNA, DNA viruses, retroviruses, transposable elements), which is the ultimate goal of symbiotic evolution, giving rise to new human genes. The phenotype/genotype boundary is thus traversable. A immunological process that initially takes an immunopathologic inflammatory form, but develops into a non-inflammatory immuno-physiological state. A process that leads from parasitism to mutualism and commensalism, and ultimately to the emergence of new species. This article hinges on the primary author's extensive experience in tropical medicine allied with meticulous bibliographic research. Our intention is to offer a fresh perspective on the different forms of physiological and pathological symbioses in humans and illustrate them with examples. The general control mechanisms of symbiosis are discussed including immune tolerance and rejection. Innate immunity requires an assumption about the evolutionary mechanisms involved in recognition of immune innate material. In adaptive immunity we develop the hypothetical role of antibody dependent cell tolerance (ADCT) in which cytophilic antibodies support immune-dependent symbiosis. This includes then the crucial role of growth and differentiation factors in symbiotic mechanisms. We will list ten areas of research and application in fundamental science (self-genomics, immune innate material), epidemiology, prevention (nuclear endomembrane, symbiogenic vaccination) and treatment (including differentiation therapy), which bring together internists, infectious disease specialists, oncologists, biologists, immunologists, geneticists, epidemiologists, nutritionists, botanists and evolutionary scientists.

Key words: antibody-dependent cell mediated tolerance; growth and differentiation factors; immune-dependent symbioses; species evolution; symbiogenic vaccination.

INTRODUCTION

In this paper, the word symbiosis (from the Greek *Sumbiōsis*) is used in its original sense and refers to all organisms which interact with each other, whether the relationship is beneficial, neutral or harmful to the host (mutualism, commensalism and parasitism). Symbiosis is found in every aspect of the living world. Our theory, entitled “From rejection to symbiosis” and the concept of antibody-dependant symbiosis, including the antibody-dependent cell-mediated tolerance (ADCT) mechanism, stem from observations made by the primary author and from meticulous bibliographic research. African and Pacific populations are ravaged by infectious diseases [1, 2] though often showing less severe or different symptoms from those observed in patients from temperate countries [3]. Among these major diseases, viral hepatitis B was discovered in a laboratory in French Polynesia purely by chance (personal communication). There are less lethal forms of malaria in Africa, although it does have high transmission rates and tends to be more permanent [4]. These paradoxes reflect an acquired tolerance in the population, passed down phylogenetically for millennia. In this paper we will present clinical observations from tropical regions and present logical and innovative biological, immunological and epidemiological interpretations, including ontogenetic and phylogenetic factors. The paper has four objectives: (a) to validate our theory of the physiology and pathology of the human-infectious agent association, based on the concept of the synchronous and/or successive duality of rejection and symbiosis. The latter is initially a mucocutaneous exosymbiosis. Through their tropism towards the host, exosymbiotes, (depending on their composition), may become tissular, cytoplasmic, nuclear or genome endosymbiontes. (b) To demonstrate the role of the different stages of symbiosis in physiology and pathology. Known or

probable mechanisms and pathways are given. Phenotypic and genotypic changes in infectious agents and their host are described.

(c) To determine the incidence of immune tolerance differentiation. (d) To identify new areas for research and applications in symbiogenesis. Ultimately, this comprehensive,compelling theory gives rise to a number of logical assumptions based on its four-dimensional evolutionary continuum.

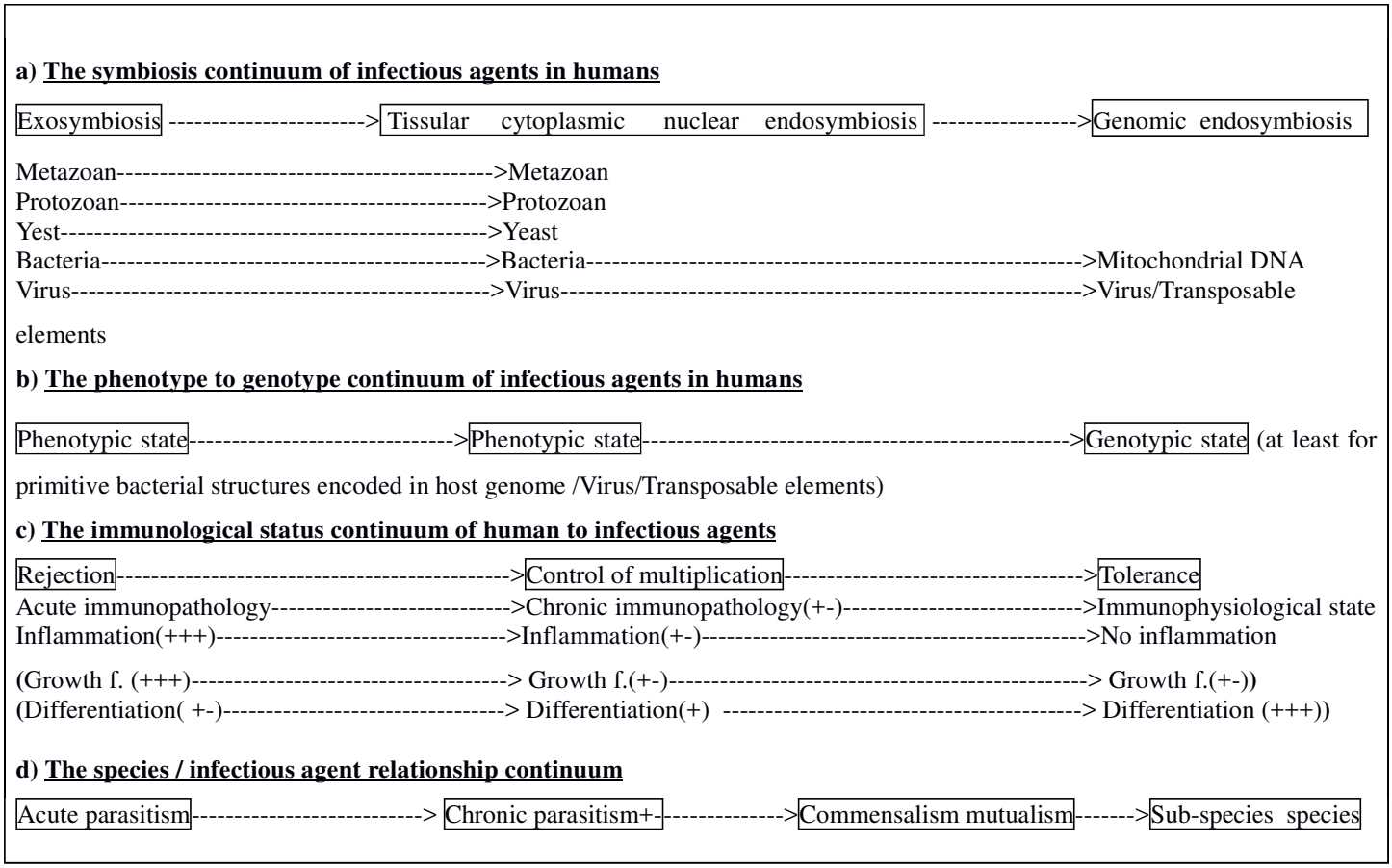

Fig 1. Symbiosis. Evolutionist continuum with four complementary dimensions a, b, c, d, leading to the emergence of new species.

SYMBIOTIC RELATIONSHIPS BETWEEN INFECTIOUS AGENTS IN HUMANS

● These symbiotic relationships are observed in parasites [5] bacteria [6] viruses and vectors of infectious agents. They help us to better understand changes in virulence of infectious agents. The T lymphocyte immunosuppression which accompanies uncomplicated malaria [7] conditions the host for simultaneous infection by the Epstein-Barr virus (EBV), and is the cause of Burkitt's lymphoma

[8]. Note also the pathogenic synergies between Salmonella and schistosomes and between HBV and the delta virus. Bacteria of the genus *Wolbachia* live in a state of symbiosis in the cytoplasm of the nematode *Onchocerca volvulus* [9] and many other pathogenic filaria [10]. In apicomplexan protozoa parasites (*Plasmodium falciparum*, *Toxoplasma gondii*, *Cryptosporidium parvum*), the apicoplast would be a vestigial cytoplasm bacteria. In all bacteria, new traits are transferred horizontally by plasmids or bacteriophages. This relocation of bacterial endosymbionts creates resistance to antibiotics. Viral endosymbionts infect all aforementioned agents [11]. The symbionts of pathogens are often the target of treatments, especially by antibiotics [12, 13].

● Symbiosis in vectors. Vectors of parasitic diseases (malaria, filariasis, etc.) tolerate a complex tissular cycle of the infectious agent [14] which subsequently becomes vector-specific. The vector, having become a strict anthropophilic partner, provides a direct route for the parasite into the host at the intratissular level.

NON PATHOGENIC SYMBIOSIS IN HUMANS

A physiological symbiosis is not detrimental to the infectious agent or host. Occasionally, they derive a mutual benefit.

Exosymbiosis

● In metazoans. In the intestine, some cestodes (*Railletina celebensis*, *Taenia saginata*, *Taenia solium*) and nemathelminthes (*Trichiuris trichiura*, *Enterobius vermicularis*) are usually well tolerated. ● In protozoa. In the tropics, typical intestinal flora include amoeba such as *Entamoeba coli*, which is never pathogenic. ● The Candida yeasts include several saprophytic vaginal, intestinal and skin species (*Candida albicans*, *Candida tropicalis*, etc.). *Malassezia furfur*, responsible for pityriasis versicolor, is a skin saprophyte mainly found in the tropics. The immunological component of this exosymbiosis is confirmed by the presence of seborrheic dermatosis [15] in subjects infected

with the human immunodeficiency virus-1 (HIV-1). ● In bacteria. Many bacteria are present on the skin, including *Staphylococcus aureus* and *Staphylococcu epidermidis*. They are potentially pathogenic, but contribute to the skin's development. Oropharyngeal mucosa home a diverse bacterial flora which includes group A streptococci, *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenza* and Corynebacteria. If the mucosal barrier is breached, local or systemic co-factors are required for the disease to progress due to these bacteria. In the digestive tract, bacteria are abundant. They synthesize essential nutrients (vitamin factors); are essential for digestion. These bacteria protect against infection by competing with newcomers, and they secrete bacteriocins. These functions are those of an organ in its own right. For the bacteria, the price of this hospitality is that they lose their reproductive freedom, which is out of control only limited by the presence of nutrients. This freedom becomes limited, adapted. Species selection takes place, and these adapt to certain nutritional intakes. This efficient mucosal exosymbiosis is controlled by the immune system. The dendritic cells of Peyer's patches are involved in the selection, as are the secretory IgA. [16] Vaginal flora is also abundant. ● Viruses: natural cavities contain many species of saprophytes (enterovirus, rotavirus, etc.).

Phenotypic Endosymbiosis in tissues, cytoplasm and in cell nuclei

● In tropical Helminths, *Mansonella perstans* is a textbook example of tissular endosymbiosis. Adults are intradermal, whereas the microfilariae reside in the bloodstream. No major diseases are attributed to this symbiosis [17]. The adults and embryos are examples of successful tissular xenografts. ● In protozoa, the asymptomatic presence of *Plasmodium falciparum* gametocytes in an immunized subject living in endemic areas is an example of cytoplasmic endosymbiosis [18, 19]. This paraphysiological state is attained during the subject's life and is the only virus reservoir in the cycle of transmission. In return for this favor, the host is spared from disease [20].

● In bacteria. Examples of successful cytoplasmic endosymbioses are mitochondria, vestigial bacteria found in the cytoplasm of all eukaryotes. On average, in humans there are 1,500 per cell. They perform essential functions including respiration and enzyme supply. They have their own DNA which, according to some authors, certain portions have become part of the host cell's own DNA [21, 22, 23]. This is an example of evolution from cytoplasmic endosymbiosis to genomic endosymbiosis. ● In viruses. Nuclear endosymbiosis is seen in single-stranded and double-stranded DNA viruses which generally replicate outside the genome in the host nucleus. The circovirus (ssDNA) is present and asymptomatic in major organs of most humans. HBV is a double-stranded DNA virus and is classified according to its method of replication: it is a nuclear endosymbiont if its DNA is not incorporated into the host DNA (90% of cases) and is a genomic endosymbiont when its DNA is incorporated into the host DNA (less than 10% of cases). Nuclear endosymbiotic HBV in inactive or immune tolerant carriers is characterized by the absence of clinical symptoms. We refer to an epidemiological study of HBV initiated in 1978 by the main author of this article in French Polynesia [3]. The study was conducted on the populations of three islands and analyzed the serum markers available at the time (HBsAg, HBsAb, HBeAg, HbeAb, HbcAb), in vitro cellular immunity and HLA phenotypes [24]. The island of Rapa was unusual in that 96% of the population were infected but the majority of individuals displayed no clinical or immunopathological symptoms. HBsAg was present in 65% of subjects. Subjects with HBeAg, presumed to be infectious (30% of subjects carried HBsAg), also displayed no clinical or immunopathological symptoms. No significant correlation was found with cellular immunity tests or HLA markers. A particular HBV sub-type, suggesting an attenuation of the viral strain through phenotype modification, was later observed in the population [25]. The island's population has developed an immune tolerance to HBV which is in all probability a widespread and harmless nuclear endosymbiosis with a specific HBV sub-type. Tolerance is probably

transmitted from mother to child via placental transfer of the HBeAg, which fosters immune tolerance to the virus [26].

Genomic Endosymbiosis

● Viruses. In Humans we refer to HIV retrovirus controllers (single stranded RNA) who display no clinical symptoms [27].

● Transposable elements (TEs). The initial discovery of these mobile elements of the genome by Barbara McClintock in 1956 gave rise to several categories of transposable elements. TEs would be of infectious origin. They are active remnants of ancestral DNA and RNA viruses [28], [29] which developed in our DNA and have lost or inactivated their gene envelope env [30]. Human genomic DNA consists of about 45% inherited TEs [31], our encoding DNA (euchromatin) only represents 1.2% and consists of about 20,000 genes [32]. The most recent classification of TEs [33] in eukaryotes, in 2007, put forward Class I elements, called retrotransposons, and Class II elements, called DNA transposons. For authors, the biological rationale for the transposition and mobility of TEs in the genome, which is capable of independent replication of genomic DNA, is that it is infectious and symbiotic. These elements invade the genome - their only biotope - just as viruses and bacteria invade an ecological niche. The aim of these initially foreign elements is to insert themselves into our genomic DNA as fully fledged, active genes, but this can be problematic. They are forced to multiply and move more often at random by transposition in a drawn-out attempt to enter the genome. During the transpositions, they may lose, by deletion, all or part of their nucleotides, or even disappear completely. We believe that this transposition mechanism is supported in our human genome with it “self-genomics” state [34] by a non-immunological recognition system of “innate genes” and "foreign genes", which recognize a true human gene from a foreign gene trying to insert itself into a locus. This system uses sensors and signals which allow

recognition. Sequences of TEs with similarities to human genes may have their implementation facilitated by certain mechanisms. This notion is supported by Sabot *et al*, who suggest that the transposition of long terminal repeat (LTR) retrotransposons occurs even in the absence of open reading frame (ORF) sequences for dimerization, packaging and integration, using as yet unknown signals [35]. Other authors suggest that the TEs and nucleic acid recognition system involves small sequence RNA epigenetic pathways including the phenomenon of RNA interference (RNA i) [36]. In the multifactorial process of endogenization, which leads to "native genes", we believe that the palindromic co-evolution of gene sequences and those at the extremities of transposable elements is a factor to consider. Once TE endogenization is complete and recognized as “self”, the phenomenon of gene transposition ceases to exist. It mostly takes the form of non-coding introns or, less frequently, coding exons.

● What is the biological consequence of TEs in our genome? Many activities necessary for life are now known to be encoded for by genes that are in fact “domesticated” TE sequences [37]. We pay particular attention to the progressive shortening of telomeres located at the ends of chromosomes which plays a role in cell aging and thus aging of the organism [38], in apoptosis [39], the onset of age-related diseases (cardiovascular diseases, neurodegenerative diseases) and cancer [40]. In Drosophila, these telomeric sequences are repeating non-LTR retrotransposons Het-A and TART [41]. Telomerase is a reverse transcriptase enzyme involved in the production of telomeres, mandatory in retroviruses and retrotransposons, which prove the link between TEs and telomerase in eukaryotes and therefore humans [42]. The interaction between telomeres, telomerase and the nuclear endomembrane is of particular interest to us. The interaction of telomeres and telomerase with the nuclear envelope is reminiscent of the phenomenon of nuclear export virus, which interacts with the phospholipid membrane of the nuclear envelope. Telomeres migrate to the periphery of the

nucleus and nuclear envelope [43]. In yeast, the formation of the chromosome bouquet is influenced by telomeres anchoring to the inner layer of the nuclear membrane [44]. The telomeres attach to and interact with the nuclear endomembrane using various proteins (Ku, Silent information regulator2 (Sir2), Sir 3, Sir4 and establishes silent chromatin (Esc1)) [45]. Telomerase enzymes, which assist in telomere elongation during the S phase of mitosis, migrate to the nuclear envelope where telomeres are anchored [46]. We believe that telomere production and telomerase activity interacting with the nuclear endomenbrane are conditioned by the integrity of the membrane. The authors therefore propose a regular diet of four components which may have the potential to promote the functional integrity of the nuclear endomenbrane and accordingly of telomeres and telomerase, possibly slowing their shortening. These components are: Omega 3 fatty acids of marine origin: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), found in oily fish, known to slow telomere shortening by antioxidant action and increase telomerase enzyme activity in normal cells [47]. The second component is daidzein and genistein, naturally occurring isoflavones found mainly in soy and kudzu (*Pueraria lobata*) and known to promote the stability of telomeres and therefore potentially reducing risk of cancers of the head and neck, lung, breast and prostate [48]. The third is resveratrol, a polyphenol antioxidant found in red wine [49] which acts on the inner layer of the nuclear membrane [45] and is a natural activator of Sir2 enzymes with a NAD (+) dependent deacetylase activity that maintains the telomere chromatin intact. The fourth is vitamin E, found in oils. The α-tocopherol form is located at certain points in cell membranes and reduces the destabilizing effects of lipid hydrolysis products such as lysophospholipids and free fatty acids. Thus, α-tocopherol stabilizes the two lipid layers of the membrane, preventing their fusion and contributing to their integrity and efficacy [50]. α-tocopherol and γ-tocopherol forms of Vitamin

E are antioxidants which protect polyunsaturated membrane lipids and have an antiapoptotic activity. [51]

● TEs pass through the barrier separating acquired genetic material from the organism's own "native" genes [52]. The organisms we observe today are partly the result of ancient symbioses which continue even to this day, including mucocutaneous exosymbioses; phenotypic, tissular, cytoplasmic and nuclear endosymbioses and genomic endosymbioses. The accumulation of infectious genetic material in humans is an ongoing process which has contributed to our evolution.

PATHOGENIC SYMBIOSIS IN HUMANS

Immunopathology is the support of the clinic. The pathology related to inflammatory reactions vary from acute rejection to symbiosis. The infectious agents involved are all moving towards symbioticrelationships.

Exosymbiosis

● Whipworm, a benign intraluminal nematode, can become pathogenic if present in sufficient numbers. This is also the case for protozoa (*Giardia intestinalis*, Cryptosporidium, microsporidia), yeasts, bacteria (Shigella, Vibrio) and viruses (rotavirus, adenovirus).

Phenotypic Endosymbiosis in tissues, cytoplasm and in cell nuclei

● Metazoans. In lymphatic filariasis, adult worms reside in the lymphatic vessels and microfilariae in the blood. Tissular endosymbiosis in adults is a relatively long and debilitating process, depending on the species (genus Brugia or Wuchereria) and on the individual. Clinical symptoms are more moderate with *Wucheraria bancrofti var. pacifica*: this indicates tolerogenesis.

● Protozoans endosymbiosis in cytoplasm: *Plasmodium falciparum* infects hepatocytes and erythrocytes. Growth and differentiation factors play an important role in the life cycle of the parasite. Multiplication of trophozoites within red blood cells up to rosette stage in a new subject

probably involves ubiquitous growth factors as insulin growth factors (IGF) [53] or more specific as granulocyte macrophage-colony stimulating factors (GM-CSF) [54], released in the presence of *Plasmodium falciparum* by peripheral white blood cells. Once immunity is established, the rejection mechanism, mainly consisting of splenic erythrophagocytosis, interferon [55] and antibody dependent cellular inhibition (ADCI) [56], reduces the number of parasites. In parallel the ADCT mechanism, specific to the surface antigens of erythrocytes parasitized by trophozoites (knobs), causes white blood cells to release differentiation factors, which trigger gametocytogenesis [57, 58]. Gradually, the schizogonic erythrocyte cycle begins to be controlled and leads to isolated gametocytaemia which is a cytoplasmic endosymbiosis. This endosymbiosis requires active immunity [59]. Partial loss of this immunity through extended absence of infections or inter-current immunodeficiency is followed by a new schizogonic cycle, resulting in a benign form of malaria. Phenotypic variation in exoerythrocytic antigens is connected with endosymbiosis [60, 61]. The normal outcome in a healthy carrier, free of clinical symptoms, is cytoplasmic gametocyte endosymbiosis, characterized by a controlled gametocytes mass in red blood cells, cell survival and host homeostasis (see figure 2).

● Bacteria. Usually found as exosymbiotes in skin and mucous membranes, bacteria display a tropism towards cytoplasmic endosymbiosis, passing through intermediate immunological and inflammatory phases. They create an acute, chronic and/or auto-immune immunopathology which mark out their permanent tropism into the cytoplasm. This final cell tropism can vary depending on the bacterium. Mycobacterium leprae enters Schwann cells and Chlamydia trachomatis enters the epithelial cells of the urethra and conjunctiva. Adaptation to the host and the species gradually improves and the microorganism gradually loses its rusticity.

● Viruses. In 90% of cases, HBV is in a state of nuclear endosymbiosis. Clinical forms of acute rejection are in general icteric, but can sometimes be fulminant. Diseases typically evolve towards chronic forms. Frequent liver diseases indicate immunopathologic conflict in areas with small numbers of chronic HBV carriers. In 2010, the HBsAg prevalence was low (<2%) in the Americas, Western Europe and developed western Pacific. Prevalence of HBeAg, which induces immune tolerance to HBV, is also low (5.7% of subjects HBsAg+). By constrast, in areas with endemic HBV (Africa, developing Western Pacific regions) there is high prevalence of HBsAg (> 8%) accompanied by a high prevalence of HBeAg (25% of subjects HBsAg+) [62]. In these areas there is a more advanced form of HBV endosymbiosis than in temperate zones.

Genome Endosymbiosis

● Viruses. The integration of viral DNA into the genome is irreversible for retroviruses. HBV combines with the genome of the host cell in less than 10% of infections. This integration is the ultimate aim of all symbioses. However, the state of genome endosymbiosis is unstable and progresses from the inactive carrier stage to the appearance of hepatocellular carcinoma. This instability, associated with genotype C of the virus and various carcinogenic co-factors (alcohol, tobacco, aflatoxin, co-infection with hepatitis C) leads to swifter development of hepatocellular carcinoma.

● Some of the most complex TEs include endogenous human teratocarcinoma-derived virus/human endogenous retrovirus-K (HTDV/HERV-K). These are responsible for viral teratocarcinoma in humans [63].

Interpreting viral autoimmune diseases and persistent viral infections

● Viral autoimmunity (RNA and DNA viruses) with immunopathological symptoms is considered to be a state of incomplete endosymbiosis with incomplete phenotypic expression. Viruses are

expressed on the surface of the host cell in the form of membrane antigens which are presented to the lymphoid system by the major histocompatibility complex (MHC) in which T helper17 cells (Th17) intervene [64]. They will cause successive rejection responses in the acute phase of infection followed by a control phase and then by a incomplete endosymbiosis with molecular mimicry, bystander activation and persistent viral infection [65]. Incomplete expression of viral agents, whether temporary or permanent, produces a number of autoimmune diseases. Mononuclear inflammatory reactions are found in type 1 diabetes, autoimmune thyroiditis, Sjögren's parotitis, Addison's disease and systemic lupus erythematosus [66, 67].

● Chronic viral infection pathogenicity is an immune-dependant, virally-activated unstable genomic endosymbiosis. The expression of viral phenotypes causes inflammatory reactions such as chronic hepatitis B. In other cases, viral activation simply results in the appearance of viral proteins found in HBsAg, following infection with HBV. This etiopathogeny is also suspected in multiple sclerosis [68]. In fact, unstable viral genomic endosymbiosis is retained for much systemic disorders encountered in neurology, rheumatology, angiology and even in mental disorders as in Alzheimer's disease.

● Latent viruses are initially in a state of stable, immune-dependant genomic endosymbiosis. As with all herpesviruses, Human herpesvirus8 (HHV8) in Kaposi's sarcoma [69] is only expressed in the phenotype during immunosuppression such as HIV infection. In type 2 diabetes, the autoimmune hypothesis is usually discarded in favor of a plurigenetic predisposition. However, Dandona et al support the inflammatory theory to explain the pathogenesis of type 2 diabetes, insulin resistance and atherosclerosis [70]. He did not mention the etiology of viruses and bacteria isolated from endothelial lesions, particularly cytomegalovirus [71] which is the primary cause of disease.

Viral agents and oncogenesis

● Viral etiology of tumors: Viruses are responsible for 15 to 20% of cancers worldwide, both in tropical and temperate zones [72]. Virions are in genomic endosymbiosis and are stable in host DNA. They are found in the genome of tumor cells in the form of incomplete fragments [73], as true oncogenes [74] and as producers of oncoproteins [75]. The Human T-lymphotropic virus-1 and 2 (HTLV-1 and 2) retroviruses are found in hyperendemic micro-foci, reaching 20 to 50% prevalence in Black Africa, Melanesia, Asia, South America and the Caribbean [76]. In relatively rare cases, HTLV-1 is responsible for T-cell leukemia [77] and neurological disorders. These HTLV endemics are believed to date back several millennia. The virus, particularly the HTLV-2 form, has gradually lost most of its virulence and oncogenic potency [78].

● Malignant transformation of cells by viruses. Viruses inserted into host cell DNA, in a state of chronic or latent genomic endosymbiosis, encode oncoproteins which interact with cellular proteins to increase viral replication rates [79]. Oncogenesis results from a destabilization of genomic endosymbiosis and involves specific immunological factors involved in the symbiosis [80] and other factors relating to the cell itself: interferons [81], defensins [82], protein kinases [83] and interleukins [84, 85]. These viral oncoproteins behave as targeted growth factors [86, 87].

● Carcinomatous process is similar to healing and scarring processes; a scar not controlled by differentiation factors. The disparity between the three consecutive stages of healing (growth, growth arrest, differentiation) is a source of oncogenesis. The atrophied tissue encountered in pathology becomes desensitized to growth factors, and are usually benign. Carcinogenesis is seen as a true "bottleneck" in the process of tissue renewal. Growth factors ensure the addition of new, undifferentiated and permanent cellular material. The insertion of these newly formed, functional

cells into the organ is regulated by differentiation factors. This process is disrupted by the arrival of the virus [88], while differentiation factors are not sufficient to ensure their role.

SYMBIOTIC TROPISM OF INFECTIOUS AGENTS AND PHENOTYPIC TRANSFORMATIONS

The aforementioned infectious agents all have a tropism for symbiosis with their host.

● In intestinal nematodes such as roundworm, the adult is an exosymbiote of the intestinal flora, manifesting its tissue endosymbiosis tropism through an intratissular cycle.

● *Entamaeba histolytica minuta*, an intestinal protozoan, reproduces extremely sucessfully. The emergence of the *histolytica histolytica* form is an attempt, albeit an unsuccessful one, to evolve towards tissular endosymbiosis.

● There are numerous examples of bacteria developing successful exosymbioses on the skin and mucous membranes, but this is no longer enough for many bacteria including pneumococcus, meningococcus, enterobacteria and Salmonella, which are attempting to move towards tissular endosymbiosis and ultimately towards cytoplasmic endosymbiosis.

● Poliovirus is an excellent example of a virus undergoing intra-tissular migration. Early on in symbiosis, we see retroviruses which, in order to match the host DNA, acquire a reverse transcriptase that allows them to be inserted into the DNA as retrotransposons. The intermediate stages of this symbiosis are marked by a progressive loss of integrity of the infectious agent, which becomes vestigial. Mitochondria have lost most of their ancestral phenotypic and genotypic structure, including cell wall, cytoplasm and DNA [89]. The missing DNA has joined that of the host [90]. Viruses which have been integrated into the host genome have generally lost their transcription ability, much like retrotransposons.

● During the initial multiplication phase, the infectious agent avoids immunological rejection through mutation [91], reflecting its genetic plasticity [92]. In tropical pathology, exoerythrocytic

antigens of *Plasmodium falciparum* and RNA viruses (influenza virus) undergo rapid mutation. The process is slower for microorganisms (HIV, HTLV) combining with host DNA. In length of the evolution all mutant forms of infectious agents have a reduced virulence compared to the ancetral strain from which they are derived [93]. This immune selection is geared towards self-preservation and that of the host species. The final step to steady state symbiosis is a lengthy process. The mitochondria in eukaryotes originate from the most primitive unicellular forms of life. The integration of HTLV began millennia ago and is still incomplete. Today's candidates are not all guaranteed eventual success.

GENERAL CONTROL MECHANISMS

The main defense mechanism against infectious agents is the immune system, with its innate, adaptive components that remain on alert throughout the host's life. A constant biological immunogenic / tolerogenic relationship called "cross talk" occurs between live microorganisms and the host's immune system. A universal effector mechanism is the growth factor/ differentiation factor pairing, which is involved in all types of host-infectious agents relationship.

Innate immunity. Evolutionary hypothesis for the development of immune innate material in humans. Sialic acids (SA) used as innate material markers in humans and as ligands in microorganisms

- We now know that these inherited mechanisms, beginning from adaptive immunity, have immunogenic and tolerogenic pathways in which dendritic cells play a major role [94]. The humoral aspect of innate immunity includes active and soluble proteins (lysozyme, complement, defensins). For these authors, immune innate material is the result of two successive and complementary evolutions.

● SA are active, vestigial molecules of bacterial origin. These unusual and diverse molecules are derived from neuraminic acid and have nine carbon atoms. They are reactive, have a high electronegative charge and are involved in many biological processes. They are very versatile with sialisation / desialisation, and are present in the distal portion of membrane polysaccharides (plasma membrane and glycocalyx), which means they are directly involved in interactions between the body and the environment. Bishop *et al* have identified similarities between bacteria and vertebrates, including humans (sialic acids, glycosaminoglycans, hyaluronic acid) [95]. Molecular mimicry of SA by bacteria to match those of the host has been described [96]. Some bacteria scavenge host SA to conceal themselves from the host's immune system [97]. We expect these SA processes to develop in other kingdoms (viruses, fungi, protozoa and metazoans) given the phylum of the last three of these kingdoms. SA, present on the cell surface in humans and set in our germ line, is an active molecule from our distant bacterial past which in part explains why we share innate material with ligands on the surface of microorganisms. As a result, during cross talk which occurs during infection by a microorganism, a SA recognition mechanism assesses the degree of homology of the SA and steers the innate immunity toward either the immunogenic or the tolerogenic route. This involves the microorganism's sialic ligands and the host cell's pattern recognition receptors (PRRs) in which the individual carbohydrate recognition domains (CRDs) intervene [98]. An example of the shift towards human bacterial tolerance and symbiosis is the presence of a small number of bacterial phyla in our intestinal flora. Of about fifty phyla, only three are present in the human intestine: Bacteroidetes, Firmicutes and Actinobacterias. It is likely that similarities between bacteria and human SA allow this tolerogenic selection to take place.

● Action of the body's innate immunity recognition receptors in multicellular evolution and the inhibitory action of SA on these receptors. The precursors of today's complex multicellular

organisms are social unicellular amoeboid protozoa which initiated symbiotic processes with multicellular eukaryotes [99]. Among them, "sentinel cells" have innate immune activity comprising immunophagocytose recognition of non-self material (bacteria) using membrane recognition molecules belonging to the Toll/IL-1R-like domain (TIR domain) [100] and eliminates the non-self material via pseudopodic motility and phagocytosis. Indeed, Chen et al (2007) and Sillo et al (2008) describe two genes (TirA and TirC) in the amoeba *Dictyostelium discoideum* which code for cytosolic proteins of the TIR domain, and which are probably activated via immunophagocytosis [101, 102]. Crespo et al (2009) found that neuraminidase clearance of human dendritic surface SA stimulates maturation and activation of MHC and a pro-inflammatory response with helper1 T (Th1) [103]. Jenner et al noted an increase in alpha2,6-sialisation of PRRs named sialic acid binding Ig-like lectins (SIGLECs) on the surface of tolerogenesis effector cells (immature peripheral dendritic cells and regulatory T cells (Tregs)) [104]. Other publications agree [105, 106]. Sialisation of PRRs induces a gene-based suppression of pseudopodic motility and phagocytosis. Consequently, the harmful phenomenon of cannibalism among multicellular eukaryotes is no longer possible. In humans, fixed tissue cells and those with non-pseudopodic mobility (e.g. red blood cells) express a modest number of Toll-like receptors (TLRs), a type of PRR discovered by Jules Hoffmann and colleagues. Takeda et al, on the other hand, found variable expression of TLRs on cells with normal state pseudopodic motility or after activation, including macrophages, monocytes, granulocytes, dendritic cells, B cells and T cells, natural killer cells, mast cells, microglial cells, astrocytes, epithelial cells and endothelial cells [107]. Evidence of our distant amoebic origin can be found in innate immune cells where dendritic cells with particularly active TLRs and other PRRs, are the main effector cells of our innate immunity [108].

● In conclusion, the path toward micro-organism tolerance can take two complimentary sialic routes. On the one hand there are similarities between the microorganism's SA and that of the host. On the other hand, there is a more quantitative and kinetic route where an increase in cell surface sialisation and PRRs causes peripheral dendritic cells to remain in their immature, therefore tolerogenic, state. Whether bacterial tolerance leads to a commensal or mutualistic state or even an exacerbation of their virulence depends on intrinsic factors such as pathogenicity islands or symbiosis islands, both of which are genomic islands [109].

Tolerogenic pathways in innate immunity

● The introduction of a microorganism carrying pathogen-associated molecular patterns (PAMPs) or the endogenous appearance of damage-associated molecular patterns (DAMPS) through Polly Matzinger's "danger model" [110] does not induce maturation of peripheral dendritic cells by means of PRRs. These cells are in a state of cross tolerance and lack co-stimulatory signals which activate naive T cells (signal 2). This produces a tolerogenic state in lymphocytes. The Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) inflammatory pathway is not activated.

Tolerogenic pathways in adaptive immunity

● Adaptive immunity is characterized upstream by a lack of develoment in dendritic cells. When the immune system is provoked, certain subgroups of tolerogenesis-aware immature peripheral dendritic cells will activate Tregs and T helper2 lymphocytes (Th2) to assist in cell cooperation, although micro-organisms and endogenous factors in the micro environment also play a role. Other factors intervene such as HLA-G, MHC class I molecules [111] and T-cell immunoglobulin domain and mucin domain 3 and 4 (TIM-3 and 4) [112]. Next, the Th2 cells switch from immunogenic pathways to tolerogenic pathways [113]. These tolerogenic Th2 cells stimulate antibody production, which facilitates tolerance and symbiosis with certain micro-organisms. These antibodies are

different from those involved in two similar immune mechanisms, namely antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular inhibition (ADCI) and are also different from those involved in antibody-dependent enhancement (ADE), for the simple reason that they keep in check the symbionts in a host cell while ensuring it remains functional. These tolerogenic antibodies belong to the ADCT mechanism.

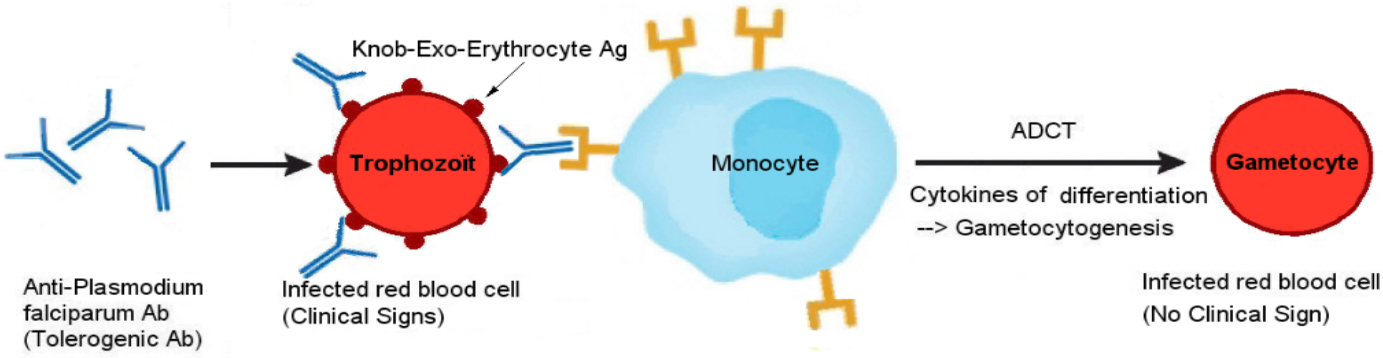

Fig 2. Mecanism of Antibody dependent cell mediated tolerance (ADCT) - e.g. Plasmodium falciparum

These cells are typically cytophilic. It is interesting to note that in the 1970s, while he was a researcher at the Institut Pasteur in Senegal and Côte d'Ivoire, Dr. Francis Parc, the main author of this article, proved the tolerogenic action of cytophilic antibodies. He found in a study that they produce a controlled increase in the non-pathogenic form of gametocyte *Plasmodium falciparum*. The objective of his study was to assess the ability of protective antibodies in a monocyte-dependent mecanism to inhibit parasite growth, in view of producing a vaccine against *Plasmodium falciparum* [114]. The obtained results led him to the concept of immuno-dependent symbiosis. This immunotolerogenic mechanism is found in filariasis [115] and it is observed in many viral infections [116].

● Finally, disease can sometimes be the result of an inadequate or inappropriate inflammatory response. In extreme cases this may be lethal, as with malignant syndrome and acute diseases. In prolonged illnesses, the persistence and nature of the condition (e.g. tuberculosis, leprosy and Chlamydia) will determine the anatomo-clinical consequences.

Ontogenetic and phylogenetic transmission of immune symbiosis mechanisms

Symbiosis and the immune symbiosis which underpins it are relatively discrete. Innate immune mechanisms, which are strictly genetic, are passed on phylogenetically.

The transmission of symbiotic adaptive immunity involves two complementary mechanisms, one ontogenetic transplacental and the other phylogenetic. The transplacental transmission is easy for *Plasmodium falciparum*. A gametocyte study in malaria-affected districts in eastern Pakistan showed that children under two months of age who still have maternal antibodies tended to have a denser gametocytaemia which decreased with age [117]. Similar mechanisms also exist for bacteria and viruses. HBV tolerance in Polynesian populations as seen before cannot be linked only to early infection. Ontogenetic immune tolerance to HBV is transmitted transplacentally to the fetus starting with HBeAg [118]. Pathogenicity defervescence is directly related to the age of the viral epidemic in these populations, as is the case for HTLV in hyper-endemic tropical areas. Tolerogenic antibodies assist in the transplacental transmission of infectious agents present in the mother, for example HIV-1 [119]. Here, we revisit ADCT, which is assisted by IgG during transplacental transmission. This tolerogenic initiation allows the embryo to develop its own mechanisms. Over many generations, transplacentally transmitted agents move ever closer to symbiosis and when the agent's immune symbiosis is registered genetically within the germline, transmission becomes phylogenetic.

Growth Factors and Differentiation

● Growth and differentiation mechanisms in host cells undergoing active symbiosis are similar to those found in embryogenesis and lead to physiological states. They differ from carcinogenesis, where only cell growth processes are involved.

● Growth factors are mitogenic factors involved in ontogeny, during the constant renewal and healing of tissue [120] and in the process of symbiosis. There are a large number of growth factors, and their importance in carcinology [121] is the subject of the work of the International Society of Differentiation (ISD) [122]. Most have an ambivalent growth / differentiation function, including soluble factor Wnt, which has a role in the growth / differentiation switch at a cellular level.

● Differentiation processes inhibit proliferation mechanisms [123] and allow the cell to express the overall phenotype necessary for its function. By definition, their action can only give rise to normal tissue. Their action on the infectious agents affects their reproductive autonomy. Differentiation processes are symbiotic processes par excellence.

● Circulating endogenous factors: These include non-specific endogenous factors, such as Insulin-like Growth Factor 1 and 2 (IGF 1 and 2) [124], specialized endocrine factors such as pituitary growth hormone [125], insulin, estrogen, steroid hormones [126], specific bloodline factors erythropoietin and granulocyte-colony stimulating factors (G-CSF). The anti-inflammatory action of insulin is now well understood [127].

● Endogenous cell-specific factors: cytokines regulate the immune response, including the type and number of mechanisms activated in the presence of a infectious agent. In innate immunity, macrophages and dendritic cells secrete pro-inflammatory interleukins IL-1, IL-6, IL-8, TNF-alpha and cytokines IL-12 and IFN-gamma, thus directing the Th1/Th2 balance towards pole Th1. In adaptive

immunity, activated T cells secrete IL-2, IL-4, IL-5, IFN-gamma, transforming growth factor-beta (TGF-beta), IL-13 and lymphotoxins. Proto-oncogenes produce growth factors as transforming growth factor (TGF) [128] whose action is not offset by differentiation factors which inhibit cell growth. Protein kinases form a network which regulates the proliferation, differentiation, migration and apoptosis of cells [129] which act in synergy with diffusible signals previously described (circulating endogenous factors, hormones and cytokines). They are the subject of numerous studies by the ISD.

● Exogenous Growth and differentiation factors:

● Phosphoglycane inositol is both exogenous and endogenous. It is an oligosaccharide, stemming from a membrane glycolipid, and it plays an important role in controlling cellular properties [130]. It boosts insulin secretion [131] and is a growth and differentiation factor [132]. An equivalent has been found in mouse *Plasmodium yoelii* [133]. Phosphoglycane inositol is widespread in eukaryotes [134], plants, protozoa and mammals.

● Retinoids are derived from the metabolism of vitamin A. Their use in cancer therapy is promising according to the ISD. They have successfully been used to treat acute promyelocytic leukemia [135] and cervical cancers caused by papillomavirus [136]. Vitamin A diet supplementation reduces measles symptoms in Africans [137] reduces mortalities from cerebral malaria, reduces malarial re-infections and accelerates immune development. Initial parasitaemia is reduced by 68% in infants between 12 and 36 months, and proliferation is slowed down [138]. Immunological studies of these subjects revealed the presence of traditional rejection mechanisms (phagocytosis, ADCI, CD36 activation) [139], but research into gametocytogenesis evolution has yet to be carried out. The intense rejection mechanisms are quickly offset by activation of the differentiation mechanisms.

● Vitamin D, and in particular calcitriol, is used in the prevention and treatment of colon cancer [140] and prostate cancer [141]. Initial results appear to be far less promising than for retinoids.

● Genistein is phyto-estrogen, a phytohormone, a member of the polyphenol isoflavones. This differentiation factor is effective against certain tumors [142].

● Resveratrol, another plant polyphenol and differentiation agent, is well known for its cardio-protective activity. It acts in human glioblastoma [143].

● The role of growth and differentiation factors in pathology. The factors mentioned above mediate the immune response and thus the composition of inflammatory granulomas. They are also involved in the replication and growth of pathogens. Their effect is regulated. These agents begin as growth factors but then become involved in differentiation. Cytokines select lymphocytes and monocytes involved in granulomatous reactions or follicular lymph nodes. Differentiation cytokines will oppose the proliferation of lymphocytes and differentiate memory cells [144].

● The importance of growth and differentiation factors in symbiotic evolution. The phase of differentiation is tolerogenic. Tolerance is low in acute diseases but plays a more important role when the host-agent symbiosis is more intimate. All infectious agents gradually entrust their reproduction to the host. Metazoans release their eggs in natural cavities or their embryos into tissue (filariasis). Protozoa (amoeba) release their eggs into cavities and their gametes into tissues (Plasmodium, Trypanosoma). Bacteria follow a similar process. In the initial phase, they reproduce autonomously using available nutrients. In the intratissular phase, they gradually become dependent on the host's growth factors [145]. In the chronic phase, their growth is controlled by differentiation factors. The final stage of phenotypic endosymbiosis is for example mitochondrial. This results in the formation of a new host-symbiont breeding pair. The process is similar with viruses. The intense cytolysis replication of infected cells is checked. In rare cases, viruses will replicate with the genome of the host cell.

● Immunopathology is the manifestation of all these factors. It is the gradual response to, and adoption of, a foreign element. This must be shaped, modified and controlled if the xenograft is to be successful.

AREAS OF RESEARCH AND APPLICATION

Biological evolution of species and their adaptation to the environment. We agree with Corning that the adaptation of species to their environment is an integration phenomenon (holistic darwinism) [146], is faster than previously thought [147] and includes mutations, symbiosis, epigenetics (DNA methylation, non-coding RNAs, transposable elements) [148] and horizontal gene transfer phenomena well known in bacteria and thought to occur in animals [149]. This provides an unexpected plasticity during adaptation to the environment. Symbiotic pressure is in our opinion universal in nature. We underline the importance of symbiosis in naturalist Jean Baptiste De Lamarck's process of complexification. We also note the importance of preservation of heritage in the phylogeny. Human sialic acids appear to be derived from bacteria and our endo-cannabinoids stem from the earliest unicellular organisms [150]. Finally, what is the impact of widespread, justified use of antibiotics and vaccination on the ecology of symbiosis?

Etiological and immuno-pathological scale of infectious agents. All infectious agents are in a relative advanced stage of symbiosis with their host. All take this pathway, obeying a tropism to biological evolution (acquisition of a configuration compatible with host receptors). A pathogenicity scale can be established for each agent, according to its overall progress with its host.

● A new, never before encountered pathogen (Spanish flu virus, Ebola virus), will cause a peracute illness often resulting in the disappearance of the agent and host. In this case, growth factors alone are involved; infectious agents multiply along with defense cells. The appearance of a new anthropophilic pathogenic strain follows the law of mutations of the originally zoophilic agent. The

creation of molecular structures recognized by human receptors is evidence of new pathogenicity. The rapid appearance of differentiation factors will prepare for a non-lethal acute form.

● In chronic diseases, the cohabitation stage is long and the pathological mechanism is often an inflammatory reaction. The symbiosis is still insufficient and is incompatible with the HLA system. Mobilization of the lymphoid system combined with ineffective rejection, incomplete control, growth of the agent and insufficient differentiation creates a state of immunopathology. During this coexistence, the agent becomes specific to the host species.

● Cohabitation becomes definitive when the symbiosis is finally complete. Final integration is mutually beneficial and without symptoms or illness. This immuno-pathological scale can be added to the classical notion of virulence. This introduces relativity in the assessment of pathogenicity.

Routes for biological research. ● More research needs to be done on the mechanisms involved in the recognition of innate and non-innate genetic material (self-genomics), at the position where TEs are implanted in the genome (epigenetic phenomena ?, evolution of palindromic sequences of the genome and those at the ends of Tes ?). Further investigation may shed light on phenomena involved in certain cancers and immunopathological processes.

● Telomere activity and the nuclear endomembrane. The important biological interaction of telomeres and the nuclear endomembrane merits further study. Maintaining the nuclear endomembrane through the dietary intake of omega 3, vitamin E, genistein, daidzein and resveratrol is also a topic for further research.

● A further study of the biology of sialic acids as species markers and as a modulators of the innate immune response should be considered.

● A study of tolerogenic antibodies and the ADCT mechanism should also be considered.

Anti-infective therapy through the inhibition of symbionts. Endosymbionts of infectious agents are necessary to their survival. Bacteria are targeted by filariasis antibiotics. Plasmodium apicoplasts are destroyed by doxycycline [151] and those of Toxoplasma by spiramycin. Chloroquine targets Acidocalcisomes [152]. Antibiotic therapy using human mitochondria may be useful in treating cancers [153, 154]; research looks very promising. An anti-symbiont vaccine is also a potential route.

Tolerogenic vaccination strategy. The general concept of immune-dependant symbiosis could be a suitable candidate for vaccine therapy. Current vaccines are based on immune rejection or competition between functional exosymbioses like the live polio vaccine Sabin which makes intestinal exosymbiosis impossible for the poliovirus. Antimalarial tolerogenic vaccination must be a priority [114, 155, 156]. This is desirable given that the vaccines available for over twenty years have not been entirely successful. This would open a new pathway in vaccinology. The fact that it is an anti-eukaryotic vaccine further underlines its importance. This parasite antigen vaccine causes a sustainable increase in the tolerogenic antibodies involved in ADCT. In a subsequent infection by *Plasmodium falciparum*, the natural process of symbiosis would be accelerated and would be accompanied by harmless (contaminating) gametocytaemia. When cultured in vitro, gametocytogenesis depends on environmental factors such as parasitaemia, oxidative stress and the action of antimalarial drugs (chloroquine). This immunological symbiosis-accelerating strategy may be used for retroviruses, because they are too close to symbiosis to be eliminated by rejection. The search for viral antigenic fractions [157, 158] which produce symbioses similar to anti-malarial tolerogenesis is a research priority given the scale of the HIV epidemic. Natural endosymbiosis without clinical symptoms, seen in HIV controllers, must be studied and duplicated. Research into symbiogenic vaccinology is possible for other illnesses. Finally, passive immunity as a form of tolerogenic immunotherapy may also be considered.

Differentiation therapy and prevention. We have shown the importance of cell differentiation processes seen in symbioses and during embryogenesis, giving rise to physiological states. A deficit in these processes leads to carcinogenesis. It is therefore recommended to extend the scope of differentiation therapy for diseases. There are many potential applications. Results in acute infectious syndromes have been remarkable. Retinoids have been successfully used to attenuate malignant measles syndrome [159, 160] and neuromalaria [161, 162, 163] in Africans. A malarial study linking vitamin A supplementation to gametocytogenesis has yet to be undertaken. This therapeutic strategy should be extended to diseases caused by chronic viral infections and also to immune-pathological diseases in general. Their use in carcinology is promising [164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181]. Resistance in solid tumors to natural retinoids (retinoic acid) could be combated by producing synthetic retinoids that are not affected by the metabolic inactivation processes encountered in such tumors [182]. Other more accessible exogenous factors should first be considered. The most obvious potential beneficiary is diabetes. Inositolphosphoglycane is an insulin corrector, and is also a growth and differentiation factor. It shows potential for controlling type-2 diabetes [183]. The study of infectious diseases would benefit from closer ties with the International Society of Differentiation (ISD); their approaches are complementary. An array of strategic therapies would be required to treat all infectious diseases, immunopathology and carcinology.

Applications in plant biology research and phytotherapy. Exogenous growth and differentiation factors, including vitamin A, vitamin D, genistein, resveratrol, etc…, are widespread in the plant world. This opens up new, compelling areas of research into molecules with similar functions. Priority should be given to research into plant phytohormones with endocrine activity such as phytoestrogens, insulin-like, Abscisic acid [184], etc…. Genistein is a phytoestrogen polyphenol

found in soy and kudzu (*Pueraria lobata*), which, via kinase antityrosine, opposes the action of growth factors in endothelial capillary cells. It slows angiogenesis in tumors. This molecule may also prevent endothelial cells from engaging in diabetic angiopathy. Insulin-like molecules are found in plants and are used in anti-diabetic herbal medicines such as *Eugenia jambolona Thomson*, in Madagascar. Consumption of vegetables rich in retinoids should be encouraged, particularly in tropical zones. The existence of similar, earlier molecules in more complex organisms is likely.

Contributions to molecular epidemiology. ● Phenotypes caused by symbiotic adaptations in infectious agents tend to share certain features: antigenic variations, appearance of sub-species and then species. In a previously uninfected population, these changes start with a simultaneous invasion phase, a phase of general immune rejection followed by a phase of epidemic defervescence and endemicity [185] and general symbiosis, which is accompanied by an increase in adaptation types.

● The global HIV-1 pandemic consists mainly of group M and involves multiple genetic variants with nine subtypes, A to K, sub-subtypes, circulating recombinant forms (CRFs) and unique recombinant forms (URFs) [186]. There is cross talk between HIV and local HLA polymorphism. At the individual level, this has an important role in modulating epidemic kinetics through the selective pressure of cytotoxic T lymphocytes (CTLs) associated with class I HLA alleles [187]. During the onset and growth phases of epidemics, we see the consensus sequence of the circulating virus matching the most frequent HLA alleles in the target population [187, 188]. There is a dominant monomorphism in the circulating HIV-1 phenotypes. This is probably the case for the epidemic in South Africa, which is almost exclusively due to viral subtype C (2007) [189, 190]. The expansion phase is followed by phase of defervescence and endemicity where the process of immune escape becomes important, whether associated or not with HLA alleles [191]. Endemicity caused by HLA/CTL pressure selecting

for immune escape phenotypes is accompanied by an increase in HIV phenotypic polymorphism (immune escape variants, forms reverting to the ancestral virus) which are better matched to the local HLA polymorphism [187, 192]. This is the case in Central Africa where there is a similar proportion of subtypes A, C, D, G, H and CRF02_AG and other CRFs and URFs (2007) [190]. This proliferation of subtypes and other variants is most likely a positive sign for the region. The lower replication rates of immune escape viral forms is a further sign of a positive symbiotic evolution, avoiding high rates of mortality in individual hosts and at the population level [187, 193]. Note the temporality of HIV-1 epidemic kinetics, where models have focused on periods of tens or even hundreds of years [191]. Over many generations, mutations and variants of HIV-1 have become less virulent [194]. This rule can be applied to all symbiotic adaptations in microorganisms.

● Note: In global influenza pandemics followed by particularly rapid defervescence, only a single viral type emerge. At the individual level and depending on the microorganism, phenotypic variability is variable. This arises rapidly in exoerythrocytic antigens of *Plasmodium falciparum* [195]. Conversely, the dengue virus is less prone to variance [196].

● Interpretation of sexually transmitted infections. These diseases represent agents in advanced symbiosis using the reproductive organ of the host, on which they are dependent. Examples include the exclusively human *Treponema pallidum* and *Neisseria gonorrhoeae*, which is fragile in the external environment. HBV and HIV both have a preference for sexual transmission. The sexual transmission hypothesis for other diseases such as multiple sclerosis [197] is compelling.

Allografts and gene therapy. ● The study of *Mansonella perstans*, a successful xenograft in humans, could be valuable.

●The use of differentiation factors in allografts may prevent rejection [198].

● Gene therapy is an artificial genomic endosymbiosis that uses viruses to transfer repair genes into the genome of host cells. Sustaining and maintaining these artificially acquired characteristics is largely dependent on stable symbiosis in the recipient DNA. Undesirable effects on native genes (oncogenes) caused by viral vectors, which can lead to leukemia, are difficult to prevent. There are, however, retroviruses in advanced natural genomic endosymbioses and genomic endosymbiont HTLV viruses with low virulence which could be used as less harmful viral vectors [199].

Immunoallergology. This is a branch of immunopathology which mainly involves IgE, basophils and mast cells in anaphylactic shock hyperacute rejection. Histamine is the main molecular effector. In acute and chronic forms, other cellular components may play a role, including lymphocytes and monocytes. Allergens are exogenous, and may be natural (nutrients, pollen, fungi and mites) or synthetic (chemicals and drugs). Tolerance in normal subjects is demonstrated by the absence of allergic response, the equivalent of immune rejection. Allergens are generally ubiquitous, and the tolerogenic immune response to heterophile Forssman-type antigens could be an interesting model for study [200]. This physiological tolerance could be used in the desensitization of patients. Differentiation strategy using Inducible T-Cell Co-Stimulator Proteins (ICOS) steers differentiation towards the tolerogenic Tregs pathway [201] is a possible therapy for prevention and treatment of allergic disorders.

CONCLUSION

Symbiosis between organisms is a universal and natural law which affects any organism with an immune system, including humans. In the 1960s, Lynn Margulis, following the endosymbiotic theory known from the beginning of the twentieth century , proposed with scientific proofs a theory on the origin of eukaryotic cells. She suggested that eukaryotes are the product of endosymbioses between primitive life forms; for example, the transformation of certain prokaryotes into eukaryotes

underlines the role of symbiosis in cell evolution [202]. There are now an increasing number of scientific professionals who acknowledge the role of symbiosis in the evolution of species. Historically, immunologists and medical professionals have regarded the immune system as one of defense and rejection, and it is only in the last two decades that research on immune tolerance has emerged. "From rejection to symbiosis", our comprehensive, compelling theory, makes a significant contribution to this new field. It assumes that the phenotype/genotype barrier is traversable as an evolutionary continuum stretching from phenotype to genotype. Indeed, acquired diseases may eventually become hereditary traits. We have highlighted the vital role of immune-dependant symbiosis in tropical infectious diseases, and this has enabled us to take a synthetic approach to immunopathology. Immune defense and rejection, despite huge success, has now reached its limits. For example, it does not explain the behavior of major endemics. It is not enough simply to develop new vaccines. In this perspective, we propose new concepts and applications bringing together medical and scientific professionals including internists, infectious disease specialists, oncologists, biologists, immunologists, geneticists, epidemiologists, nutritionists, botanists and evolutionary scientists. We light with a fresh look growing applications such as differentiation in therapy and prevention. Partial successes with tolerogenic vaccines or immunotherapy which would to reduce numbers of lethal forms of infectious diseases, including malaria would be major victories for those of us who have witnessed and fought these deadly diseases in Africa and Oceania.

Conflicts of interest statement

None for all authors

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“To Doctor Francis Parc”

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