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Hereditary Immunity against Infectious Diseases

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ABSTRACT

This chapter contains review of the main achievements in the discovery of hereditary immunity that has accomplished in different areas of infectious pathology and contra-infectious health care which has been published mainly at the edge and over the beginning of 21st century. It includes a synopsis of fundamental principles and origin of hereditary immunity. Special focus is on molecular executors of hereditary immunity and their strong adequacy to bimolecular ecology of relevant infectious diseases. The responsibility of immune mosaicism for the recurrence of infectious epidemics discussed too. Exploitation of immune heritage of humankind is present from the viewpoint of optimized strategy of genetically individualized tactics of contra-infectious health care. Super-excessiveness of total prophylaxis pointed as a matter of extraordinary importance. The need accentuated to focus contra-infectious prophylaxis on the revealing and defense of defenseless. Special attention is devoted to debunking the myphs of annihilating total epidemics, bioweapons and bioterrorism.

KEYWORDS

Contra-infectious immunity; Emergence of epidemics; Immune mosaicism; Voluntary vaccination; Annihilating epidemics; Myths of Bioweapons; Myths of bioterrorism; Defense of Defenseless

INTRODUCTION

Hereditary or constitutional immunity is genetically determined ability of a living structure to resist relevant impact of either ecological (e.g. infectious) or physiological agents [1-5]. The existence of hereditary immunity to infections was known over many hundreds of years. Nevertheless, W. Boyd [1] was probably the first who stated near 50 years ago in his handbook on the fundamentals of immunology that this kind of immunity was a fundamental trait and expressed his regret for the lack of scientific knowledge of this type of resistance.

For many decades of 21st Century, the discovery of hereditary immunity was out of the mainstream of fundamental immunology. It has considered as being beyond importance, comprehension and utilization. Even at the threshold of the last quarter of 21st century, a little bit known about these kinds of immunity. Moreover, a little bit done to explore this area. Almost all immunologists and pathologists focused their attention on responsive immunity elaborated by lymphatic system of vertebrates. However, another form of immunity, namely the constitutionally predetermined ability to prevent disease overlooked. Immunity of Invertebrates, Plants, Fungi, Bacteria, Viruses and other kinds of living beings were out of the mainstream of immunology [6].

At the threshold of the third millennium, the situation began to change. First experimental and theoretical publications about the matter including presentations to worshipful international congresses have begun to appear since the last quarter of 21st century. A lot of information has been revealed about manifestations of the phenomenon on the levels of species, populations, individuals, organs and tissues as well as on the level of cells and their molecular constitution [4,5,7-10]. First trials of generalization and theoretical comprehension of the data about hereditary immunity performed [4,5]. Some primary proposals to exploit the new knowledge in the health care have been formulated [11]. For instance, the current achievements in the revealing of hereditary immunity have allowed humanity to open their eyes on the impotency of bioweapon [9,12,13] and bioterrorism [14] as well as on the pointlessness of compulsory total vaccination against infectious diseases [5,13,14].

What is more, the mechanisms and functions of hereditary immunity began to be revealed and characterized for the first time [5,15] in the origin and pandemic spread of most flagrant diseases of today (cancer, obesity, atherosclerosis, osteoporosis, senescense, mental disorders). Immune update to Universal Theory of Diseases has been performed [5,15]. Absolutely new field of applied immunology was formed by proposition to use the knowledge of hereditary immunity and relevant approaches for the discovery of evolutionary way from apes to humankind [16,17].

The present article contains the review and analyses of main achievements in recent discovery and exploitation of hereditary immunity that has accomplished in different areas of life discovery and healthcare, which published mainly over the beginning of 21st century. It also contains necessary synopsis of fundamental principles and origin of hereditary immunity. Along with contra-infectious hereditary immunity suitable attention is devoted to the functions of hereditary immunity in the origin and subsistence of 'non-infectious' diseases.

Special focus is made on the moving function of hereditary immunity to malaria, tick borne infections, rabies over evolution of ape human predecessors but especially on the spurt descent of early humankind [5,18] over African Pleistocene (anthrax, botulism, salmonelloses, brucellosis, tetanus, gangrene) and in consequent evolution of races over dispersion of humans around the world (influenza, measles, HIV/AIDS, tuberculosis, smallpox). The main focus was on the integration of up-to-date achievements of both evolutionary and historic anthropology with relevant data regarding genetics, immunology, epidemiology, molecular biology and molecular evolution.

The present chapter also concluded with the exploitation of the knowledge of hereditary immunity in the dating of the first emergence of various human epidemics, which was performed at different places and far earlier than it before. The use of hereditary immune echo of previous long lasting counteraction of humankind to infectious epidemics is present from the viewpoint of optimized strategy and tactics of contra-infectious health care. Various appropriate achievements regarding the theme from the literature were summarizing with the data of long-term investigations performed by the author's team.

TYPES OF CONTRA-INFECTIOUS IMMUNITY

Immunity (resistance, unresponsiveness, insusceptibility, invulnerability, tolerance, resistivity) is all-biological phenomenon that means the capacity to withstand something, especially the state of increased resistance against the effect of an ecological or physiological agent, e.g. the natural capacity of a living organism to withstand infectious disease [10]. Immunity against infective diseases understood as the group of phenomena in virtue of which an organism is able to resist the attack of the microorganisms that produce these diseases. It is impossible, at present, to give a more precise definition, and useless to insist upon it [2,3].

Today's conception of immunity means the inherent or acquired capacity to withstand the effect of ecological or physiological agents, e.g. the capacity of a living organism to withstand an infectious disease [4,5,19-21]. As any all-biological phenomenon, immunity involves an extremely complex set of surveillance defensive agents and systems, geared to the maintenance of a healthy existence.

Two main kinds of immunity are known today: inherent (i.e. constitutional, genetic, intrinsic) immunity and individually adaptive i.e. reactive (responsive) one. Hereditary immunity provided with inborn traces of the body elaborated by its evolutionary predecessor over their counteraction

of relevant ecological agents. Hereditary immunity performs the protection of appropriate living structure from a first impact by the power of inherent traits of immunity. Responsive immunity begins to launch individual immunogenesis only after the threatening action began i.e. only in the response to it. It noted that the state of responsive immunity elaborated individually. It cannot be inherited.

Each kind of immune self-defense, either inherent or responsive one is created by relevant innate system of immunogenesis. As well of a sole 'immune" system the immunology operates now with four immunogenic systems: constitutional (hereditary), simplest responsive, phagocytic and lymphatic ones (Figure 1).

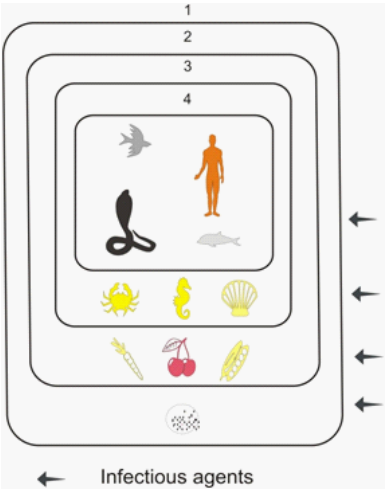

Figure 1: Main systems of immunogenesis: heritable constitutive (1), simpliest responsive (2), phagocytic (3), and lymphatic responsive (4). According to [22].

All the systems are of innate origin, however only constitutional and phagocytic systems are able to perform the protection of appropriate organisms from a first ecological attack by the power of inherent traits of immunity. In the cases of hereditary immunity pathogenic effect of either microbial, plant, fungal, animal or any other life threatening agents may be prevented without individually performed response of attacked victim. Hereditary immunity performs its protective action by means of evolutionary developed genetically determined structures of the agent's targets in relevant bodies. The huge variation in individual sensitivity as well as in clinical course and severity of response to identical infecting pathogens is the result of genetic variation in relevant components of molecular constitution of threatened organisms [23].

THE SIGNS OF HEREDITARY CONTRA-INFECTIOUS IMMUNITY

Constitutional immunity against infections encompasses several specific structures. These structures present a variety of either molecular or mechanical barriers such as the absentness of cell receptors, modification of the specific cell receptor, modification of specific nutrients, lack of a specific microbial nutrient, presence of specific antibiotic or poison, as well as other traits

[5,24,25]. The lot of already discovered protective traits, the signs of hereditary immunity is a result of very wide observations performed on different levels of various epidemic processes.

The signs of hereditary immunity exist and revealed in the structures of both phenome and genomes of individuals, populations and species. To evaluate the creative potential of infections in the context of human evolution, it was important to consider the selective effects of infectious diseases, focusing on their current individual and ethnic features. In recent years, there has been considerable progress in identifying the traces of infectious selection that have been performed under pressure of a wide variety of epidemics [5]. Today, researchers can unearth the remnants of archaic human selection for inherent immunity against infectious diseases, focusing on the results of field (epidemiological), clinical, cellular, molecular, immunological, and genomic investigations [26] .

In Field Observations of Epidemic Processes

In accordance to their different ecological features, living beings, their populations, and species differentially subjected to selection for heritable immunity against significant infectious agents. Humankind always had and continues to have, the most extensive and broad ecological contacts with the world of microbes [4,13,27-29]. It becomes evident that the selection for hereditary immunity in humans probably involved all infectious agents known today. As a result, most modern people are hereditarily immune to most known infectious diseases [5].

In the natural environment, influenza disease typically arose either as respiratory or food-borne illness. Diseased organisms become the sources of reproduction and dissemination of the virus. In the bodies of sensitive animals, the microbes multiply explosively, causing the victim to have the disease and die. Both the diseased and dead victims serve as new sources of subsequent dissemination of the virus. The infection of the next victim performed through the nutritional or respiratory tract.

The Spanish influenza H1N1 (1918–1919) was the deadliest human pandemic ever known in the written history of humankind. It spread across the globe and killed more people than any other disease of similar duration. Nevertheless, it annihilated only 1–2% of the worldwide population at the time. The remaining 98% escaped death without vaccination or specific medication but through their own hereditary make-up of self-defense elaborated over ancient natural selection that developed during previous epidemics [13,30-32]. The acquisition of inherent immunity to influenza could have been induced by humans historically continual and ecologically inevitable, intensive carnivorous contact, primarily with aquatic birds and various infected animals and their remains [30,31].

As a result of their evolutionary adaptation to inevitable coexistence with natural environment of influenza virus over a great many generations, aquatic birds also possess inherent resistance to influenza infection [33]. In contrast to humans, aquatic birds (Figure 2a,2c) and other omnivorous animals, the populations of domestic poultry do not have regular contact with natural sources of

the influenza virus and thus do not experience natural selection for genetic immunity to the agent (Figure 2b) [30].

Tuberculosis is also accounted as one of the world's most pernicious diseases. However, it kills approximately 0.027% of the current world's population each year. Only a minority of afflicted individuals develop the clinical disease. Most infected individuals fail to progress to the full-blown disease. The observed inter-individual variability of clinical outcomes is also a result of variability in the human genes that control victim's defenses [34].

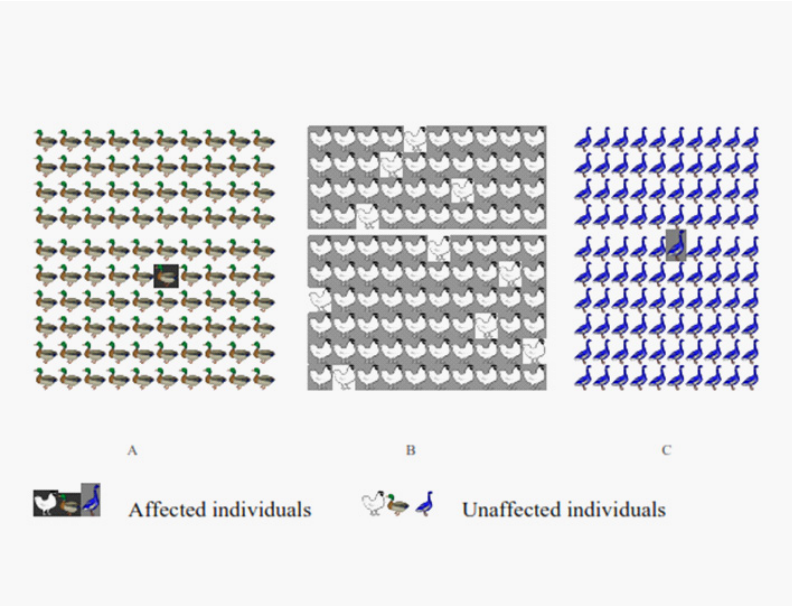

Figure 2: Avian influenza virus H5N1 is nearly nonpathogenic for wild ducks and geese (A, C, mortality less than 1%) but highly pathogenic for domestic poultry (B, mortality up to 90%).

Mutual affection by tuberculosis in both members of married couples observed to be more rare (7%) than in a pair of dizygous twins (25%). The afflicted monozygous (identical) twins share susceptibility to tuberculosis, if one is ill, the other one has an 87% chance of also being ill [35]. Recent studies have indicated that humans were exposed to tuberculosis-mediated molecular selection pressure much earlier than was previously assumed [36].

Natural anthrax can be induced either by inseminated food or by inhalation of anthrax contained dust. Self-reproduction and dissemination of *B. anthracis* occurs in and from diseased animals. In the bodies of sensitive animals, the microbes multiply explosively, producing toxins that cause the victim to go into toxic shock and die. The dead victim then attacked by scavengers, most of which can resist anthrax. Human infection with anthrax carried out especially by nutritional contact with diseased animal bodies, including their uncooked or poorly cooked flesh, bone and hide, as well as hair, excrement and soil inseminated by any of these substances. The infection can also be initiated by inhalation of inseminated dust [37,38]. However, according to Brachman 1980 [39],

natural infection with anthrax annually affects 0.00003% of the world's human population.

Salmonella infection affects its prey exclusively by eating the flesh of the affected organism. According to a WHO estimate [40], the infection annually kills 0.01% of the world's human population. Reported mortality associated with salmonella infection varies among different ethnic populations. For instance, the incidence of mortality due to *S. typhi* infection in Indonesia and New Guinea is higher than in other countries in southeast Asia [41,42].

In Experimental Infections of Humans and Animals

According to widely known epidemiological observation, none infectious agent can cause illness in all members of an observed human population. In some individuals, the microbes cause illness, while the majority displays hereditary immunity to the infection. For instance, very wide individual variations in human susceptibility to salmonella infection have been revealed in volunteer infection studies [43] which have established individual minimal infective doses for *Salmonella typhi* ranging from 100,000 to 1,000,000,000 microbial cells (Table 1).

Table 1: Artificial infection of humans with abdominal typhoid [14,43]

Dose		Effect	
Number of microbes in a dose	Number of injurious doses	Number of unaffected persons (%)	Number of injured persons (%)
1,000	0,01	100	0
100,000	1	72	28
10,000,000	100	50	50
10,000,000,000	10,000	5	95

In April 1979 an accident, which waft out of a biological weapons factory, caused the military-grade anthrax aerosol to disperse over a south district of the city of Sverdlovsk, U.S.S.R [13]. The weaponized aerosol cloud that formed then spread over 60 km from the military facility to the southernmost suburb where it killed some sheep at a farm. The stochastically dispersed human victims of the incidence were observed only in the area up to 4 km from the facility. The area was inhabited approximately by 7,000 people. Their exposition to the weaponized anthrax resulted in a total of 68 fatalities from anthrax (1%) and 11 (0.16%) survivors of a light form of the disease [36]. Thus, the accident demonstrated the lethal potential of anthrax aerosol on 1.1% of exposed people. The other 98.9% were not afflicted although they lived in the same area with doubtless deadly concentration of the aerosol. In the area between 4 km and 60 km, the potency of the deadly cloud was less and killed only sheep, which are far more susceptible to anthrax infections than humans, dogs and even pigs [13].

A far less effective anthrax attack that appeared in October 2001 in the United States were performed by the dispersal of anthrax spores trough posted mail [44,45] distributed on a territory stretching out over 1000 km along the very populated East Coast of the country. The total number of contaminated envelopes distributed not known with any certainty and the quantity

of dispersed anthrax is not certain. However, the dispersion of the cases of anthrax illnesses and deaths implies that spores situated not only in the mail envelopes but also in the air of different postal, government and media offices. Reportedly, the samples of several grams contained extremely high concentrations of anthrax spores. This professional recapture considered better than that found in the U.S.A. and Soviet bioweapons programs. The anthrax-tainted letter attacks induced 22 victims with anthrax, 5 of whom died [45]. The 22 cases of anthrax were identified in residents of seven states: Connecticut (1 case), New York City (8 cases), New Jersey (5 cases), Pennsylvania (1 case), Maryland (3 cases), Virginia (2 cases), and Florida (2 cases). The widely dispersed spores killed five people: two postal workers in Washington, D.C., a New York City hospital worker, a Florida photo editor and a 94-year-old Connecticut woman who had no known contact with any of the poisoned letters. Seventeen other afflicted people were sickened without fatal complications [45].

The largest numbers of infected persons were postal workers. For example, 170 employees were present inside the Mail Processing and Distribution Center (New Jersey) when the anthracis-contaminated envelopes were sorted on October 9, 2001, but only two of 170 employees became ill [44]. The rate of infection among this contingent was 1.2%. In media and governmental facilities, the processing of the envelopes and letters led to exposure of some workers, co-workers and visitors as well as contamination of facilities. Like in the case of Sverdlovsk incident, the anthrax aerosol manifested injury potential but only against two of the 170 coworkers. The incident demonstrated that anthrax aerosol possess the diseased potential on 1.2% of exposed persons.

The first person who died from the 2001 anthrax attack was Robert Stevens, sixty-three, a citizen of Florida; He worked on the third floor as a photo editor at a media company, which employed about 300 people. Stevens believed to have contracted the disease after inhaling anthrax from a tainted letter. Traces of anthrax microbes found both in Stevens' workspace and in the company mailroom located on the first floor. He entered the hospital with flu-like symptoms and died three days after.

Other people who worked in the building or visited it for extended periods of time have also been tested for the anthrax disease. However, only tests performed on a mailroom employee, Mr. Ernesto Blanco, seventy-three, found that he felt ill and exhibited flu-like symptoms at work. He also infected with anthrax. Mr. Blanco became the second of two victims of the anthrax attack on the collective accounted 300 people (less than 0.7%). He spent three weeks in the hospital and was once near death. Investigators believe the letter sent to the enterprise offices. Thus, the 2001 anthrax-tainted letter attacks on the East Coast of the United States highlighted the impotence of biological weapons' exploitation by terrorists. The majority of current humankind is characterized by hereditary immunity to anthrax. The same trait is characteristic of some animal species.

The chances of different animal species contracting anthrax depend on their ecological features namely their mode of nutrition. The data of experimental infection with anthrax [46]

allow to conclude that razing herbivorous animals can only occasionally contract the disease by swallowing or inhaling the infectious agents. Consequently, the typical herbivorous animals, such as guinea pigs, mice, rabbits, cattle, sheep, horses, mules, camels, and goats, are the most susceptible to both natural and experimental infection with anthrax (Table 2) [46].

Table 2: Levels of genetic immunity to experimental anthrax infection in a selection of vertebrata species [46].

Species	The grade of ecological interaction with *B. anthracis*	LD_{50} (number of spores)
White mice	1	5
Guinea pigs	2	50
Macaca rhesus	3	3,000
Rabbits	3	6,000
Rats Fisher	4	700,000
Black rats	4	1,500,000
Pigs	5	1,000,000,000
Dogs	5	10,000,000,000

In contrast to herbivores, the predators and other carnivorous animals, as well as omnivores (dogs, cats, rats, and pigs) possess constitutional genetic immunity to the disease. They seldom made ill by anthrax, both in their natural habitats and in experiments. The meager lethal power of *B. anthracis* for humans is analogous to its weakest effect on other carnivores. One could account that natural selection of humans for hereditary immunity to anthrax may have begun after regular contact of *Homo sapiens* ancestors with diseased animals, their flesh, bones, hides, hair, and excrement.

Natural botulism develops in some humans following the ingestion of some foodstuffs (imperfectly preserved meat, fish or some preserved vegetables) that meet adequate conditions for the production by *Clostridium botulinum* of its specific neuroparalytic toxin. The corpses of both diseased and even contaminated animals can serve as a source of *C. botulinum* self-reproduction accompanied by biosynthesis of the lethal toxin. Ingestion of contaminated corpses leads to continued reproduction and toxinogenesis, thus providing further transmission of the pathogen [27].

Because of the features of their nutrition, herbivorous animals such as guinea pigs, rabbits and horses do not regularly contact the sources of *C. botulinum* self-reproduction. They are very sensitive to botulism because they have not experienced natural selection for genetic immunity to the disease [27]. In contrast, carnivores (minks, dogs, cats) and some omnivores (mice, macaques, doves) possess genetic immunity to all or some kinds of botulinic toxins (Table 3).

Table 3: Levels of hereditary immunity/sensitivity to botulinic toxins types A, B, C, D, E, and F in a selection of vertebrata species [27].

Animal species	Minimal lethal doses of toxins					
	A	B	C	D	E	F
Herbivorous animals						
Guinea pig	1.0	2.0	1.6	0.7	0.8	1.2
Rabbit	1.0	0.5	0.6	1.5	1.2	1.0
Horse	0.4	-	2.0	-	0.6	-
Omnivorous animals						
Mouse	5.0	2,500	5.0	20.0	1.2	2.0
Macaca rhesus	4.0	36.0	2.0	2,000	4.0	0.5
Dove	200	100.0	20.0	2,000	25.0	-
Carnivorous animals						
Mink	10.0	>200,000	10.0	-	>250	-
Dog	500	150,000	5,000	>800,000	125.0	-
Cat	500	250,000	4,300	300,000	500	-
Hen	10	20	2,000	100,000	25	-

In trying to evaluate the botulinic toxin as a potential bioweapon, a group of the Soviet experts performed very difficult, dangerous and precise tests on themselves. They demonstrated that although botulism type A is more dangerous for men than types B, E, and especially C and D are, humans seem over 500-1000 times more resistant to type A botulism than horses, rabbits and guinea pigs are and that, for botulinic toxins, dogs are the animal model most relevant to humans [5,14,47]. Thus, like other carnivores and many omnivores, humans possess hereditary immunity to botulism.

Over Observations of Diseased Persons

Every infectious disease affects usually only focal areas in the infected organism [48-50]. Multiple foci of infectious damages even more clearly demonstrated in infectious exanthemas. That focal (mosaic) exanthema is seen, for instance, during poxvirus infection in human and animals. It consists of a number of skin lesions scattered over the surface of the body, each of which is the seat of inflammation so intense as to lead to the formation of small abscesses in the course of 4 to 5 days (Figure 3).

Figure 3: Mosaic distribution of specific lesions in a severe form of smallpox infection [14].

Beyond the edge of the lesions, the skin is normal. The number of lesions present may be less than a dozen in a minor case of illness, or they may number in the thousands. In a severe course of disease, lesions may be set so closely as to conceal almost the whole cutaneous surface. The smallpox rash is most severe on the face, then the hands and upper extremity. From the hands upwards, the scabs diminished in density. On the front part of the trunk they are scarce, especially on the abdomen. The areas adjacent to the specific damage found almost intact, though all the skin is presumably homogeneous.

Each infectious disease expressed in the infected organism in at least two categories of the same tissue, outwardly identical and differing only in their relationship to a given microorganism. The phenomenon of constitutional (hereditary) immunity allows the explanation of why parts of one category are affected by a given microbe, while at the same time, other morphologically identical components of the organism remain uninvolved. Both exist under the same conditions and may be equally attacked by the infectious agents. These morphologically identical parts differ only in resistance. The mosaic arose as a result of heterozygous interbreeding between parents one of which was susceptible whereas other possessed hereditary immunity [15,23,51].

Anthrax infection in human also occurs mainly in secure focal (cutaneous) form, which accounts for over 95% of cases on record. The focal lesions of the cutaneous form vary in size from about 2 cm to several centimeters across. The lesions begin to resolve about 10 days after first appearance. The resolution takes from 2 to 6 weeks and leaves minor scarring. This form is unpleasant but secured. The most common naturally occurring skin form of anthrax infection in humans affects 2,000 people around the world annually [39]. In the United States, 224 cases of cutaneous anthrax reported between 1944 and 1994, that is, nearly 4.3 cases yearly. Hyperacute and acute forms are characteristic of anthrax disease in herbivorous animals. In contrast, neither the deadliest nor serious forms of anthrax illness are common in humans [52].

The largest reported epidemic occurred in Zimbabwe between 1979 and 1985, when more than 10,000 cases of anthrax were reported, nearly all of them cutaneous, that is secure [53]. Some healthy people were reported to carry hundreds of anthrax spores in their noses and throats without incurring any disease [54]. These incidents of anthrax contamination failed to produce illness.

Analogous stochastically disseminated foci of specific damages clearly demonstrated in many kinds of infectious diseases in humans. Mosaic distribution of damages is characteristic of herpes infection, hepatitis, syphilis, tuberculosis, smallpox (Figure 3) and all other infections [48,55]. Any epidemic can result in both fatal and nonfatal cases, which are usually prevalent. This diversity is a result of heterozygous interbreeding between parents with opposite grades of hereditary immunity. It highlights both individual and intra-individual differences in susceptibility of various parts of the organism under consideration [56].

Thus, within the human body, there are at least two co-existing homologous parts with both unequal make-up and relations to an infectious agent. The parts exist in a form of separate patches of different sizes and locations being stochastically dispersed around the body. The quantitative correlations between such patches within specimens of a species are variable in size and location. This is the reason for the organism's varied individual predisposition to different diseases and to their existence, spread, relevance, courses and severity [15,23,51].

This kind of biodiversity arises as a result of sexual self-reproduction that inevitably forms this or that grade of heterozygosity. Each case of intra-individual biodiversity considered here is a result of hybridization between two genetically different organisms: one of them was constitutionally immune to the relevant ecological or physiological agent, whereas its mating partner was constitutionally sensitive to it. As a result, the descendant's body cells formed under control of two codominant allelomorphic genes.

Such biodiversity in infectious diseases predestined by the organism's heterozygosity resulting in coexistence of two active allelomorphic genes and two allelic cell clones in the body. Both of these alleles function dominantly. The heterozygous individual shows both alleles expressed equally, although in different locations of the body. One of these cell clones possess the genetic immunity to an infection whereas the other one possesses the alternative feature of the other parent, i.e. genetic susceptibility to the same infection [56]. The mating of resistant and susceptible individuals gives rise to progeny with intermediate degrees of susceptibility to the infection and extent of infectious foci.

In Cytological Investigations

Besides the above data concerning epidemiological, clinical and experimental observations, the traces of previous natural selection, signs of hereditary immunity unearthed by *in vitro* testing of the influence of relevant microbes, or their molecular ecological agents, on the cells extracted from the organism under consideration. Cells of constitutionally immune individuals are resistant

to a pathogenic agent whereas cells of constitutionally sensitive individuals are destroyed by the same pathogenic agents [11,57,58].

Hereditary immunity of a whole body is a consequence of immunity of it cells. We have discovered a key step of meningococcal infection - the attachment of *Neisseria meningitidis* to outer membranes of mucosal and blood cells of humans and animals. It was known that meningococcal infection can infect only some humans but not other species. *In vitro* testing revealed adhesion of meningococci only to cells of some human individuals, whereas analogous cells of naturally immune animals (mice, guinea pigs, rats, hamsters, rabbits, goats sheep, donkeys, horses, bulls, and hens) were absolutely immune to this key step of cell invasion by the parasite [11].

Bacteria of the *Salmonella* genus can provoke destruction of appropriate victim cells, although this effect not manifested in every case. The nature of the differences in Salmonella infection found between constitutionally immune and susceptible chicken lines *in vivo* indicates that resistance is also expressed at the level of the mesenchymal cell, for instance in the mononuclear phagocyte system [25].

Various Salmonella strains investigated for the organism's influence on mesenchymal cells of 10 biological species as well as 1,565 humans. All representatives of the four herbivorous species investigated (guinea pigs, horses, rabbits and white mice) possessed cells with very high sensitivity to destruction by salmonella. In contrast, the cells of omnivorous species were usually not destructed by salmonella, they were genetically immune to these infectious agents. Only some individuals in the group of omnivorous species (humans, dogs, cats, hens, monkeys and sheep) possessed cells weakly sensitive to some strains studied. Most representatives of an examined chicken population (1,042 out of 1,059) demonstrated hereditary immunity in their cells and only 1.6% (17 individuals) had weak sensitivity to destruction by some of the salmonella strains [59-61].

Analogous immunity of human cells revealed in most representatives of urban populations in St. Petersburg (Russia), Kishinev (Moldova), Tartu (Estonia), and Alma-Ata (Kazakhstan). Only some individuals had cells sensitive to one or more of the salmonella strains tested. Nearly 90% had cells resistant to salmonella [59-61].

While Salmonella infections affect their victims by means of the victims nutrition (via the alimentary tract), the origin of differences in cell sensitivity to salmonella discovered between mainly herbivorous species (guinea pigs, horses, rabbits and white mice) and mainly omnivorous ones (humans, dogs, cats, hens, monkeys and sheep) can be considered as a result of their unequal interaction in this specific "microbe-victim" ecological system. The above data also confirm both the genetic origin of the diversity in species and individual sensitivity to the molecular ecological agent of salmonella virulence [61].

Expressive traces of lengthy ecological interactions revealed by *in vitro* observation of the

interaction of the rabies virus with mesenchymal cells of 10 animal and avian species. Rabies infection exists thanks to the alimentary influence of predators on the species that inhabit dry land spaces. In contrast to aerospace inhabitants (the goose, rhesus monkeys and vervet monkeys), the cells of land inhabitants (chickens, rats, guinea pigs, rats, sheep and humans) were immune to rabies virus intrusion [5,62]. Thus, the farther a species moved away from the ecologically determined possibility of interacting with the source of rabies infection (foxes and wolves), the higher its level of cell susceptibility to the virus and vice versa.

Analogous ecologically understandable traces of foregoing selection found during the testing of animal cells for immunity/susceptibility to intrusion of tick-borne encephalitis virus. This infection is transferred by a tick that inhabits the woods. Maximum sensitivity to the virus found in donkeys, the well-known inhabitants of the steppes. Bulls, whose pre-descendants lived in the woods, revealed high resistance to the virus. Goats revealed features intermediate between donkeys and bulls [5].

We have observed analogous interspecies and individual diversity [30] in relation to the intrusion of influenza virus types A (subtypes H0N1, H1N1, H3N2), B and C in the cells of 12 vertebrate species (chickens, dogs, guinea pigs, mice, Syrian hamsters, horses, donkeys, pigs, cats, goats, sheep, rabbits and humans). The highest levels of cell sensitivity to intrusion of most viruses tested revealed in domestic poultry (the leghorn chickens). The lowest indices of cell sensitivity to all tested viruses were found in rabbits. The highest levels of cell immunity to most viruses were found in the other eight species. The greatest diapason of individual differences was observed in humans (in the relation to all viruses, up to 40-fold), donkeys (in relation to virus H3N2, up to 32-fold), and horses (in relation to virus B, over 64-fold). The intra-species differences in cell sensitivity to influenza viruses type A among leghorn chickens were substantially less (up to fourfold) than among humans. Human cells also revealed relatively less sensitivity to viruses B and C, which reflects the lower epidemic potential of these viruses among human populations.

Over Investigations of Body Molecular Make-up

The protective power of hereditary immunity results from the evolutionary disappearance of mutual complementariness (congruence) between molecular combining regions of both a microbial agent and its target in the attacked body. As a result of natural selection, the choleraic toxin is able to interact only with such ganglioside macromolecules on the attacked cell membranes, which contain the subunits of ceramide, lactose, galactosamine, galactose, and the only radical of sialic acid joined with the radical of lactose (Figure 4a).

The victim cells are able to resist the same toxin if their outer membranes contain gangliosides of other types, for instance, such as ones that do not contain galactose, or have an additional radical of sialic acid in the end position [63]. Botulinum toxin can affect only those membrane ganglioside macromolecules that contain two sialic acids joined with the radical of lactose at the same position as in the case illustrated in Figure 4b. Hereditary immunity to tetanic toxin

depends on the absence in the cell membranes of other ganglioside molecules (Figure 4c).

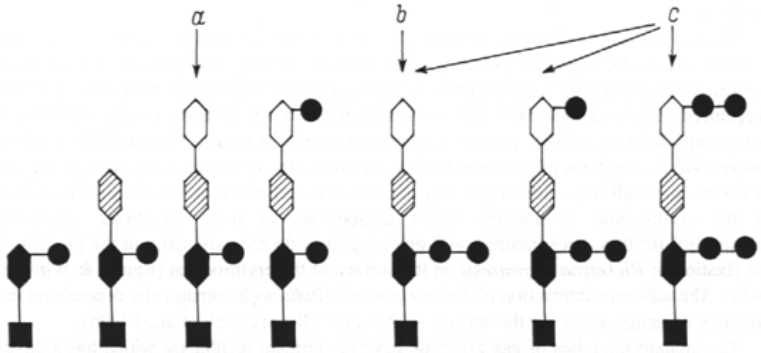

Figure 4: Dependence of organism's vulnerability by microbial agents on the presence of gangliosides (1-7) in cell membranes. Choleraic (a), botulinic (b) and tetanic (c) toxins [29].

Influenza A viruses (H1, H2 and H3 subtypes) cannot attach to attacked cell membrane receptors that do not contain terminal a-2,6-linked sialyl-galactosyl (a2,6 SA) moieties [64]. In addition, a relevant density and arrangement of receptors on the cell envelope are needed for virus binding to ensure that the virus particle is well attached, no fewer than 3,000 ganglioside receptor molecules are required for the attachment of a single virion [65]. The intensity of interplay between HIV-1 and its chemokine receptors on the cell surface has a fundamental role both in cell penetration by HIV-1 and in immunity to this clue step of the infection thus determining the diversity characteristic of HIV infection [66,67]. Age-related changes in resistance of cells to mengo virus and encephalomyocarditis are conditioned by corresponding changes in maturation of the cell membrane's molecular composition, namely, the structure of the molecular receptor [68].

Plasmodium malariae demonstrates selectivity toward a particular age group of erythrocytes. The factor involved in such a phenomenon may be that the young erythrocytes contain more lipids in their membranes than the older cells [69]. Moreover, there is a possibility that the large ribosomal RNA component in malarial ribosomes provided, in part or entirely, from the victim's cell ribosomes. In the young red cell, the total volume of ribosomal RNA is greater than in the older red cell, and this volume decreases with age [69]. In addition, there may be a factor that prevents the plasmodium from entering cells of a certain age due to changes in the red cell surface receptor sites that known to bind merozoites.

An "irrelevant " change of amino acid composition in the hemoglobin molecule makes it inaccessible for the nutritive systems of *Plasmodium malariae* and thus creates insusceptibility to malaria [70]. These mutant haemoglobin molecules constitute the red cells of aborigines in malarial regions, who are therefore not subjected to this infection because of previously performed natural selection for this trait.

The non-availability of uncombined asparagine in guinea pigs makes this organism immune to the aggression of such varieties of plaque microbes, which cannot exist without the given amino acid. Such "defectiveness" of molecular constitution in these animals is conditioned by the presence of a large quantity of the ferment of asparaginase in their blood, this ferment splits the given amino acid as soon as it appears to be in an uncombined state [71]. The unequal contents of glycoproteins and glycolipides in the cellular membranes of rats and people is as a result of the inability of definite bacteria to affect the cells of the rat tongue in contradistinction to the human cells [72].

The absence of gangliosides that are susceptible to sialidase in horse's erythrocytes provides them with immunity to the action of a molecular factor that performed and implements the pathogenicity of hemolytic vibrions [73]. The variations in the quantity and order of arrangement of definite gangliosides on the surface of the cellular membranes make them invulnerable to the affecting action of parainfluenza viruses [65] and meningococci [74]. The invulnerability of some molecules of collagen to the baneful action of the microbial collagenase is also determined by the specific and individual peculiarities of the structure of this protein molecule.

In a Genome Make-up

Genes that control constitutional immunity to some infections in humans and animals have been identified and mapped to specific chromosomal locations [75-79]. The structure of the chemokine co-receptor for the HIV virus coded by the CCR5 gene has been mapped to a chromosome [67]. The mutant allele CCR5-[Delta] 32, which is characterized by a 32 bp deletion in the single coding exon of the gene, was identified as responsive for coding the receptor structure not compatible to relevant molecular ecological agent of the HIV virus [66]. The CCR5 gene 32-base pair deletion provides strong constitutional immunity of human homozygotes to HIV infection [80], in the heterozygous state, it may provide relative immunity, thus delaying the progression of HIV infection to AIDS in affected individuals [81].

The modified co-receptor along with CD4+ receptor for HIV-1 is incapable of promoting cell penetration by HIV. Individuals homozygous for CCR5-[Delta] 32 display no clinical symptoms and appear to be healthy. They possess structural (constitutional) cell immunity to the infection. Heterozygous individuals also exhibit slower progression of AIDS. Thus, the risk of acquiring HIV infection is individually modulated by genetic polymorphisms in the chemokine receptor ligand. The CCR5 gene 32-base pair deletion provides strong constitutional immunity of human homozygotes to HIV infection [80]. In the mosaic heterozygous state, it may provide relative immunity, thus delaying the progression of HIV infection to AIDS in affected individuals [81].

This mutation occurs at an allele frequency of 9% and a carriage frequency of 15%–18%, among white European individuals, which considered a trace of natural selection for genetic immunity against HIV. The frequencies in other major racial groups are negligible, which reflects probable ethnical differences in ancient performance of specific selection. Additional variants,

most of which are codon-altering, have also been identified. Some of these variants may also protect against HIV-1 infection as a result of severe alteration in the conformation of the molecule. The effects of host genetic variation on acquiring HIV infection are inextricably bound to the well-established and powerful genetic variants that can function at different stages of infection [66,82].

Recent reports focusing on the inherent basis of genetic immunity to salmonella infection in animals contained information on a number of different lines of chickens that shown to be either resistant or susceptible to systemic salmonellosis. Immune lines show only moderate pathology and low mortality rates, whereas susceptible lines display extensive pathological changes and higher levels of mortality following salmonella infection. Genetic immunity to the salmonelloses in chickens was dominant and not linked to sex, MHC, or Slc11a1 (formerly known as Nramp1), which leads to resistance in mice and other species. A novel locus-encoding immunity to salmonella infection has been identified on chicken chromosome 5 and designated as SAL1 [25].

ORIGIN OF HEREDITARY CONTRA-INFECTIOUS IMMUNITY

Creation of hereditary immunity depends on the appearance in the attacked population of mutant alleles that bring about relevant modification of appropriate target in the threatened victim. If the modification is competent it will reduce or even eliminate molecular impact of aggressive agent and, accordingly, prevent the aggression [5,29,83,84].

The unique set of human defensive traits includes multiple molecular, physical, physiological and even cognitive features. The origin and further development of specific human defensive traits initiated by relevant changes in a genome molecule, followed by subsequent transformation of the molecular phenotype performed by natural selection. The human genome contains roughly more than 3.4 billion base pairs and between 20,000 and 25,000 protein-coding genes. The overall difference between the genomes of the human and chimpanzee make up about 2% of the entire genome [85], equaling more than 68 million base pairs and between 400 and 500 protein-coding genes. Each of these specific human genes singled out for future existence by particular selective forces. The union of current anthropological, immunological, ecological, genetic and evolutionary methods can now lead us in deciphering the origin of these forces. Special attention paid to the traces of natural selection that performed among human ancestors by predators and infectious agents.

The evolutionary importance of infectious selection is conditioned by many exclusively substantial circumstances. First, all decisive events in antagonistic microbe-victim ecological systems take place exclusively at the molecular level, the starting point of any evolutionary transformation [29]. The plethora of extraordinary features underlying the process of infectious selection was recently evaluated in detail for the first time [5,18]. Second, microbial parasitism sharply surpasses any other marauding forms of symbiosis in many of its characteristics.

The penetration of infectious agents inside the victim's body mainly carried out by means

of the victim's ecological communications, through which the regular physiological functions provided. It carried out mainly through feeding (as an alimentary intrusion) and breathing (respiratory intrusion). Of the two, the alimentary transfer of infectious agents functions most widely and effectively [27]. The affected victims, their excrements, corpses, or partial remains serve as a source of microbes to new victims.

The microbial world characterized by a very broad variety of species, subspecies, and populations that are all different from one another in their molecular ecological properties and qualities. The significance of such biotic interactions participating in the processes of human evolution has been studied recently [18].

The number of microbial species that become potentially dangerous for a victim species can vary from a dozen to many hundreds, depending on the ecological features surrounding the victim. Considerably more than 500 species of potentially deadly microbes continue to threaten human settlers around the Earth today [86]. The variety of infectious agents that exists allows their interaction with a large number of various biomolecules (lipids, carbohydrates, proteins, nucleic acids, etc) and their structural derivates, providing natural selection with many versions of the co-actor's molecular constitution [5,29]. Molecular agents of microbial pathogenicity and their molecular targets inside the attacked body are unique and thus extraordinarily specific for each existing microbe-victim system. The ways in which microbial parasitism is realized are multiple and very diverse.

The antagonism of life-threatening molecular relations between microbes and their victims induces changes of relevant features of both co-actors. From these evolutive interactions, the victims of harmful microbes elaborate specific traits of hereditary immunity, the traces of foregone selection for the molecular means of self-defense against relevant infection. Next, the mutual evolution of microbes leads to improvement in their aggressiveness. These mutual evolutive responses function as effective forces in the mutual evolution of co-actors [18]. Thus, both microbial pathogens and their victims are in a continual evolutionary struggle-each side exploits new avenues of attack while simultaneously patching breaches in its defenses.

In contrast, the members of predator-prey ecosystems are unable to gain relevant responses by means of a primary mutation. To improve their capacities, both the predators and their prey need to be performed with a chain of consecutive genome mutations. As a result, the evolution of this kind of ecosystem slowly performed during the change of generations.

Immunity (resistance, unresponsiveness, insusceptibility, invulnerability, protection, tolerance, resistivity) is all-biological phenomenon of the defense of living beings from any life threatening influence. "Immunity against infective diseases should be understood as the group of phenomena in virtue of which an organism is able to resist the attack of the microorganisms that produce these diseases. It is impossible, at present, to give a more precise definition and useless to insist upon it" [2,3].

Today's conception of immunity means the inherent or individually acquired capacity to withstand the effect of ecological or physiological agents, e.g. the capacity of a living organism to withstand an infectious disease [4,5,19-21]. Just like all-biological phenomenon, immunity involves an extremely complex set of surveillance defensive agents and systems, geared to the maintenance of a healthy existence.

Creation of hereditary immunity depends on the appearance of mutant alleles that bring about relevant modification of appropriate target in the threatened victim. If the modification is competent it will reduce or even eliminate molecular impact of aggressive agent and accordingly, prevent the microbial aggression [5,29,83,84].

Organisms possessing mutantly modified molecular constitution rendering them incapable of being infected with the microbe, are constitutionally immune to a particular disease. They give rise to immune progeny while susceptible individuals of the same species become ill and die without reproducing [83]. On repeated exposure of many generations to a given pathogen, the progeny of immune variants eventually predominate in a population (Figure 5).

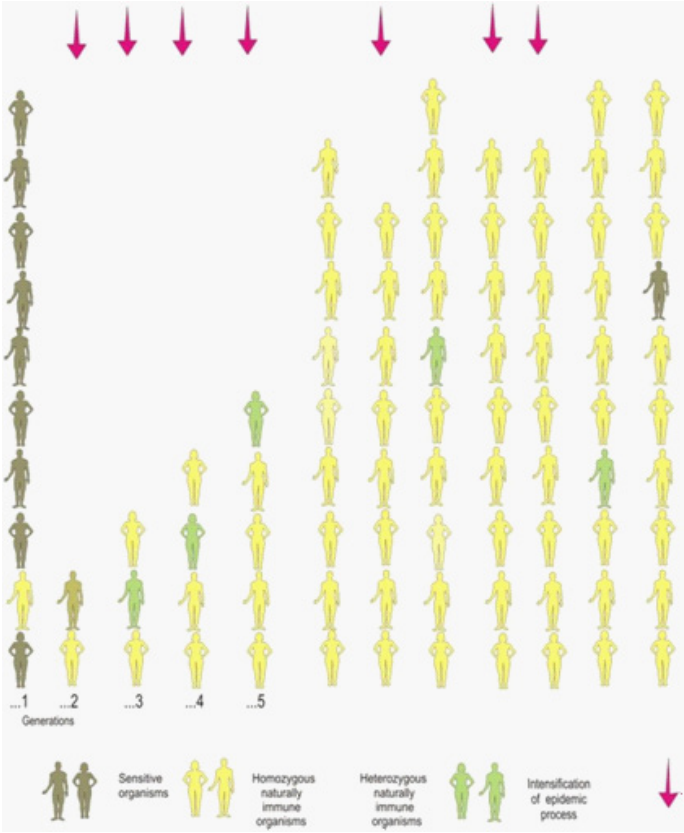

Figure 5: Evolutionary transformation of hereditary immune state of a human population transformed over the emergence (1) and further evolution (2, 3 , 4 ...) of epidemic process [7,23] updated.

Finally, an individual protective variation becomes the property of a group, then of a population and finally, most of the species [10,28]. Thus, the achievements of hereditary immunity lead to the appearance in a population of new molecular structure. The molecular constitutions of the population become changed. The changes saved in the make-up of every future generations of either the species or population. This is initial event and a crucial step to their further evolution [10,29].

MOLECULAR MAKE-UP OF HEREDITARY CONTRA-INFECTIOUS IMMUNITY

Molecular Ecology of Infection-Victim Interactions

The most information on the essence of hereditary immunity has been obtained by examination of molecular biology of microbe-victim interactions i.e. of molecular pathogenesis of relevant diseases. Main aim in this chapter is to illustrate how a molecular focus on infectious pathogenesis has been used to organize available information about immunity and how did it inspire new approaches to the discovery of intimate structures of constitutional immunity, its evolutionary origin and exploitation in relevant areas of humankind activity.

Molecular pathogenesis of any infectious process is a very complex phenomenon encompassing several common and specific strategies that harmful organisms use to overcome the victim barriers and sustain themselves. More exhausting information was gained by analyze of microbe-cell interactions and mutual functions of specific molecular agents which are performing the processes under investigation.

The victims of microbial parasites occur among all forms of organisms (Figure 6). In addition to that, there exists evolutionary adaptation and specialization of parasites to definite kinds of victims due to which the universal biological phenomenon of microbial parasitism is represented by a majority of exclusively various evolutionally formed microbe-victim ecological systems. The parasitic microbes exist in nature only within the frames of such systems and only due to ecologically determined interactions with their victims [27,29].

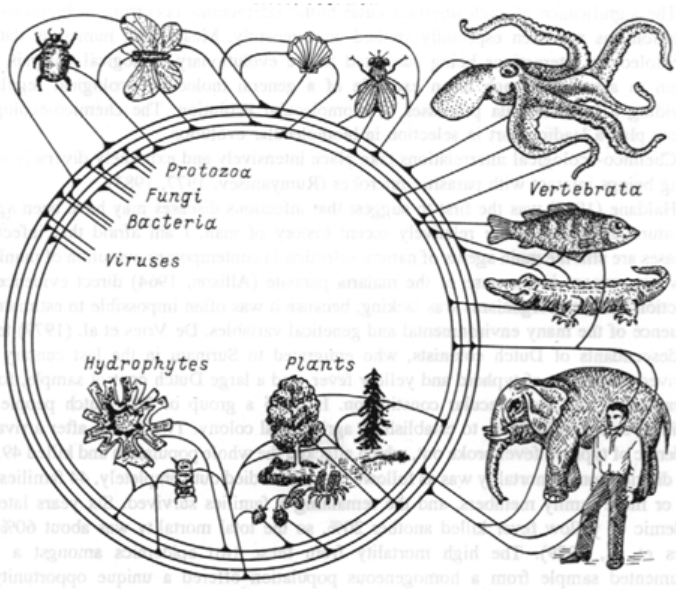

Figure 6: Victims of microbe parasitism – all the forms of living beings [29].

The existence of parasitic microbes goes in the bodies of their selected victims as a process of extraordinary intensive self-reproduction of microbes from some dozen to their multi-billionth populations. Self-reproduction is a major requirement and inherent goal for microbial aggression. Pathogenic microbes are parasites. They survive inside invaded organisms at the expense of physiological processes carried out by victims.

Compared with environments such as the soil or sea, the living bodies constitute a relatively rich sources nutrient and energy. Large collections of various living beings, beside microbes are trying to colonize or exploit these sources. In this regard, microscopic parasites resemble predators and macroscopic parasites. But in contradistinction to predators and macroscopic parasites microbes haven't any organs for physical coercion over the bodies of victims. In particular, they cannot cleave the barriers and integuments or break the envelopes by which any organism on the whole and each of its cells are separately protected by nature against the environmental influences. Microbes cannot damage mechanically the living structures at all. Nevertheless, they penetrate through the integuments inside organisms and inside cells, they reproduce and develop in them affecting the structures and functions significant for victim's life.

The affected victims, their corpses and remains serve as the sources of subsequent dissemination of the microbes and the affection of new preys. The ways in which the parasitism is realized are very multiple and extraordinary diverse in their details. The means by which microbial aggression is realized is in principle due to the other factors [4,10,87].

Penetrate microbes attack organisms and enter cells exclusively through particular molecular processes controlled by specific biomolecular substances. The molecular bases of the microbial

requirements are the determinants of their pathogenicity and the victim's receptivity. The goal of investigations is to identify them and relate their chemical structure to mutual infectogenic functions [88]. If microorganisms lack any of these biological requirements for pathogenicity they become less pathogenic or non-pathogenic [4,89]. Harmful microbes usually attack the animal or human victims at the mucosal surfaces of the respiratory, gastrointestinal, or genitourinary tract i.e. at the expense of victims either respiratory, nutritional or reproductive functions.

Microorganisms must bond firmly to epithelial cells to avoid being swept away by the secretion bathing the mucosal surface. Some microbial products are not necessarily toxic but overcome victim defense barriers, allowing the pathogen to invade and proliferate in the host.

Considerable effort has gone into understanding the molecular basis of parasite entrance into cells. The intrusion requires recognition by the parasite of the appropriate victim cell during one or more steps that include parasite adhesion, reorientation and entry into the cells. Some microbes prospect a situation and find victim by means of chemotaxis. They swim directionally through the mucus to the cell surface. The mucus bathing epithelial cells on mucosal surfaces constitutes a barrier to close contact between the microbes and the victim cells. Some microbes contain a sialidase which could render mucus soluble and less viscous by removing sialic acid residues from mucus such that close contact can occur [90]. There was a correlation between microbial pathogenicity and ability to reduce mucus viscosity by sialidase activity. Sialidase may help microbial penetration through the mucus. Mutant vibrions lacking this enzyme are inefficient in causing infection.

In many of common strategies that pathogenic microorganisms use to overcome victims defense, the first step is the firm adhesion of the microorganism to victim cell membrane. Many different microbial adhesins described. A surprising variety of adhesin molecules found in pathogenic viruses, bacteria, fungi and protozoa.

Adherence of microbes to target cell surfaces is becoming increasingly recognized as an important determinant of their pathogenicity. It enhances the microbe ability to colonize the victim surface by allowing them to replicate. Adherence may also increase the toxin delivery by minimizing the distance between the surface and the pathogen. The molecular basis of microbial adherence must result from the mutual recognition and interaction of surface structures on both the microbe and victim cells. Current terminology defines the adherent structure on the microbial surface as an adhesin and the complementary structure on the victim cell surface as microbial receptor.

Adhesion of microbes to surface of cell attacked by them seems to be a general prerequisite to disease. There is a clear correlation between microbial adhesion and pathogenesis. Adhesion is a clue factor of pathogenicity, however diseases are not caused by microbe adhesion which is realized by means of special molecular ecological agents. The relevant agents of microbes were

referred as adhesins, those of victims were referred as targets or receptors. Most adhesins seem to demonstrate species, tissue and cell specificity.

Many if not all infections are initiated by the attachment of parasites or their molecular ecological agents to the victim cell surface. The ability of parasites to attach to the victim surface is considered to be an essential first step in microbial parasitism and is a prerequisite for penetration in to the host cells. Certain biomolecules expressed on cell surface play a clue role in the attachment of microbes as the first step in infection.

Surface protein components, the so-called hemagglutinins play a similar role in influenza infection [91]. It functions in binding to the pray cell sialoglyco-saccharide receptors. This binding is crucial for the initiation of an influenza virus infection. Some viruses, such as Sendai virus, have surface glycoprotein spikes which adsorb to specific receptors on cells attacked by virus. The receptors on erythrocyte membranes contain sialic acid. The rabies virus envelope contains a single glycoprotein with hemagglutinating activity [92].

The adhesive properties that Plasmodium falciparum confers on the victin's erythrocytes are central to its pathogenicity. After the parasites mature within erythrocytes they express ligands on the erythrocyte surface that mediate adhesion to the endothelial cells lining postcapillary venules. The parasites are thus sequestered within the peripheral circulation and avoid passage through the spleen. In addition, parasites express ligands either for uninfected red blood cells which leads to the formation of rosettes [93] or for other parasitized cells to form auto-agglutinates. These adhesive events could cause local obstruction to blood flow or local metabolic disturbance and so lead to organ damage. The victim receptors mediating these parasite-cell interaction have been intensively studied and it appears that different receptors are used by different parasite stocks [93].

The cardioviruses and influenza A and B viruses bind to the glycophorin A molecule on human erythrocytes and this glycoprotein also carries the M and N blood group antigens. Glycophorin A contains one–linked complex chain and 15 O-linked tetrasaccharides, six of which are clustered within the first 30 amino acids at the NH2 terminus. The O-linked tetrasaccharides have the following structure: Neu5Ac (alpha-3) Gal (beta 13) GaINAc (alpha)-serine or treonine l (alpha2-6) Neu5Ac. These oligosaccharides make up circa 60% of the molecular weight of glycophorin A and are each capped with sialic acid (Neu5Ac), according for circa 60% of the total syalic acid at the surface of the human erythrocyte [94].

HIV infection is initiated by ligand specific binding of HIV to CD4 receptors on target cells (e.g., neurones, TH-Iymphocytes and/or macrophages). The ability of HIV to enter cells depends on the presence of the glycoproteic CD4 on the surface of an attacked cell [95]. CD4, the molecular target for human immunodeficiency virus, and ICAM-1, the receptor for human rhynoviruses contain three and five immunoglobulin-like domains, respectively.

Following replication of the viral genome in infected cells causes dysfunction and destruction of affected cells. The loss of the cells that follows is accompanied by progressive reduction in relevant physiological capacity. For example, the loss of a CD4+ lymphocytes clone is accompanied by progressive reduction in relevant immunogenic capacity of the lymphoid immunogenic system. Thus, AIDS leaves an individual vulnerable to some or other opportunistic infection. The cell surface T4 (CD4) protein molecules in human cell membranes function as a major receptor for HI virus [94,96].

The amino acid residues critical for virus binding have also been identified. Two receptors have their primary virus binding site in domain I. In both cases deletion or amino acid change in other domains affects virus binding on the receptor [79]. Similar phenomenon may occur with regard to domain I on poliovirus, since virus receptor activity appears influenced by the deletion on domain(s) II and/or III. It is possible that deletion on domain (s) I, and/or 1 affects to some extent the three dimensional structure on domain I and that in conformational changes caused by deletion on other domain as result in reduction of the amount on the virus bound to the cell surface. The distance on domain from the cell surface may also affect its accessibility to virus [79].

Rickettsia prowazekii adsorb onto red cell membranes due to their chemical affinity to cholesterol, but lecithin, phospholipid and glycopeptides do not participate in this process [97]. The adhesion of enteric bacilli to erythrocytes does not occur if the cell surface does not contain glycophorin Am [98].

Invasion of mammalian cells by Trypanosome cruzi depends upon the ability of the parasite to interact with specific receptor molecules on the victim cell membrane. According to Davis & Khun, 1990 [99], the initial attachment of Trypanosome cruzi to the mammalian cells before invasion required two host cell membrane polypeptides with molecular mass approximately 32 and 34 Kilodaltons.

Diphtheria toxin first binds to the membrane surface and then extends a process across the membrane core, which probes the other side. If the diphtheria toxin finds phosphoinositide, and binds to it, anchoring it in place and allowing channel conformation can occur. The critical steps in diphtheria intoxication may be as follows. Diphtheria toxin binds to a cell-surface receptor and internalized. Once in the endosome, the acidic environment induces a conformational change in diphtheria toxin molecule that, in concert with the membrane potential, promotes the binding and insertion of toxin molecule into the endosomal bilayer. The consequent binding to phosphoinositides anchors diphtheria toxin, allowing channel formation and concomitantly, the translocation of the enzymatic moiety of toxin into the cytoplasm [100].

Pseudomonas exotoxin, like a diphtheria toxin, inhibits protein synthesis in sensitive cells by catalyzing the transfer of the ADP-ribose moiety of NAD to elongation factor 2 (EF-2). Pseudomonas exotoxin A and diphtheria toxin have the same mode of action in the cell but they utilize absolutely different receptors or mechanism of uptake [101].

Verocytotoxin of *Esherichia coli* (VT1) determine the hemorrhagic colitis and the hemolytic uremic syndrome following VT1 E.coli induced gastrointestinal infection. Hemolytic, i.e. membranotropic, E.coli strains appear to have more marked adhesive properties than non-hemolytic one [102]. VT1 is subunit toxin made up of an active (A) subunit and as many as five binding (B) subunits. It binds specifically to glycosphingolipids such as globotriaosylceramide (Gb3) and1 galabiosylceramide having a terminal Gal-alpha1-4Gal disaccharide sequence [103].

H.pylori produces cytotoxin Vac A that causes gastric tissue damage, leading to gastric ulcers when administered intragastrically. This effect is associated with the ability of the toxin to cause vacuolation and death of gastric epithelial cells both *in vivo* and *in vitro*. In contrast, mice deficient in protein tyrosine phosphatase receptor type Z Ptprz gene do not show mucosal damage by cytotoxin Vac A, although Vac A is incorporated into the gastric epithelial cells to the same extent as in wild-type mice [104].

Glycosphingolipids are components of the outer leaflet of the plasma membrane. They are thought to have physiological roles in cell-cell interaction [105] and as cell-surface receptors for some pathogenic bacteria and function as antigen through their sugar [106]. Gb3 is Pk antigen of the P blood group and a major component of the human renal glycolipid fraction [107]. Internalization of cell-bound VT thought to occur by receptor-mediated endocytosis. Inside the cell the A subunit of VT1 is proteolytically nicked and reduced to the A1 fragment suppressing protein synthesis through the inhibition of elongation factor 1 [108].

After intrusion inside of victim's body and its cells, the microbes reproduce themselves affecting the victim's structures and functions significant for the life. All this reached exclusively by means of the chemical influences exerted by the microbes upon the affected organisms. The originality of interactions in the ecological microbe-victim systems in contradistinction to, for instance, the beast of prey-victim systems is that its determinants and most specific events take place at the level of specialized biomolecular structures peculiar to co-actors. The functions of the "organs" of intrusion and influence over the victims among parasitic microbes are performed by their special chemical substances, unique for each microbe species, the so called factors of aggression synthesized by them.

The influence of microscopic parasites over the bodies of their victims is realized exclusively by chemical means with the help of the molecules, which the parasites produce. Such molecular-ecological agents of pathogenic microbes are, for example, their polynucleotides (RNA, DNA), proteins, various toxins (choleraic, tetanic, botulinum, diphteric etc), ferments (DNA-ase, RNA-ase, amylase, hialuronidase, sialidase, collagenase, elastase, various proteases, sphingomielinase, lecithinase etc), surface-active matters, for instance, glycopeptides and glycoproteins, acting as various adhesines, hemagglutinines, cytolysins, hemolysins (streptolysin-O, tetanolysin), oligo- and polysaccharides, saccharides, lypoteichoic acid, hydrogen peroxide etc. Any of enumerated substances are different for each microbial species 76, 85 [29]. The given list of agents is not comprehensive.

The detailed study of the molecular biology of the mechanisms that pathogenic organisms employ to successfully parasitize their victims has been very productive. Many of such microbial ecological agents now understood in detail. An important part of the microbe's armamentarium is the ability to evade either partially or totally one or more of the normal defenses of the victim.

Each of enumerated large groups of molecular-ecological agents unites many types of biomolecules highly specific for each microbe species, varieties and even for each strain. The targets for these microbe chemical arrows are specific molecular structures in the body of a victim, which are mutually complementary and peculiar in each system.

Infectious disease develops as a result of interaction between molecular ecological agents of pathogenic microorganism, on the one hand and the affected body molecular structures on the other. Molecular ecological approaches have greatly increased our appreciation for the sophistication of successful microbial pathogens. During the past 30 years, we have obtained evidence from molecular biology that demonstrates the chemistry (chemical ecology) of microbe-victim interaction and the nature of constitutive immunity.

The harmful molecular ecological agents of microbes influence the affected organisms by means of victims' polynucleotides (DNA, RNA), oligonucleotides, for instance, nicotinamide adenindinucleotide, splitted by diphteria toxin, physiologically active proteins, structural proteins including collagen, elastin, various enzymes (for instance, glucoso-6-phosphate-dehydrogenase, alkaline phosphatase, adenyl acetylase, asparaginase, restrictase, translocase, peroxidase, trypsin, other proteases, cholinesterase), immunoglobulines, albumin, phetuin, fibrin, actin, haptoglobins, hemoglobin, ceruloplasmin, various glycopeptides and sialoglycoproteins (glycophorin, mucin), amino acids (f.e. lysine, asparagine), mono- oligo- and polysaccharides (starch, glycogen, pectin, lignin, cellulose, galactosids, galactosamine-N-acetyl, glucosamine-acetyl, other hexoses, erythritol, sialic acid, sialomucopolysachharides), lipids and fatty acids (lecithin, cholesterol, linoic acid, oleic acid, sphingomielin, phospholipids, ceramide, cerebrosides, gangliosides), metalloorganic compositions (ovotransferrin, ferritin), complement, interferon, vitamins, steroids, colchicine, various aldehids, ketones, chitins etc [29].

To affect a victim every infectious agent uses original set of unique molecular ecological agents, which are able to affect only such targets in the body of victim that are specific for this kind of attacking agent. For instance, separate receptor structures are involved into interaction of human cells with influenza viruses and meningococci [11]. Besides, in any case the efficacy of microbial aggression is strongly dependent on very precise chemical or stereo-chemical fitness between biomolecules involved in the antagonistic relations. Moreover it depend very strongly not only the presence of competent molecules but also on their quality, quantity and density of distribution on a cell and its substructures.

Thus, the pathogenic effects of microbes and microbial molecules on molecular targets of a pray are provided by genetically determined molecular structure of targets, thereby defining

constitutional susceptibility to infection or invasion. Due to this property of a molecular constitution, viability and propagation of intruders can be either restricted or stopped. The power of hereditary self-defence precisely directed to counteract such intermolecular relations and thus prevent a disease.

The Types of Executors of Hereditary Contra-Infectious Immunity

The successfulness of microbial pathogenesis is provided with its unprecedented specificity which is equal to those of antibody/antigen recognition [109]. This undoubted merit forms not only the power of microbial attack. The vulnerability of microbial pathogenesis is also hided into its main merit. Any competent mutation which disturbs intermolecular complementariness creates constitutional insusceptibility [10,87].

According to existent great number and specificity of both microbial molecular weapons and their molecular targets, the genetically determined mechanisms of hereditary immunity are of very diverse molecular origin and extraordinary specific for each microbe-victim ecological system and subsystems. Genetic immunity of relevant organism is provided by molecular properties of its cells, namely their pathogenetically competent molecular structures. These properties can be revealed by relevant procedures, for instance, by observation of a microbe attachment to the cell envelope, which is the key step of infection by intracellular parasites [4,8,110,111].

Constitutional antimicrobial immunity encompasses several specific and common structures possessed by the attacked organisms and functioned in defense against molecular ecological aggression of harmful micro-organisms. These structures form a variety of molecular barriers: the lack of specific cell receptors, modification of specific cell receptor, modification of specific nutrients, lack of a specific nutrient, presence of specific antibiotic and\or poisons, nonspecific mechanisms. Its study illustrates not only extraordinary diversity of molecular anatomy of various living forms but also the sense and the origin of this diversity [4,10].

In many of specific strategies that pathogenic organisms use to overcome common victim defense, the very significant step is the firm attachment of microorganisms or their molecular ecological agents to victim cell membrane. Certain biomolecules expressed on cell surface play a clue role in the attachment of microbes as the first step in infection. This role may be related to the presence on the cell of specific molecule acting as receptors for chemically complementary either adhesive or toxic molecules of microbes. The absence, quality, quantity and density of molecular targets distribution play a vital role in the phenomena of constitutional immunity to infection. If adhesion of a parasite or its product onto victim cells is restricted, infection interrupted and disease prevented [4,8,10,87,112].

Bacteria have evolved various means of beating off viral attackers at almost all stages of the bacteriophage life cycle. The most effective defense is to prevent any productive contact between the bacteriophage and the bacteria. This can be done by mutation of bacteriophage receptors on

the-cell surface or by secretion of a barrier that prevents the adhesion of bacteriophage, such as a capsule or slime layer.

A strong correlation has been found between receptor expression on cells and their constitutional immunity to encephalomyocarditis (EMC) virus infection [112,113]. Cell lines that did not express detectable receptors were not susceptible to infection. In contrast, the majority of the cell lines with demonstrable receptors were capable of being infected. Normal and stimulated murine macro phages and mitogen stimulated lymphocytes express EMC virus receptors and were capable of being infected. In contrast, nonstimulated lymphocytes did not bind the virus and were resistant to infection.

Some antigenically indistinguishable but ecologically different cardiovirus variants appear to utilize receptors on the cells of different species [112,113]. Receptors on murine and rat mammary cells can differentiate different isolates of mouse mammary tumor viruses [114]. The presence of microbe specific constitutive receptors on macrophages are also important [115].

HIV - infection can affect and destroy a variety of human cells that express the CD4 receptor molecule on its surface. The virion envelope glycoproteins (gp120) interact not only with the CD4 molecule on the target cells but also with its chemokine co-receptors thus performing, the first i.e. clue step of intracellular invasion of the virion. Physiologically, the more discovered targets of HIV infection (CD4+ T cells, macrophages and dendritic cells) function as the vital components of reactive production of antibodies performed the lymphatic system. Macrophages and microglial cells are the cells infected by HIV in the central nervous system. In a case when enough CD4+ T cells have been destroyed by HIV, the production of antibodies by the lymphatic immunogenic system decreases leading to the syndrome known as AIDS.

The intensity of interplay between virus and its receptors on the cell surface receptors and ligands has fundamental role both in cell penetration by HIV-1 and in immunity to this clue step of the infection thus determining all levels of diversity characteristic of HIV infection. The structure of chemokine co-receptor is coded by CCR5 gene that has been mapped to chromosome [67]. The mutant allele CCR5-Delta32, which is characterized by a 32 bp deletion in the single coding exon of the gene, was identified as responsive for coding the receptor structure not compatible to relevant molecular ecological agent of the virus [66].

The modified co-receptor along with CD4+ receptor for HIV-1 is incapable to promote cell penetration by HIV. Individuals homozygous for CCR5-Delta32 display no clinical symptoms and appear to be healthy. They possess structural (constitutional) cell immunity to the infection. Heterozygous individuals also exhibit slower progression to AIDS after seroconversion and protection from AIDS-related lymphoma. Thus, the risk of acquiring HIV infection is individually modulated by genetic polymorphisms in the chemokine receptor/ ligand and the antigen-processing/presentation systems.

This mutation occurs at an allele frequency of 9% and a carriage frequency of 15%–18%, among white European individuals, but the frequencies in other major racial groups are negligible. Additional variants, most of which are codon-altering, have also been identified. Some of these variants may protect against HIV-1 infection as a result of severe alteration in the conformation of the molecule. The effects of host genetic variation on acquiring HIV infection are inextricably bound to the well-established and powerful genetic variants that can function at different stages of infection [66,82]. The separate effects of these variants tested at cellular and molecular level.

Efficacy of HIV infection (HIV titer) decreased with decreasing CD4 receptor expression. However, certain CD4-negative cell types may also be susceptible to infection. This fact suggests that CD4 is probably not the only receptor, which can be used by HIV. In contrast, in other human cell lines even high levels of CD4 expression failed to assignment HIV infection. Though the CD4 protein expressed in these cell lines was capable of binding HIV virions they were unable to be infected. Thus, in addition to CD4, other cell surface molecules appear to be required for successful HIV infection of these human cell lines [116].

Primary cultures of gastric epithelial cells from Ptprz+/+ and Ptprz-/- mice also showed similar incorporation of *H. pylori* cytotoxin VacA, cellular vacuolation and reduction in cellular proliferation, but only Ptprz+/+ cells showed marked detachment from a reconstituted basement membrane 24 h after treatment with VacA. This toxin bounds to Ptprz-receptor and the levels of tyrosine phosphorylation of the G protein-coupled receptor kinase-interactor 1 (Git1), a Ptprz substrate, were higher after treatment with VacA, indicating that VacA behaves as a ligand for Ptprz. Furthermore, pleiotrophin (PTN), an endogenous ligand of Ptprz, also induced gastritis specifically in Ptprz+/+ mice when administered orally. Taken together, these data indicate that gastric ulcers are induced by erroneous Ptprz signaling [104].

Certain biomolecules expressed on cell surfaces play a key role in the attachment of micro-organisms as the first, i.e. clue step in infection. This role related to the presence on the cell molecules acting as receptors for chemically complementary adhesive molecules of microbes. The non-sensitivity of cells, e.g. of animal cells and cells of most humans to adhesion of N. meningitidis indicates that molecular constitution of such cells does not provide the reception of these infectious agents. The attachment of Neisseria meningitidis to cell surfaces involves lectin-like sites on the microbial surface which bind to specific ganglioside radicals on affected cells. This phenomenon has been illustrated by ganglioside-inhibited binding of meningococcus to erythrocytes, epitheliocytes and leukocytes [74]. According to the data, it is becoming increasingly clear that certain peculiarities of the molecular constitution of cells can contribute to whether or not a child or adult will develop meningococcal infection. The revealing of such species, age and individual distinctions is the first step to decoding of their molecular basis.

The phenomenon of newborns resistance to meningococcal infection may be associated with some age constitutional peculiarities of the organism, namely with impotence of cellular receptor

structures, responsible for the stage of agent's adhesion that is a key stage of relevant infectious process. The spectrum of disease incidence and severity in N. meningitidis also attributed to heterogeneity of human population in susceptibility of cells to adhesion of the infectious agent.

The conjoint effects of the victim ontogenesis and followed heterogeneity in the ability of their cells to adhesion of N. meningitidis can help to explain some intriguing epidemiological and clinical observations. However extended investigations at the level of individuals are necessary in order to draw comprehensive conclusions. Whether an individual infected with N. meningitidis will develop disease or not, will depend on a variety of risk factors. Certainly, adhesive ability of victim's cells is one of them. The second, third and other factors could be found on transmembrane and intracellular stages of pathogenesis.

The presence or absence of specific cell surface receptors can influence the victim range and tissue tropism of viruses. Receptors for poliovirus, for example, are known to confer susceptibility on human and some primate cells while cells of any other species lack such receptors and are immune to the infection [113,117].

A strong correlation found between receptor expression on cells and their constitutional susceptibility or immunity to encephalomyocarditis (EMC) virus infection. Cell lines, which did not express detectable receptors, were not susceptible to the infection. In contrast, cell lines with demonstrable receptors were capable of being infected [118]. Poliovirus receptor activity appears to be influenced also by the deletion on domain(s) II and/or III [79].

Rabbit diarrheagenic Escherichia coli-1 (E.coli RDEC-1) is only able to induce diarrhea in rabbits. The adherence of RDEC1 to intestinal brush borders is a species-specific event, occurring with the rabbit but not with guinea pig, rat, or human brush borders. Furthermore, after the onset of the diarrhoea phase, the microbes RDEC-1 found to have colonized the ileal and cecal regions of these rabbits heavily with minimal colonization found in the jejunum. This species and tissue specificity of *in vivo* colonization and infectivity clearly correlates with the specificity of *in vitro* adherence.

The receptors for RDEC-1 selectively localized only on the brush border surface of rabbit ileal epithelial cells and are not present on the basolateral membranes of epithelial cells or on any of other membranes of underlying tissue. This remarkable degree of species, tissue and cell specificity possessed by RDEC-1 indicates that the rabbit intestinal mucosa contains receptors specific for RDEC-1, which are not present in other tested mammalian species [119].

In contrast, the non-adhesive strain of E.coli, HS, failed to colonize rabbit ileum and the extent of cecal colonization by HS was 10,000-fold less than that seen with RDEC-1. The inability of RDEC-1 to colonize the ileum and caecum of rats and guinea-pigs demonstrated the lack of RDEC-1 receptors on the mucosal surface in these animals, which is likely to be a factor of their constitutional immunity to the diarrheagenic effect of RDEC-1. The failure of RDEC-1 to colonise

their intestines, due to a lack of receptors in these animals would lead to rapid clearance of nonadherent RDEC-1 [119]. The adhesion of enteric bacilli does not occurs if the cell surface does not contain glycophorin Am [120].

Pigs have a genotypic trait governing the adherence of E.coli possessing the K88 molecule to their intestinal brush borders and called the genotypes “adhesive” and “nonadhesive”. The “adhesive” trait inherited in a simple Mendelian dominant manner. After challenging these two genotypic variants with a K88 strain of Ecoli, it was found that 88% of the “adhesive” pigs developed diarrhea while only 8% of the “nonadhesive” pigs showed some clinical symptoms. The extent of E.coli colonization was 1,000 fold greater in the sensitive pigs [121].

Erythrocytes without Duffy blood group molecules on their surface are constitutionally resistant to invasion by P. knowlesi. The initial attachment of the merozoites by their apical complex to Duffy-negative erythrocytes can occur, but the junction that follow invasion not formed. Erythrocytes of most West Africans, many East Africans and certain other populations (e.g., Bedouin Arabs) lack detectable Duffy blood groups [122] and they are constitutionally immune to this kind of malaria infection. Duffy-negative blacks who were exposed to bites of P. vivax-infected mosquitos did not develop parasitemia, while blacks who had Duffy determinants on their erythrocytes were susceptible [70,123]. 90% of West Africans have Duffy negative erythrocytes and this explains the constitutional immunity of this population to P. vivax and P. knowlesi. Untreated infections with the same parasites in white visitors to this region would often be lethal.

Bacteria possess various means of self-defence against viral attackers at almost all stages of the bacteriophage life cycle. The most effective defence is to prevent any productive contact between the virus and the bacteria attacked by it. This can be done by mutation of bacteriophage receptors on surface of the bacteria or by secretion of a barrier, which prevents the adhesion of the bacteriophage, such as a capsule or slime layer.

The biomolecular target of a phytopathogenic microbial toxin plays a key role in the evolution of spotted disease in sugar cane, the target biomolecule exists in nature in two forms, differing in amino acid structure. One variant is incapable of interacting with the toxin because the plant possessing the modified membrane protein that is not susceptible to this disease and is constitutionally resistant to it. This particular structure involves a change in only four amino acid positions out of the 110 amino acids of the given membrane protein [124].

The insecticide (e.g. dieldrin) resistance mechanism seems to be the same in all species of test insects used. Dieldrin is ineffective against resistant insects because their mutated receptors have become incompatible to this insecticide [125]. The specific immunity of contemporary cultivated potato stocks to late blight derived from hybridization of wild resistant potato with cultivated varieties. Cultivated immune plants are almost immune to some species of the fungus,

while susceptibility to other species is unaffected. Specific resistance is controlled by at least nine dominant genes [126].

Some myxoviruses and paramyxoviruses, such as Sendai virus, have surface glycoprotein spikes, which adsorb to specific receptors on cells attacked by virus. The receptors on erythrocyte membranes contain sialic acid. That is why myxoviruses and paramyxoviruses cannot adsorb to erythrocytes that have been treated with sialidase. Furthermore, sialoglycoproteins inhibit adsorption of the viruses on erythrocytes. The adhesion of Sendai virus to artificialliposomes of different compositions was studied [105]. Liposomes A were prepared with only phosphatidylcholine and cholesterol, liposomes B were prepared with phosphatidylcholine and cholesterol or with phosphatidylcholine and cholesterol plus phosphatic acid or phosphatidyl serine. They did not adsorb virus. Liposomes A containing also stearyl amide or ganglioside did, however, adsorb virus. Liposomes containing ganglioside, but not those containing stearyl amine, could compete with erythrocytes for virus. It concluded that gangliosides can serve as Sendai virus receptor and that a multiplicity of receptors was needed for virus binding.

Sendai virus, which itself negatively charged, will adsorb to positively charged liposomes but not to any of the negative liposomes tested except those containing gangliosides. This virus interacts with cell surface gangliosides that contain terminal sialic radicals but no less than 3,000 such receptor molecules are required for the attachment of a single virion [65].

Special gangliosides appear to serve as viral receptors, which can specifically interact with the glycoprotein spike on the viral surface. But a negative charge alone is not sufficient for bonding. Ganglioside GM1, which lacks a terminal sialic acid radical does not act in a virus adhesion whereas mono-, di-, and trigangliosides with terminal sialic radical do. The sructure of ganglioside suggests particularly the possibility of electrostatic or hydrogen bonds. The fact that sialidase treatment removes the ability of cells to adsorb virus makes it seem likely that a terminal sialic acid radical is required for receptor activity. Glycolipids and glycopeptides do not interact with virus when free, but do when they are arrayed in a membrane or in protein. The most likely reason for requirement for an array of receptors is that when any bond in array is disassociated, it is still held in a position favorable for reassociation. The glycolipids in the membrane are probably held not only in a position favorable for reassociation but also in defined orientation [65].

Sendai virus has surface glycoprotein spikes which can attach to specific receptors on the cells attacked by the virus. The successful receptors on erythrocyte membranes contain sialic acid. Sendai virus cannot attach to erythrocytes after they have been treated with sialidase. Gangliosides appear to serve as viral receptors, which can interact, specifically with the glycoprotein spike on the viral surface. Ganglioside GM1, which lacks a terminal sialic acid radical does not allow a virus adhesion to cell envelope, whereas mono-, di-, and trigangliosides with terminal sialic radicals do. The terminal sialic acid radical is required for receptor activity [65].

Gangliosides can serve as Sendai virus receptor and a multiplicity of receptors is needed for virus binding to ensure that the virus particle is bound to enough, no fewer than 3,000 such receptor molecules are required for the attachment of a single virion. The binding of the virus to the ganglioside is specific, tight and not readily reversible [65].

A large number of receptors is necessary for the liposomes to bind a virus particle tightly enough. The binding of the virus to ganglioside liposomes is specific tight and not readily reversible. Glycolipids of the cell surface, such as gangliosides as well as glycoproteins can serve as targets in as much as they contain sialic radicals. The ability of group C influenza virus to adhere to human red blood cells depends on the presence of O-acetylated radicals of sialic acid. The erythrocytes from any of 35 different individuals were found to contain influenza virus-binding sites though their number was variable among the individuals and was much less than that on mouse, rat and chicken erythrocytes. Human-erythrocytes have a low level of 0-acetilated sialic acid-containing glycoconjugates that can interact specifically with the HEF glycoprotein of influenza C virus [127].

Choleraic toxin is able to interact only with ganglioside macromolecules that contain the subunits of ceramide, lactose, galactosamine, galactose and the radical of sialic acid joined with the molecule of lactose (Figure 4a). But the same toxin does not interact with gangliosides of other types, for instance, those that do not contain galactose or have an additional radical of sialic acid in the end position [128]. Cells whose membranes have no ganglioside Gm1 are insensitive to cholera toxin [129]. Receptors for botulinic and tetanic toxins as well as for influenza virus possess different ganglioside compositions. Accordingly, any un-fitted ganglioside composition of cell membrane envelope restricts the attachment that is absolutely necessary for infectious agent to intrude the attacked cells.

Biomolecular target of a microbial toxin plays a key role in the progression of spotted disease in sugar cane. The target biomolecule exists in nature in two forms differing in amino acid structure. One variant is incapable of interacting with the toxin because the plant possessing this modified membrane protein, is not susceptible to this disease and is constitutionally resistant to it [130]. They are not infected by the corresponding microbe, but in contrast, continue to develop normally and give rise to healthy progeny while other individuals of the same species not having this molecular structure become ill and die. This particular structure involves a change in only four amino acid positions out of the110 amino acids of the given membrane protein.

Different cells may be resistant to pseudomomas toxin due to an alteration in the binding, uptake or delivery of toxin to the target site in the cell. CHO-K1 cells contain normal levels of elongation factor 2, the target site for Pseudomonas exotoxin A, but are resistant to the toxin due to a defect in the delivery of active toxin to target site in the cell. The immunity in one cell line apparently related to a defect in a normal mechanism for the acidification of endocytic vesicles. Other cell line is immune to diphtheria toxin, Pseudomonas toxin and four enveloped RNA viruses. This line also has an increased sensitivity to the plant toxin ricin. The immunity of this line appears

to be related to a defect in a cellular mechanism required for the maturation of Sindbis-virus that is likewise required for the entry of active Pseudomonas toxin [101].

Some of human cell lines are very sensitive to cytotoxin produced by Shigella shigae, which killed the cells by picomolar to fentomolar quantities. In contrast, certain other human and animal cells are resistant even to nanomolar concentrations of the toxin. Binding studies with labelled cytotoxin showed that all toxin sensitive cell lines contain 300 000 binding sites per cell, whereas the most insensitive cell lines did not contain measurable amounts of toxin receptors [131].

African green monkey kidney cell lines (Vero, CV-1) have approximately 10-20,000 surface diphtheria toxin binding sites per cell and are exceptionally sensitive to this toxin [132]. BHK and HeLa cells are 100-1000 times less sensitive. There are at least two general classes of mutant cell lines resistant to diphtheria toxin [133]. There are those in which resistance is due to an altered EF2 molecule, which cannot be ADP-ribosylated, and there are those, which affect the translocation of fragment A across the plasma membrane. A number of last mutants have been isolated, not only for diphtheria toxin, but also for abrin and ricin. The increased resistance to diphtheria toxin in a CHO cell line is attributed to a mutation giving rise to receptors with reduced affinity for toxin.

It generally recognized that protein-lipid interactions are of crucial importance in membrane transport phenomena. Different cell lines and species differ in their sensitivities to diphtheria toxin - this is due at least in part to differences in the number of diphtheria toxin surface receptors on the cells [132] but may also arise from differences in the membrane transport step [100].

The effect of cell membrane composition on the interaction of diphtheria toxin with lipid bilayer membranes was investigated [100]. Measuring relative conductance induced by diphtheria toxin in lipid bilayers of different composition [100], that interaction of diphtheria toxin with bilayers depends on membrane phospholipid composition. It was shown that phosphatidylinositol in asolectin membranes was responsible for their sensitivity to diphtheria toxin. Membranes formed with purified soybean phosphatidyl cholin, phosphatidylethanolamine and phosphatidylinositol are comparable to asolectin membranes, but substitution of phosphatidylserine for phosphatidylinositol in this mixture rendered the membrane insensitive to diphtheria toxin. Membranes consisting of phosphatidylcholine, phosphatidylinositol, and phosphatidylethanolamine are consistently much less sensitive to diphtheria toxin.

Glycolipids or gangliosides do not sensitize the membrane to diphtheria toxin. Diphosphatidylglycerol (cardiolipin) seems to confer some slight sensitivity, but greater effects result from the presence of inositides in the membrane. The interaction is optimal when inositides are present within the membrane and the inositides are required on the side of the membrane opposite to that in which diphtheria toxin introduced. Phosphoinositides exert their effect not so much on the binding of diphtheria toxin but on the insertion or channel formation step.

They mediate this effect from the side opposite to that on, which the diphtheria toxin is bound. Adenosintriphosphate when added to the transside of the membrane, does not affect diphtheria toxin channel formation [100]. The effect is specific, only inositol phosphate (or phosphoinositide) on the opposite side of the membrane induces diphtheria toxin channel formation.

Thus the interaction of diphtheria toxin with bilayers depend on membrane phospholipid composition and disposition. The diphtheria toxin first binds to the membrane surface and then extends a process across the membrane core, which probes the other side. If the diphtheria toxin cannot find phosphoinositide and binds to it, anchoring it in place and allowing channel conformation, cannot occur. The critical steps in diphtheria intoxication may be as follows. If diphtheria toxin cannot bind to a cell-surface receptor it cannot be internalized. Once in the endosome, the absence of acidic environment causes a conformational change in diphtheria toxin molecule, the binding and insertion of toxin molecule into the endosomal bilayer cannot occur. On the other hand, the consequent binding to phosphoinositides anchors diphtheria toxin, allowing channel formation and concomitantly, the translocation of the enzymatic moiety of toxin into the cytoplasm [100].

Verocytotoxin 1 of Esherichia coli (VT) binds specifically to glycosphingolipids , the components of the outer leaflet of the plasma membrane, such as globotriaosylceramide (Gb3) and galabiosylceramide having a terminal Gal-alpha1-4Gal disaccharide sequence [103]. Changes in the ceramide composition of Gb3 might define VT-iduced pathogenesis. Thus, Gb3 fatty acid heterogeneity may play an important role in constitutional immunity to VT-induced disease (hemorrhagic colitis and the hemolytic uremic syndrome).

Differential expression of this glycolipid, for example, the containing a specific fatty acid in it, might prevent the VT binding and thus prevent any individual hemolytic uremic syndrome following VT E.coli infection. Binding of VT1 to its receptor is influenced by differences in receptor fatty acid content. The fatty acid content of human renal Gb3 may play a role in restriction of the binding affinity of VT to renal target cells and may thus influence the possible clinical consequences of VTEC infection [134]. VT immune mutant cell lines were found to lack Gb3 [135,136]. Incorporation of Gb3 into receptor-deficient cells resulted in the induction of VT sensitivity [137].

Fatty acid chain length has little effect on sensitivity or immunity to verotoxin but Gb3 molecular species containing different fatty acids that can interact to provide a lower affinity toxin receptor than any of individual component receptor species. There is evidence to suggest that fatty acid chain length can have a stereoselective effect on carbohydrate conformation. According to Kannagy et al., 1982 [138], the changes in the ceramide composition of the glycolipids were associated with variations in the reactivity of different cells with glycolipid-specific antibody.

The results of some experiments clearly indicate that the cholesterol level in a particular cell

markedly influences saponin induced hemolysis. But cholesterol does not serve as the specific binding site for these hemolysins, because decrease in its level affects the susceptibility through secondary structural changes in the membrane [139].

The limitation of nutrient resources necessary for infectious agents forms very effective mean to provide the self-defense of attacked victim. Several such molecular factors contribute to constitutive immunity of certain African, European and Asian human populations to malaria. Some of these, such as mutant modification of hemoglobin, a specific protein nutrient of Plasmodium malaria, have been investigated in detail and provide information of interest from the point of view of constitutive immunity to malaria parasites.

The discovery of this immunogenic agent has been induced by relation between sickle cell anemia and hereditary immunity to malaria which is now a well known example of genetically determined specific individual immunity. In 1949, Linus Pauling traced sickle cell anemia to a specific defect in the structure of hemoglobin. He found the existence of two variants of hemoglobin molecule, the ordinary hemoglobin (A) and abnormal one (S). The molecule of both variants is constructed by four subunits: two alpha-globin chains, each 140 amino acids long and two beta-globin chanes, each with 145 amino acids. Alpha- and beta-globin are coded by different genes.

The sole defect in the abnormal haemoglobins was the inherent replacement of one amino acid by another:

Ordinary (A) beta-globin chain amino acid sequence is:

Positions 1 2 3 4 5 6 7

Sequence -val-his-Ieu-thr-pro-glu-glu-

Abnormal (S) beta-globin chain amino acid sequence is:

Positions 1 2 3 4 5 6 7

Sequence -val- his-Ieu-thr-pro-val-glu-.

In the beta-polypeptide chain of S hemoglobin, the sixth amino acid radical is replaced by another amino acid valine. In an ordinary adult (A) molecule, this residue is the negatively charged glutamic acid, whereas in sickle-cell (S) hemoglobin, the presence of uncharged valine in this position allows the deoxygenated molecules to polymerize into rod-like helices which cannot support the Plasmodium falciparum reproduction but distort the red cell form and function. P. falciparum could not grow in SS erythrocytes if the oxygen tension is low (3% contrast to 18%) [140].

C-variant of hemoglobin molecule constitution, common in West Africa and associated with beta-talassemia, and E-variant in Asia are all present in high frequencies in formerly malarias regions, these were selected by P. falciparum. Erythrocytes from beta-thalassemic patients

cannot support the reproduction of P. falciparum under the oxidant stress conditions. Also the reproduction of the parasite is retarded in erythrocytes with high concentration of hemoglobin F. The levels of this hemoglobin decline more slowly during the first year of life in children heterozygous for beta-talassemia than in AA-children, which might provide some protection for the heterozygotes against malaria [70].

Similarly, deficiency or absence of glucose-6-phosphate dehydrogenase (G-6-PD) determines the constitutive immunity to falciparum malaria in some groups of New Guinea aboriginals. G-6-PD is the enzyme that reduces NADP to NADPH, maintaining reduced glutatione and protection the cells against oxidant stress. Observations on children in Tanzania and Nigeria provided evidence that G-6-PD deficiency protects against severe falciparum malaria [70]. Mice deficient in vitamin E, an antioxidant, showed increased constitutional immunity to rodent malaria. An oxidant stress in the environment, such as ingestion of fava beans, which is common in Mediterranean countries, or selenium deficiency, which is common in parts of Africa, act synergistically with G6-PD deficiency to protect against severe malaria [141].

The immunity and sensitivity of red blood cells to hemolytic action of specific leptospiral enzymes is determined by phospholipid composition of the cells. Leptospiral haemolysin is most active on sheep erythrocytes, less active on human erythrocytes, still less active on rabbit erythrocytes and only very slightly active on guinea-pig erythrocytes. The phospholipid composition of the red cell membrane is characteristic for each animal species. There are marked differences between the species in the proportions of the main types of phospholipids, especially in those of the choline containing phospholipids [142].

The red cell membranes of rat, guinea pig, rabbit, man, ox and sheep reveal a progressive decrease in the content of lecithin from about 60 to 0 per cent of the total phospholipids and a corresponding increase in the content of sphingomyelin from 26 to 64 per cent. The strains of leptospires that did not degrade either lecithin or sphingomyelin do not show hemolytic activity. The parasitic leptospirae degrade sphingomyelin much faster than the other phospholipids.

The erythrocytes of sheep and ox, with their large content of sphingomyelin and minimal content of lecithin are lysed by Parasitic leptospirae more rapidly than are the erythrocytes of other animal species. The lysis of human, rabbit and rat erythrocytes, in which the amount of lecithin is greater than that of sphingomyelin, appeared only after a longer incubation than was required for lysis of sheep erythrocytes.

The enzymatic degradation differed not only between the different types of phospholipids, but also, in some cases, between phospholipids of the same type present in the erythrocytes of different species. Thus, lysolecithin in rat erythrocytes, in contrast to that in human, rabbit and sheep erythrocytes, very slowly degraded by the leptospirae. The phosphatidyl ethanolamine and phoaphatidyl serine in sheep erythrocytes appeared to be resistant to degradation by leptospirae, but, when present in rat erythrocytes, these phospholipids were degraded [142].

Absence of specific nutrient:. Research on brucellosis, which is mainly a disease of cattle (caused by Brucella abortus), sheep and goats (Brucella melitensis) and pigs (Brucella suis) provides a demonstrative example of identification of a nutritional factor of constitutional immunity. The stimulant of *brucella* reproduction was identified as erythritol, a foetal product that is concentrated in structures of a victim body structures. Erythritol, rather than glucose, is a preferred nutrient for B. abortus, B. melitensis and B. suis. B. abortus infection in new-born calves is enhanced by erythritol. The inherent absence of this component of molecular constitution of some species and their tissues is responsible for hereditary immunity to brucellosis created by the restriction of brucellae reproduction. This is a major factor of constitutional immunity to brucellosis [89].

The effects of phosphatidylserine starvation on the infection with sindbis virus (an enveloped RNA virus) have been investigated in a chinese humster ovary (CHO) cell mutant (strain PSA-3) which lacks the ability to synthesize this phospholipid. When PSA-3 cells were grown in the absence of phosphatidylserine the cellular contents of the latter decreased whereas the cell growth viability and syntheses of protein, DNA and RNA remained normal. Sindbis virus production in the mutant cells decreased immediately upon phosphatidylserine deprivation. Although the binding and internalization of sindbis virus in tested PSA-3 cells was almost normal, viral RNA synthesis was greatly reduced in the cells. These results indicate that nucleocapsids of the internalized Sindbis virus not normally released into the cytoplasm. The deficiency of phosphatidylserine in victim cells may suppress the fusion of the viral membrane with the endosomal membrane [143].

At culminant stage of bacteriophage life cycle the virus injects its genome polynucleotide into the bacterial body. Once bacteriophage's DNA injected into bacterial cell, the victim's DNA restriction enzymes ensure the survival of the bacterium. Bacteria use the enzymatic restriction of DNA and modification of the enzymes to maintain own genetic stability when foreign genome polynucleotides introduced into their bodies. The enzymes within the victim may destroy the polynucleotide. Thus, the own DNA restriction enzymes provide the antiviral immunity of bacteria [144].

On the other hand, the bacteriophages possess antirestriction mechanisms and are able to defend themselves by inhibition of restriction enzymes either by DNA genetic modifications or by their own proteins. The anti-restriction mechanisms play very important roles in hereditary immunity of viruses. Bacteriophages T3 and T7 protect their DNA from restriction by producing specific antirestriction proteins. Although of different molecular constitution, the two phage proteins act using the same mechanism. The most striking feature of bacteriophage anti-restriction is the wide variety of specific mechanisms possessed by different viruses [145,146].

Heritable changes in the molecular organization of bacteria, for example, the existence or appearance of metabolites which can either neutralize or destroy one or another antibiotic, inhibit the annihilating action of certain antibiotic agents. Due to this property of the victim molecular constitution, the viability of attacked bacteria can be saved [147].

Plants produce a diverse array of smaller antimicrobial proteins (less than 100 amino acid residues), most of which are cysteine-rich peptides (CRPs) that inhibit bacterial and fungal growth. Many forms of CRPs are believed to comprise an important part of the immunity of both plants and animals. In plant tissues, CRPs produced mainly constitutively, for example in seeds and reproductive tissues, where they can provide a constant defensive role. It is discovered that at least one class of plants CPRs, the plant defensins, are believed to act through interactions with specific components of the surface membranes of fungal pathogens [148].

Constitutional immunity of western red cedar wood, Thuja plicata, to insect attack is attributed to the presence in its body of monoterpenss, of which methyl thujate is toxic to larvae of the black carpet beetle, the furniture beetle, and the case-making beetle [149]. The diterpene gossypol decreases weight gain in larvae of the tobacco budworm and pink bollworm [150]. Specific biochemical modes of action have been assigned to few such compounds [151]. The terpenoids inhibit or inactivate acetylcholinesterase, cause acetylcholine to accumulate at the cholinergic site, producing continuous stimulation of insect cholinergic nerve fibers throughout the central and peripheral nervous system, followed by paralysis and death of animal [152].

The release of HCN from living plant's cells plays as an agent of plant defence against the damage caused by grazing animals. Cyanogenesis performs plant defence mechanisms against herbivores, in particular against molluscs [153]. Herbivorous animals and insects, for their parts, have evolved acetylcholinesterase to become inhibited by HCN more slowly than that in susceptible animals.

Genetic immunity to influenza virus infection is associated with the existence of Mx gene, which controls biosynthesis of specific Mx protein. The murine Mx1 protein acts at an early stage of viral infection by inhibiting primary transcription of the virus genome. The human Mx A protein performs a subsequent act in the cytoplasm of the cells infected by influenza virus [154]. Human Mx A conferred a high degree of immunity to influenza A virus and to the vesicular stomatitis virus. The highly variable regions of Mx proteins constitute the domain which determines the specificity [155]. The intrinsic antiviral activity of Mx proteins indicates that their ecological role related to virus defense. However, Mx protein might serve not only antiviral but also cellular physiological functions [155].

Specifity of Hereditary Contra-infectious Immunity

It would be metabolically impractical for any living being to develop a new chemical against every species of parasite, which threatens, but form of life forced to do so. For this reason, constitutional immunity is mainly very specific, as is acquired immunity, which induced by the lymphoid system of reactive resistance. The idea of specificity operating between pathogenic micro-organisms and the target of these micro-organisms is encompassed by species specificity, population and individual specificity, tissue specificity and the specificity of cell clones and molecular targets. Specificity of constitutional immunity is result of the specificity of the

microorganism-victim molecular ecology. Specificity is not surprising, as the molecular ecological agents and modes of their interaction and application to various microbe-victim systems differ significantly. However, in contrast to individually induced responsive immunity the hereditary immunity against microparasites may be both specific and nonspecific.

The specificity of confrontation between pathogenic microorganism and its victim is predetermined by specificity of microbe victim molecular ecology. For example, gonococcal infections are limited to humans [156] and chimpanzees [157]. All other animals tested were constitutive immune to the infection.

Specificity is not surprising, since the various microbe-victim systems differ significantly in their molecular ecological agents and modes of interaction and application. The cholera toxin is able to interact only with such ganglioside macromolecules, which contain the subunits of ceramide, lactose, galactosamine, galactose and the radical of sialic acid joined with the molecule of lactose. But the same toxin does not interact with gangliosides of other types, for instance, with such ones which do not contain galactose or just the opposite have an additional radical of sialic acid in the end position [128].

The cholera toxin and heat-labile enterotoxin of Esherichia coli have many properties in common. Both toxins being composed of five B subunits which mediate binding to cell surface receptor and A subunit which stimulates the adenilate cyclase-cyclic AMP system. Both toxins cross react antigenically. Meanwhile, of the 103 amino acid monomers of the B subunits, 20 found to differ between two toxins. Futhermore, the intestinal receptors also found to differ between the two toxins.

Like many other toxic proteins [158] e.g. the toxins of C. botulinum and C. tetani as well as abrin and ricin, the choleric toxin consists of two components, effectomer (A) and haptomer (B), which perform different function. Haptomer is responsible for the binding of entire structure to the cell surface, then effectomer reaches its site of action and performs the specific biological effect [158].

Cholera toxin binds selectively to GM1 ganglioside receptor sites of rabbit small intestine. Studies of various cells, including small intestinal mucosal cells of different species, have demonstrated a direct relationship between the cell content of GM1 and the cell susceptibility or immunity to the toxin. In contrast, rabbit intestinal receptor for Escherichia coli heat-labile enterotoxin has properties consistent with glycoprotein nature and lack affinity for cholera toxin [159].

Diphtheria toxin also contains two fragments, A and B. The mechanism of diphtheria intoxication involves a step in which B part of the toxin molecule inserts into cell membrane, facilitating the transport of the second (enzymatic) fragment A of the toxin molecule into the cytoplasm [160]. B fragment (40,000 dalton) interacts with receptor on sensitive cell membranes

and facilitates the translocation of N-terminal enzymatically active 21,150 dalton A fragment across the plasma membrane.

There are approximately 10-2000 specific diphtheria toxin receptors per cell. Only fragment A reach the cytoplasm, the remainder of the molecule is either left behind in the membrane or rapidly degraded in the cytoplasm. Upon reaching the cytoplasm fragment A catalyzes the NAD-mediated ADP-ribosylation (ADPR) of the eukaryotic polypeptidyl-tRNA translocase (EF2), thereby blocking protein synthesis. The introduction of a single molecule of A fragment into a cell should inactivate almost all its EF2 within a day or two. Thus a single molecule can actually kill a cell.

Inactivation of translocase is the primary target for diphtheria toxin within eukaryotic cells. The reaction is extremely specific. ADPR moiety linked to a unique posttranslationally modified histidine residue (diphtamide) present in a 15 amino acid sequence that has been highly conserved in all eukaryotic EF2 examined, including yeast and wheat germ, as well as mammalian tissues. To date, diphtamide has not been found in any other eukaryotic protein. Mutant cell lines, in which EF2 lacks the modification, are completely immune to diphtheria toxin [133].

Constitutive expression of interferon-induced murine protein Mx1 led to inhibition of influenza virus reproduction, but did not effect on vesicular stomatitis virus life cycle [155]. Constitutive expression of the cytoplasmic human MxA conferred a high degree of immunity to influenza A virus and to the vesicular stomatitis virus, whereas encephalomyocarditis virus and the mengo virus were not affected by Mx A. The highly variable regions of Mx proteins constitute the domain which determines the specificity [155]. Intrinsic antiviral activity of Mx proteins indicates that their physiological role is related to virus defense. However, Mx protein might serve not only antiviral but also cellular physiological functions [155].

Inherent immunity to HSV-1 infection is specific but independent of inherent immunity to murine cytomegalovirus infection and vice versa. In contrast, P\2G mice possess genetic immunity to various myxoviruses. This immunity is attributed to a single dominant gene designated Mx. Many West Africans and Afro-Americans are resistant to infection by Plasmodium vivax although susceptible to other three species of human malaria and AIDS.

Pseudomonas exotoxin A, like a diphtheria toxin, inhibits protein synthesis in sensitive cells by catalyzing the transfer of the ADP-ribose moiety of NAD to elongation factor 2 (EF-2). Both the toxins have the same mode of action in the cell but they utilize different receptors and mechanism of uptake [101].

Two very closely related bacterial viruses such as T 4 and T 6 may use different receptors. On the other hand, two different bacterial viruses may use the same protein receptor. In contrast, it has been shown that two or more animal viruses can compete for attachment sites [161].

Specific immunity of contemporary cultivated potato stocks to late blight is derived from

hybridization of wild resistant varieties of potato with cultivated one. Immune plants are nearly resistant to some races of the fungus, while susceptibility to other races is unaffected. Specific resistance is controlled by at least nine dominant genes [126].

Insecticide (e.g. dieldrin) resistance mechanism seems to be the same in all species of test insects used. The normal toxic action of dieldrin is to bind to receptors on chloride channels of nerves and thereby prevent entry of chloride ions and block transmission of inhibitory impulses. Dieldrin is ineffective against resistant insects because their receptors have become incompatible to this insecticide. Perhaps the mutation to the dieldrin receptor has increased the permeability of chloride channels, causing hyperinhibition of the nervous system [125]. Erythrocytes of most West Africans, many East Africans, and certain other populations (e.g., Bedouin Arabs) lack detectable Duffy blood groups and are resistant to invasion of Plasmodium vivax. Duffy-negative blacks who exposed to bites of P. vivax-infected mosquitoes did not develop parasitemia, while blacks who had Duffy determinants (Fya or Fyb) on their erythrocytes were susceptible. In laboratory experiments human erythrocytes without Duffy blood group molecular constitution (Fy/Fy) were resistant to invasion by simian parasite P. knowlesi (experiments have been performed with simian parasite because the human parasite Plasmodium vivax cannot be maintained in culture). Constitutive immunity of erythrocytes with Duffy molecular constitution is specific. The initial attachment of the P. knowlesi merozoites by their apical complex to Duffy-negative erythrocytes can occur, but the junctions that follow invasion not formed. However, P. falciparum invades Duffy-negative erythrocytes normally [70].

The striking specificity of constitutive immunity results from the possession by agents and their targets of mutually complementary combining regions. According to Pauling, 1975 [162], the theory of molecular complementariness was suggested around 1930 by Breinl and Haurowitz (1930), Alexander (1931) and Mudd (1932). There is some imitation of it in the early work of Ehrlich and Bordet. Max Delbruck and Linus Pauling (1940) published a paper on the general nature of the intermolecular forces that are responsible for the specificity of biomolecular ecological interactions. The idea of molecular complementariness is a basis of the specificity of molecular ecological interactions and constitutional immunity. Both the power and specificity of hereditary constitutional immunity provided by exclusively precise congruence of its protective mechanisms with the principal factors of relevant microbial pathogen.

PHENOMENON OF IMMUNE MOSAICS

The origin and existence of hereditary immunity are closely associated with the development of very broad diversity in it manifestations. This is a special kind of biodiversity, which is referred under the term of 'the phenomenon of immune mosaics'. Multiple manifestations of this phenomenon characterize the unique potentials of manifold ecological (protective) and physiological functions of herediary immunity. This kind of biodiversity is manifests itself in a spectrum of a disease clinical signs, with resultant clinical courses which range from acute to

chronic and possible persistence in the victim in a latent form, in broad variability of the locations and sizes of diseased affections, in individual differences of the severity of a disease and so on. Most demonstrative diversity is seen in the setting and sizes of infectious damages that demonstrate multiple foci of specific affections.

The Spottedness of Infectious Damages

Every infectious disease exhibits its specific affections in a form of irregularly dispersed patches specific to each kind of infectious agents. Every infectious disease is able to infect only selected parts of the attacked organism. Such loci of infectious damages are even more clearly demonstrated by the appearance of infectious exanthemas. Measles, for example, is characterized by separate appearance of damages on the skin. Similar rashes are characteristic of smallpox, scarlet fever, German measles, chicken pox, typhoid fever, syphilis, leprosy, and many other infections. As a matter of fact, on the skin of any infected patient the areas adjacent to the specific elements of exanthema are found almost undamaged, though all the skin were seen presumably homogeneous (Figure 3).

Multiple foci of spotted damages of mucous membranes are typical of cholera, dysentery and influenza. Local bone lesions were characteristic of some infections in Pleistocene bears which lived over 10,000 years before Christ [163]. Such local damages are regularly observed also in infectious diseases of plants [50] and invertebrates.

The rabbit diarrheagenic Escherichia coli, RDEC-1 heavily colonized the ileum and cecum of rabbit. However, only minimal colonization observed in jejunal brush borders of the animal. A gradient is observed in the localization of E. coli bacteria (strain RDEC-1) along the mucosal surface of the rabbit small bowel, with more microbes localized distally in the ileum than proximally in the jejunum [119].

Variability in the number of influenza virus particles adsorbed on endodermal cells of chicken embryos has been reported too [164]. The Sindbis virus receptors randomly distributed over the surface of chicken embryo fibroblasts and of BHK cells. The density of these receptors on the cell surface varies from cell to cell, ranging from 20 to 160 virus particles adsorbed per square micrometer. Areas of different particle densities were sometimes found on the same cell [165]. Random distributions have also been reported for other cell surface receptors, such as the concanavalin binding sites on normal and transformed cells [166].

Poliovirus infection initiated by ingestion of virus followed by its primary multiplication in the pharyngeal and intestinal mucosa. Far more extensive viral multiplication occurs in the tonsils and Peyer's patches of the ileum. From these sites, virus drains into deep cervical and mesenteric lymph nodes and then into blood, resulting in viremic phase. Although many tissues exposed to the virus during the viremic phase, the sites of remarkable poliovirus replication are restricted to certain tissues. Paralytic poliomyelitis occurs as a result of destruction of some (either that or

other) motor neurons in the central nervous system [167]. The like dapple (mosaic) alternation of susceptible and immune areas is characteristic also of intestinal infections (dysentery, cholera) and the ones, affecting chiefly internal organs (hepatitis, glanders, syphilis, leprosy, etc.).

The same situation exists by development of bacillary pulmonary tuberculosis (BPT) in humans and animals. Initial step in pathogenesis of human tuberculosis is the establishment of the primary lesion and associated lymph node (primary complex) via airway of a droplet nucleus containing viable tubercle bacilli. The unique feature of this stage is that the primary local lesion may occur anywhere in the lung. In contrast, the secondary (cavitary) lesions characteristic of tuberculosis occur most often in the apical-subapical region of the lungs that it is a privileged site where bacilli can survive in low numbers [168-170]. A crucial prerequisite in human for the progression from tuberculous infection to tuberculous disease is a consequent seeding of the crucial sites in the lung [171]. In contrast, in aerosol infected very sensitive guineas pigs, all six separate lung lobes were culture positive from day 26 after experimental challenge by the respiratory route [172].

Thus, each infectious disease is expressed in the attacked organism by at least two categories of one and the same tissue, outwardly identical and differing only in relationship to a given microbe. The parts of one of these two categories are affected by a given microbe while at the same time morphologically identical components of the organism remain.

Variations in the Dispersion and Sizes of Infectious Affections

Every infectious disease affects only local areas in the infected organism. Local vascular affections i.e. a rapid development of petechial rash or purpura fulminans is characteristic of sepsis and septic shock induced by Neisseria meningitides. Intra-individual variation observed also in the distribution of influenza virus particles on the surface of human trachea.

The local lesions specific for poxvirus infection consist of a number of skin lesions scattered over the surface of the body, each of which is the seat of local inflammation so intense as to lead to the formation of small abscesses in the course of 4 to 5 days. Beyond the edge of the lesions, the skin is normal. The number of lesions present may be less than a dozen in a minor case of illness or they may number in the thousands. In a severe course of disease, lesions may be set so closely as to conceal almost the whole cutaneous surface [49].

The smallpox rash is most severe on the face, then the hands and upper extremity. From the hands upwards, the scabs diminished in density. On the front part of the trunk they are scarce, especially on the abdomen. The areas adjacent to the specific damage are found almost intact, though all the skin is presumably homogeneous [48,49].

The name of athrax disease has been given following by its local (cutaneous) form, that accounts for over 95% of cases on records. The local lesions vary greatly in size from about 2 cm to several centimeters across and begin to resolve about 10 days after the appearance. The

affections vary stochastically not only in their size but also in their number and location. The resolution of affection takes from 2 to 6 weeks living minor scarring [48].

Poliovirus infection targets nerve cells at random although the virus is present throughout the nervous system [173]. The brain and spinal cord are involved in every case of poliomyelitis, but not every area of these organs is susceptible to the virus. This can only mean that nerve cells in certain areas are susceptible to viral damage, whereas those in other areas are not. In the worst cases, nearly every skeletal muscle may be paralysed. In the mildest cases, paralysis may be limited to part of one muscle. All degrees and combinations of paralyses can be observed [48].

Mosaic distribution of damages is also characteristic of hepatitis, tuberculosis and many other infections that chiefly affect internal organs [48,55]. The major recognized forms of rickettsial Q fever are pneumonia, hepatitis and sometimes meningoencephalitis, vascular infection, bone infection, osteomyelitis, endocarditis, unexplained fever and flu-like form [174].

Typhoid fever produce inflammatory foci in many organs and in some areas, necrosis and sloughing of tissues. Necrotic or inflammatory foci are commonly seen in the spleen and the liver and sometimes in the kidney, the meninges, the bones, the endocardium, the joints and many other portions of the body [48].

The same kind of intrabody diversity is characteristic of infectious diseases in animals. A viral skin disease of green sea turtles was characterized by either circumscribed papular skin lesions or spreading grey skin patches [175]. Such local damage regularly observed in infectious diseases of plants and invertebrates. Analogous mosaicism are regularly observed in infectious diseases of plants [176,177].

Diversity in the Course and Severity of Infectious Diseases

The severity of every infectious disease appears to vary very widely among individuals, members of different families, populations, races and ethnical groups according to individual variability in the correlation between the degree of genetic predilection to a disease and the strength of hereditary immunity to it is an indispensable property of any disease. It reveals itself at each disease processes and their manifestations. This area of infectology takes very important place in both strategic and tactic orientation of a disease clinical treatment. However, for the long time the origin of this kind of diversity in clinical manifestations of diseases investigated very meagerly.

Recent advances in immunology especially in identifying constitutional mechanisms of hereditary immunity [4,10,24] have contributed to our understanding of the origins of this kind of biodiversity in infectious diseases.

Immune Mosaicism in Cell Populations

When cell culture was affected by some a microbial pathogenic factor, many cells have been killed. At the same time, however, a number of outwardly indistinguishable cells fully preserved

their basic form and functions despite the conditions unfavorable for other cells of the same kind [178]. Such immunity may involve only few cells or a majority of cells in a culture. In all cases, the culture consists of both cells, which are not susceptible to the infection along with those cells, which are susceptible to contamination and thus damaged. The number of sensitive cells in a cell population may be extremely small or may form the majority.

Analogous situation usually observed in a whole organism. Some of its cells may be sensitive to infectious agent, whereas other clones of the same kind reveals immunity to the same agent. Immune polymorphism of cell populations contributes to the topography of the affected tissue areas and the favorite focus localization typical of observed infectious diseases. Local character of infectious affection is due to the resistance of certain cell clones in their sensitivity to an infectious agent and their local distribution.

For instance, the effect of diphtheria toxin on cultured human cells is lethal for only a portion of them. Other cells, identical in all outward appearance, turn out to be resistant to the toxin [178,179]. Such constitutional resistance may involve either a few cells in the tested cell population or the majority of cells. This phenomenon is highly specific, one and the same cell may be immune to the microbial agents of one type, but susceptible to another.

The amount of immune cells in the cultivated population may be extremely small, but they might as well form the majority. These peculiarities of cell clones distribution adequately applied to the whole organism. For instance, some areas of the urinary tract may be more susceptible to bacterial attachment than others. Women susceptible to urinary tract infection may have a higher proportion of target cells within different areas of the urinary tract [180].

Some people possess the predominating clone of cells susceptible for example to pox virus, so the specific rash is covering their skin almost entirely, whereas in other patients the disease is manifesting itself with a few isolated pustules, the latter people have the lightest form of infection with the fairly favorable outcome.

We studied intra-individual variations in sensitivity of human epithelial (buccal) cells to adhesion of Neisseria meningitidis, counting under microscope the number of microbes attached to every of 25 cells derived from every of 20 tested humans. While the quantities of attached cells have varied among tested persons from 12 to 86 microbes per cell, some attached up to 200-250 microbes whereas each of the most resistant cells has attached less than 10 microbes (Table 1). Thus, each of observed individual cell population represents by itself an innate mixture of cells with different grades of genetic immuniy to adhesion of N. meningitidis.

The diversity of red blood cell populations and its grade can be observed also by *in vitro* quantitative measuring of the reaction of haemagglutination induced by N. meningitidis, influenza, smallpox, rabies, tick-borne encephalitis viruses or any other hemagglutinating microorganism [11,13,62]. Therefore, the hereditary dissimilarities (mosaicism) of certain homogeneous parts of organism (revealed by germs) are dependent upon the differences of molecular set-up.

Origin of Immune Mosaicism

The examples considered above illustrate the manifestation of the mosaic configuration within attacked homogenous structures. The local nature of infections is not explained by the lack of uniform predilection of microbes for the organism. The presense of measles virus, for instace, was revealed in the typical elements of the rash as well as in the neighboring parts, which remain uninfected. The phenomenon of local infections is not explained by an uneven distribution of humoral factors in the body. Evidently, the ubiquitous phagocytes and immunoglobulins are not functional in this phenomenon. It is likely that in all cell populations there are clones that are resistant to any given pathogen. The mechanisms involved in the discussed phenomenon are of constitutional i.e. genetic origin.

Mosaic alternation immune and susceptidle cells in the make-up of any organism is formed over the mating of resistant and susceptible individuals that gives rise to progeny with intermediate degrees of infectious loci, the severity of infectious disease [50,181]. These genetically predetermined differences serve a manifestation of heterozygosis: one of the parents, constitutionally immune, grants his (her) descendant the unreceptiveness of some parts of organs to a certain infection, while the susceptible parts of a different molecular setup are inherited from the other parent.

In a population reliant on inherent constitutional immunity to an infectious agent, individuals conveniently divided into three categories:

1) Absolutely resistant organisms, that have no susceptible structures,

2) Mildly susceptible organisms in which a few foci appear and the infection runs a benign course,

3) Organisms in which the number of susceptible structures is large and the infectious process develops in a severe form with formation of many foci of specific infection [4,51].

Differences in severity of the course of infectious diseases and the phenomenon of immune mosaicism are due to hereditary differences in susceptibility to infection as observed clinically. Absolutely resistant organisms do not have any susceptible structures. In other organisms of the same species during infection only a few foci appear and the infection runs a benign course. In the third type the number of susceptible structures is large and the infectious process develops in a severe form with formation of many foci of specific infection [7,51].

EXPLOITATION OF IMMUNE HERITAGE IN CONTRA-INFECTIOUS PROPHYLAXIS

The Myth of Global Annihilating Attacks of Known Infections

Antagonistic coexistence between infectious agents and their victims is a form of parasitism i.e. the existence of a living entity (a parasite) at expense of energy, stoffs and functions of exploited

organism, a victim of the parasite. Parasitism of this kind has very long history just equal to the age of life on our planet. Natural selection for life saving hereditary immunity performed over the cruel coexistence possessed the function of principal driver of molecular evolution, the initial stage of any other form of evolutionary transformations and relevant progression.

Ancient insect eaters, the earliest mammalian ancestors of humankind began evolve around 93.5 mya (million years ago) when tropical forests spread all over the Earth's continents. This stage continued 33.8 my under natural molecular selection that could be performed at the time mainly by alimentary infections as well as by malaria, rabies, tick born diseases, ebola and other infectious agents transmitted by bloodsucking animals [5,16,17].

The stage of further transformation of ancient insect eaters into apes lasted 59.7 my. The later descendants of earliest insect-eaters came to rely on of a plethora edible plant from the forest and this change in diet set the stage for the initial emergence of herbivorous primates. The descendants inherited from their advanced ancestors not only a plethora edible plants and infectious movers but although the results of molecular evolution of hereditary immunity achieved over relevant natural selection [5].

Fresh vegetarian food could not serve as a source of infectious agents dangerous for plant-consuming animals. Vegetarian foraging restricted the interrelation of earliest apes with infectious agents. The tropical forest provided its inhabitants with vegetarian food of quality and quantity necessary for their intensive self-reproduction. Million generations of apes have changed, one after another, during this 59.7 my long period of very slow primate evolution until nearly 100 species of herbivorous apes have evolved including the predecessors of modern chimps, gorillas and Macaques emerged between 23.8–5.3 mya.

The evolution of apes toward earliest Homo sapiens began after the rise of global cooling on the Earth (5.3 mya). The global cooling dried out the former woodland. The tropical forests shrank and replaced by savannah grasslands. These sharp shifts transformed both flora and fauna in very large geographical areas. The existed herbivorous primates (over 100 species of apes) have forcedly lost the forest and appeared in the expanding grasslands. The fauna of the Earth lost 90% of its vegetarian apes within this period of five million years. However, the predecessors of modern chimps, gorillas and Macaques have avoided the worst influence of global cooling as well as subsequent holocaust and selection induced by the savannah environment. They escaped at the remnants of the tropical forest.

The primates in the expanding savannah areas must have faced many new dietary challenges. New ecological conditions forced them to eat whatever was at hand. Instead, the plethora of ripe fruit and other moist tropical products they get the choice to eat either dry grass or the bodies of hunted and dead animals that were extraordinary rich in proteins, carbohydrates, vitamins and minerals. The former fruits eaters have been forced to become the meat-eaters like predators or consumers of carrion [18].

On the other hand, the new way of nutrition brings the new omnivorous feeders in contact with a lot of various animal sources of new food and a plethora of very harmful infectious agents inhabiting the bodies of hunted or died animals. Among these new infectious agents could be named the broad set of bacterial nutritional infections associated with the forage of animal origin (anthrax, botulism, tetanus, salmonellosis, brucellosis, has gangrene, enteral clostridioses and many others).

Most of the infections were absolutely new for yesterday's eaters of tropical fruits. They did not meet the infections before and thus not subjected to the transformation of their molecular constitution through previous selection by new infectious movers of evolution. The set of the above considered data implies that not climate change itself but infectious epidemics which have been conditional upon it, could be primarily responsible for wiping out most vegetarian apes including the Ardipithecus and Australopithecus, the most acknowledged ancestors of future hominids [5,18]. The descent and subsequent extinction of Australopithecus lasted 2.7 my (between 4.5 mya and 1.8 mya).

The Australopithecus predecessors of human chose the last of the two nutritive choices and began to eat the corpses of died animals including relatives. The nearest ape predecessor of future humans began to become a predator and carrion eater. Most Australopithecines perished being unable to counteract the cruel selection and were replaced by first representatives of Homo genus. In the beginning of Pleistocene that has gone 1.8 million years before present time, the last of consecutive species of *Australopithecus genus* went extinct. But some of its mutant descendants appeared to become constitutionally immune and thus were able to counteract all these life-threatening challenges of infectious origin.

The survivors got larger brains and became the founders of Homo genus. The mutual impact of infectious agents and immunogenic selection began in the savannah stage of human evolution (3.5 mya) and led to the appearance of Homo sapiens (1.8 mya). The newborn species of the Homo genus appeared to have been inherited from their evolutionary ancestors the immunity to rabies, malaria, ebola, tick born encephalitis, anthrax, botulism, tetanus, salmonellosis, brucellosis, has gangrene, enteral clostridioses and many others. The infections could improve inherited immunity through natural selection continuously performed by relevant epidemic processes [5,18]. Modern immunology is able to observe numerous of immunological traces of archaic epidemics which could create the Homo sapiens and give evidence of this statement [5,18,26].

Further stage of human progression, the evolution of humankind has performed over its dispersion from the area of its origin toward other parts of the earth [5,18]. According to the generally accepted Out of Africa Theory and its latest development, anatomically modern humans emerged in one place, probably the northern Africa's savannah – Early *Homo sapiens* possessed an anatomical make-up essentially like our own, but the mutual evolution of humankind and its microbial co-actors have not finished at that time [5,18].

Nearly 75,000 – 62,000 ya, some small (20-60 persons) groups of early *Homo sapiens* began to sweep east out of Africa [182], while some other groups continued to stay behind them in the African savannah. In addition, the intra-African expansion should not be ignored, i.e. the possible migration of except for the bipedality inherited from *Ardipithecus* through *Australopithecus*, the early *Homo sapiens* differed from ape ancestors in that they had a far bigger brain, naked body, the ability to run, could use primitive tools and elaborate on them. It also had a crude ability for conscious thought and speech and a short stature with a height of near 1.2-1.4 m, similar to modern pygmies and bushmen [85,183] as well as the traits of hereditary contra-infectious immunity earned and improved over previous stages of evolution [18].

The exodus of ancient humans east out of African savannah and their dispersion around the world initiated new stage of human evolution. Over the dispersion, different groups of humankind appeared in epidemiologically various ecological environments. A part of the initial sapiens tribe moved from the savannah's "Eden" back into Africa's tropical that was the homeland of it ape predecessors [5,18]. In the reawaken tropical environment this branch of ancient humankind met the same agents of natural selection that induced very slow evolutionary transformation of insect eating mammals into herbivorous hominid apes [18].

Other groups began migrations along either South Asian or North Eurasian directions. The south branch of Asian migration has continued toward Australia and eventually reached this continent ~50,000 ya. Since then, the first settlers of Australian continent lost any interrelations with other parts of humankind. For 50 millennia this branch of *Homo sapiens* has been in almost total isolation from other subpopulations of the species [182] as well as from the set of new immune drivers of human evolution (Influenza, Measles, HIV/AIDS, Tuberculosis, Smallpox) that have appeared among the settlers Eurasian continent fare later [184-186]**.** In contrast to Australians, the American subdivision of humankind has split from Eurasians by geographical barriers fare later, nearly 15,000 ya [187].

The new immune/infectious drivers of human emerged among the Eurasian branch of humankind after African, Australian and American subdivision of the species physically separated from Eurasians by geographical barriers. Consequently, influenza, measles, HIV, tuberculosis, smallpox could impact only the evolution of Eurasian part of humankind.

Consequently, influenza, measles, HIV, tuberculosis, smallpox could impact only the evolution of the Eurasians most of whose representatives reveal today the signs of hereditary immunity against all known infectious agents (Figure 7).

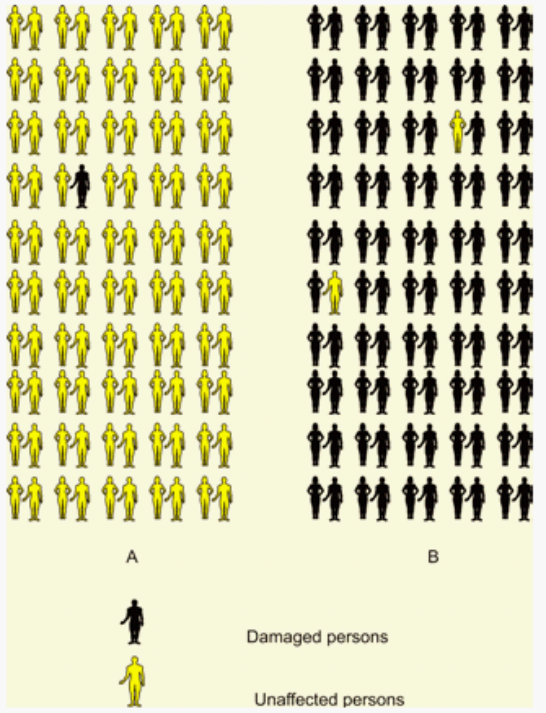

Figure 7: Correlation of died and healthy persons among the populations of medieval London (A) and XIX Century Amerindians (B) after infection with smallpox [14].

The named movers could include in the evolution of Indigenous Americans, Africans and Australians and in the earning of relevant hereditary immunity per interbreeding only under the impact of Grate Geographical discoveries, i.e. about 600 ya when they began to suffer from these infections extraordinary cruelly [184-186]. The set of discussed circumstances allow state the impossibility of global annihilating epidemics induced by known infectious agents.

Debunking the Myth of Bioweapon

A biological weapon is a kind of battle armament, based on exploitation of some living organisms, presumably miicrobes, or biological poisons (toxins) able to damage other living organisms (plants, insects, birds, animals, or humans). In ancient times, some other kinds of living beings, dogs and elephants, were used as the means for international fighting. The list of potential infectious agents of bioweapons is very large. The U.S. Center for Disease Control and Prevention published a list of bioagents that can be used against the human population (Table 4).

Table 4: Official List of Bioweapon's Agents (abridged)

Number	Agents	Diseases
1.	*Bacillus anthracis*	Anthrax
2.	*Clostridium botulinum* toxin	Botulism
3.	*Yersinia pestis*	Plague
4.	*Coxiella burnetii*	Q fever
5.	*Salmonella* species	Salmonellosis
6.	*Shigella*	Shigellosis
7.	*Francisella tularensis*	Tularemia
8.	Pox virus	Variola major (smallpox)
9.	Alphaviruses	Viral hemorrhagic fevers
11.	*Brucella* species	Brucellosis
12.	Salmonella species	Food safety threats
13.	Ricil toxin from *Ricinus communis* (castor beans)	Intoxication
14.	Vibrio cholerae	Cholera
15.	*Rickettsia prowazekii*	Typhus fever
16.	*Salmonella* Typhi	Typhoid fever
17.	*Chlamydia psittaci*	Psittacosis
18.	Staphylococcal enterotoxin B	Intoxication
19.	*Burkholderia pseudomallei*	Melioidosis
20.	*Burkholderia mallei*	Glanders
21.	Alphaviruses Venezuelan equine encephalitis, eastern equine encephalitis, western equine encephalitis	Viral encephalitis

The agents are thought to be used instead of the battle dogs and elephants of ancient wars. Like any other weapon, they can be planned to be used in the battlefield. Potential aggressors have a very large selection of choices here. But the choice is not simple. Infectious agents that can be used as biological weapons are expected to cause sufficient numbers of illnesses and deaths and thus cripple a city, region, or entire population of a country. Anthrax, botulism, and smallpox considered the most serious of those agents. The above-mentioned list accounts for nearly 30 agents/diseases. Some sources name up to 80 of those agents, including influenza and SARS. We may not understand how they made last conclusion, but we should trust them.

A microbial recipe for bioweapons should be able to disseminate them as an aerosol spray. The acting agents of microbial weapons exploited, mostly in the form of very fine dust consisting of dried microbes. Being dispersed in the atmosphere over the target objects, the particles of the dust can be inhaled by victims of the biological attack and induce infectious disease.

The problem is to modify the microbes so that their bodies can be efficiently disseminated in tiny aerosol particles. Plague and most other disease-causing bacteria and viruses are simply too difficult to grow and dispense. The smallpox virus can be responsible for widespread human epidemics because it readily transmitted from human to human by aerosol.

According to the anonimous and non-questioned position of experts, including officials from the Arms Control and Disarmament Agency, bioweapons can rival thermonuclear weapons-possibly producing hundreds of thousands to several millions casualties in a single incident. Mortality levels from a biological attack, both by living microbes and toxins, could also exceed that of a large nuclear explosion [188].

This kind of armament considered undisputedly as the most dangerous letal weapon ever devised. There are speculative scenarios that were created to examine the effects of catastrophic terrorists attacks. The goal of these scenarios is to highlight the needs of society during such events by identifying the potential effects of the attacks.

According to experts, unlike most chemical weapon agents, the kilogram quantities of a biological agent such as the anthrax bacterium can be militarily compared with many tons of a chemical agent like sarin nerve gas. That means a thousandfold advantage of bioweapons over chemical weapons! Besides, the bioweapon's attack would be especially difficult to predict, detect, or prevent. Unlike many chemical agents, the microbial cloud does not smell. Currently, there are no effective atmospheric warning systems to detect its presence. The extraordinary advantage of bioweapons is provided by its capability to annihilate only the targeted living objects.

In 1970, a World Health Organization (WHO) expert committee estimated that casualties following the theoretical aircraft release of fifty kg of anthrax over a developed urban population of 5 million would be 250,000, 100,000 of whom would be expected to die without treatment [188,189]. A 1993 report by the U.S. Congressional Office of Technology Assessment estimated that between 130,000 and 3 million deaths could follow the aerosolized release of 100 kg of anthrax spores upwind of the Washington, D.C. area-lethality matching or exceeding that of a hydrogen bomb [190].

The fear continued to grow. The Biological Weapon Convention, started in 1975, banned the development, production, stockpiling, and transferring of terrible weapons. Nevertheless, the fear of bioweapons continued to increase. Twenty years later, at least seventeen nations were believed to have offensive biological weapons programs [191]. In the beginning of the twenty-first century, the Central Intelligence Agency assessed them as "the world's most frightening weapons"[192]. In his presidential statement of November 1, 2001, President Bush said " we know that the scourge of biological weapons has not been eradicated…Rogue states and terrorists possess these weapons and are willing to use them." Homeland Security Presidential Directive 10, given in May 2004, states the president's view that biological weapons "could cause catastrophic harm."

The fear of bioweapon attacks continued to arise because there were some nations that supported terrorism and had bioweapons programs, for instance Iraq [193]. Today, the fear of a bioweapon attack is a high-priority concern for some governments, the media, most epidemiologists, and many citizens. Assistant Secretary of State Carl Ford, the Director of the U.S. Department of States' Bureau of Intelligence and Research, testified to the U.S. Senate on the

proliferation of biological weapons. “Terrorists interest in chemical and biological weapons has been growing and probably will increase in the near term. The threat is a real and proven. The ease of acquisition or production of some of these weapons and the scale and terror they can cause, will likely fuel interest in using them to terrorize. The transport and dispersal techniques also are manageable and made effective easily, as seen recently in using the mail as a delivery system to spread anthrax. Many of the technologies associated with the development of chemical and biological agents have legitimate civil applications.

The increased availability of these technologies, particularly if a group is already in the United States and therefore not subject to many of the controls in place that monitor and limit the export of these technologies, coupled with the relative ease of producing chemical or biological agents, makes the threat very real. In addition, the proliferation of such weapons raises the possibility that some states or rogue entities within these states could provide chemical or biological weapons to terrorists. It remains unlikely that a state sponsor would provide such a weapon to a terrorist group. But an extremist group with no ties to a particular state (but / which likely does have friends in state institutions) could acquire or steal such a weapon and attempt to use it [194]. Deepening the alarm is the prospect of new genetically engineered pathogens that could be more deadly and more difficult to detect and treat. A 2003 CIA study described the effects of these genetically altered strains as potentially “worse than any disease known to man”[195].

The image of a person diseased with smallpox (Figure 3) is very expressive. It can induce fear and relevant psychological effects. The smallpox virus can be responsible for widespread human epidemics because it readily spread and transmitted from human to human. A person infected with smallpox can infect many others whom he comes in contact with anywhere. Therefore, theoretically, only one infected individual can initiate a worldwide smallpox pandemic.

The most recent speculative mathematical model estimates, for instance, a large scale anthrax attack on a major U.S. city. The model argues the need for extremely aggressive and timely use of antibiotics by all asymptomatic within the dangerous zone [196] or prophylactic vaccination for all citizens made in good time.

On September 8 2009 former Florida senator Bob Graham, former Missouri senator Jim Talent, Sen. Susan Collins, R-Maine and Sen. Joseph Lieberman, I-Conn. initiated on Capitol Hill new round of the discussion about legislation to protect against bioweapon and bioterrorism. On behalf of bipartisan Commission on the Prevention of Weapons of Mass Destruction created by Congress last year the politics declared the Obama administration is working hard only to curb nuclear threats but failing to address the more urgent and immediate threat of biological terrorism.

The commission warns that anthrax spores released by a crop-duster could “kill more Americans than died in World War II”. The government’s efforts “have not kept pace with the increasing capabilities and agility of those who would do harm to the United States,” the Commission’s report says “The consequences of ignoring these warnings could be dire.” Says commission Chairman

Bob Graham, a Democratic former senator from Florida: "The clock is ticking." Commission Vice Chairman Jim Talent, a Republican former senator from Missouri, says: "The fact is, it is only getting easier and cheaper to develop and use biological weapons". Regretfully, the evidence and arguments of above declarations are not disclosed by commissioners. The declarations remained unsubstantiated.

The Obama administration asked for $305 million in its fiscal 2010 budget request. "Insufficient by a factor of 10," the report says. Disease surveillance programs fall short. The government needs to invest in rapid diagnostic tests to "improve the nation's ability to treat people by providing a more timely and accurate diagnosis" — something that can be critical to treating the victim of a biological attack. The failures on biosecurity policy by the White House the Commission says have left the country vulnerable.

Meanwhile, since Baghdad fell on April 9, 2003, U.S. and U.K. forces have been unable to find any traces of Iraq's biological weapons. A large discrepancy has arisen between prewar descriptions of the terrible threat and what has been discovered in the year since the war. Did the proposed bioterrorist possess bioweapons or not? If he did, why had he preferred to disarm himself? Is it likely that Iraq could have destroyed, hidden or sent the tons of biological weapons and facilities engaged in the ongoing production of these weapons (that officials claimed were present) out of the country? There are so many questions but there is only one crucial question that, if answered, can give a key to solve each of the others. What real effect can be achieved by every kind of bioweapon? Finally, the confusing situation brings about an unexpected question: do bioweapons really possess the proclaimed mass annihilating capability?

Five sources of evidence can be used to substantiate the answer to the above question: 1) the history of epidemics, 2) the results of some accidental, experimental, and real exploitation of bioweapons, 3) data on genetic immunology, 4) an evolutionary ecological interpretation of all the data in the aggregate and finally 5) evidence of the Soviet bioweapon disarmament.

Anthrax bioweapon. One terrorist group, the Aum Shinrikyo cult, embarked on its campaign of bioterrorism in April 1990. In 1992, the cult began culturing anthrax. The next year, it disseminated anthrax spores in Japan, apparently with the aim of killing a large number of people. All 8 attacks failed to produce illness [197]. Mass annihilation did not happen. The lack of success in real exploitation of the biological weapon by Aum Shinrikyo was explained by difficulties in making of effective bioweapons devices. Samples of Aum Shinrikyo cult spores were obtained from the release site in Japan, cultured and characterized by molecular genetics typing. The isolates were consistent with a well-known non-pathogenic vaccine strain, Sterne 34F2, which has been used in Japan for animal prophylaxis against anthrax [198]. It is not easy to make a bioweapon. Most experts concur that the manufacturing of a lethal anthrax aerosol is beyond the capacity of individuals or groups without access to advanced biotechnology. However, autonomous groups with substantial funding and contacts may be able to acquire the required materials for a successful attack.

However, information about the effectiveness of professionally created, weaponized anthrax spores does not concur with the worst-case scenario of human devastation. In 1979, an accident inside a biological weapons production factory in Sverdlovsk, U.S.S.R., caused military-grade anthrax to waft out in a plume over a city of 1.2 million [199]. The source of the aerosol was at the military microbiology facility located in the southern area of the city. According to a retired counterintelligence officer, General Andrey Mironyuk, on the day of the accident, an operator in the facility switched on a ventilation system without switching on the filtration system and thus allowed the military-grade anthrax aerosol to rush out of the work box [200]. There was a northerly wind blowing from the facility to the southern city limit. The aerosol cloud that formed then proceeded from the military facility over sixty km to the southernmost suburb [201].

Most of the fatally affected people lived or worked in a zone up to one km wide and four km long, extending from the source of the aerosol to the southern city limit. Approximately 7,000 people lived in the area of doubtless deadly concentration, marked by the daytime location of people who contracted the anthrax disease. Meanwhile, experimental evidence suggests that following an outdoor aerosol release, persons indoors exposed to a similar threat as those outdoors. Inside the zone, the effect resulted in a total of approximately 68 fatalities from anthrax and eleven survivors of a light form of the disease [201]. Thus, the accident demonstrated the lethal potential of anthrax aerosols on 1 percent of exposed peoples (Figure 8).

Figure 8: Correlation of damaged and unaffected persons among Sverdlovsk population exposed to weaponized anthrax aerosol [14].

In the distance between four km and sixty km, the deadly cloud could kill only sheep [201], which are more susceptible to anthrax infections than humans, dogs and pigs are. Meanwhile, unlike the dogs, pigs or other carnivorous animals, only sheep were used for trials of the anthrax

bioweapon, which have been performed for many years on the top-secret Soviet testing ground for the open-air testing of bioweapons, located in the midwestern part of the Aral Sea, on the Vozrozhdeniye Island, Kazakhstan, U.S.S.R. One should note that all of the affected citizens were over twenty-three years old. Paradoxically, children and teenagers certainly seemed more resistant to the infection than adults [200]. Analogous paradoxical increasing of individual constitutional susceptibility with age is only characteristic of meningococcal infection [202].

Thus, near only 1 percent of the population of 7,000 people contracted the anthrax infection as the result of the accident. Even the dispersal of professional, military weapons-grade anthrax did not guarantee mass annihilation among the exposed population. Even a mass release of weapons-grade anthrax, therefore, does not necessarily mean mass deaths.

The October 2001 anthrax incidents in the U.S.A. were consequent to the dispersal of anthrax spores by means of posted mai1 [44,45]. Bacillus anthracis spores intentionally distributed through the U.S. postal system. Reportedly, the samples of several grams contained extremely high concentrations of anthrax spores and were included in the particles, most of which were under five microns in size. This size is optimal to facilitate easy aerosolization and subsequent aspiration by humans. This professional recepture was better than that found in the U.S.A. and Soviet bioweapons programs, especially in terms of the purity and concentration of spores. High-quality dry powder contained 100 percent pure anthrax spores. The anthrax strain contained in all envelopes was the same, the well-known Amen strain. It became available to the U.S. biodefense program in the early 1980s. The October 2001 anthrax-tainted letter attacks on the East Coast of the United States highlighted the real danger of biological weapons exploitation by terrorists.

The attack induced twenty-two cases of anthrax. The cases were identified in residents of seven states on a territory stretched out over 1000 km along the very populated East Coast of the United States: Connecticut (1 case), New York City (8 cases), New Jersey (5 cases), Pennsylvania (1 case), Maryland (3 cases), Virginia (2 cases), and Florida (2 cases). One can think that somebody sent anthrax around the main part of the country. Thus, the first major bioterror event in the modem history of mankind induced only twenty-two cases of anthrax (five people were killed and seventeen other people became ill [45]. Twenty-two people fell ill, of whom five died, in a U.S. population of 275 million.

This incident declared “the fatal anthrax attack on the United States”. News agencies throughout New York City inspected for anthrax contamination. The anthrax letters killed five people, but paralyzed political activity for some days. Only four envelopes containing anthrax spores recovered, although there were possibly more. All the letters mailed from a mailbox located at 10 Nassar Street, Princeton, New Jersey, U.S.A. The entire country ensnared in the anthrax scare. Letters containing weaponized anthrax sent to the offices of U.S. Senators Tom Daschle of South Dakota and Patrick Leahy of Vermont and to television news anchors Tom Brokaw and Dan Rather. Post offices became relay points of anthrax spores and the U.S. House, Senate, Supreme Court and the White House inspected for evidence of the disease.

The processing of the envelopes by postal machines led to exposure of postal workers and to the contamination of facilities. Consequently, the largest numbers of infected persons were postal workers. In media and governmental facilities, the processing of the envelopes and letters led to exposure of some workers, co-workers, and visitors as well as to contamination of facilities. In most of the facilities, the level of contamination was recognized as medically insufficient and too small to induce human infection. A letter sent to Senate Majority Leader Tom Daschle tested positive for anthrax as the bioterrorism scare rattling the nation reached the halls of Congress. Daschle was in the Capitol and not exposed to the letter, which opened in his other office a block away in the Hart Senate Office Building. Nevertheless about forty other people were in his office when the letter opened. Nobody has been affected by the disease. Meanwhile, by evidence of antibody response, the number of individuals exposed is guessed at several hundred in Senate offices [203].

Although the total number of contaminated envelopes distributed not known with any certainty and the quantity of dispersed anthrax is also not certain, the epidemiology of the illnesses and deaths implies that spores situated not only in the mail envelopes but also in the air of different postal, government and media offices. Most of the victims became ill after exposure in places where they worked or had visited, yet hundreds of co-workers and other visitors did not become ill. For example, 170 employees were present inside the Mail Processing and Distribution Center (New Jersey) when the B-anthracis-contaminated envelopes were sorted on October 9, 2001, but only two of 170 employees became ill [44]. The rate of infection among this contingent was 1.2 percent. Thus the incident demonstrated that anthrax aerosol possess the diseased potential on 1.2 percent of exposed persons. The same quantitative correlation observed in Sverdlovsk (Figure 8). Like in the case of Sverdlovsk incident, the anthrax aerosol used manifested very high injury potential but only against two of 170 coworkers (1.2 percent).

Robert Stevens, sixty-three, a citizen of Florida, was the first person who died from the 2001 anthrax attack. He worked on the third floor as a photo editor at a media company, which employed about 300 people. He entered the hospital with flu-like symptoms and died three days after. Traces of anthrax microbes were found both in Stevens' work space and in the company mailroom located on the first floor.

Other people who worked in the building or visited it for extended periods of time have also been tested for the anthrax disease. But only tests performed on a mailroom employee, Mr. Ernesto Blanco, seventy-three, found that he felt ill and exhibited flu-like symptoms at work. He also infected with anthrax. Mr. Blanco became the second of two victims of the anthrax attack on the collective accounted 300 people (less than 0.7 percent). He spent three weeks in the hospital and was once near death. Stevens believed to have contracted the disease after inhaling anthrax from a tainted letter. Investigators believe the letter sent to the enterprise offices.

Thus the doubtlessly lethal concentration of anthrax spores existed in the company offices, but among 300 company staff personal, the dispersed bioweapon agent could damage only

two victims, i.e. less than 1 percent, comparable with those observed in Sverdlovsk (Figure 8). Nevertheless, in the weeks following the incident, the fear of anthrax became daily occurrences in Floridian life. As a result of the fear, the state passed a law that anyone convicted of delivering an anthrax threat could get fifteen years in prison.

Thus, the October 2001 anthrax attack of bioterrorism on the U.S.A. East Coast persuasively illustrated both the real level of anthrax bioweapon effectiveness and the ability of society to respond adequately to epidemic threats of this kind. The events in the United States in the fall of 2001, with identification of anthrax in the United States Postal System, should induce a new sense of awareness for the potential of biological terrorism and warfare. After the attacks, Congress approved a twenty-fold increase in biodefense research funding within the National Institute of Health. Changes also have occurred in the small but growing world of scientists who work with anthrax. Methods of diagnosis, treatment and cleanup improved and anthrax funding and research increased.

Some experts concluded that this method of the anthrax distribution is not capable of producing mass dissemination of infectious agents and mass annihilation of victims. Meanwhile by evidence of antibody response, the number of individuals exposed guessed at 50-100 among postal sorting workers and several hundred in Senate offices.

Thus, the 2001 terrorist release of anthrax also failed to cause mass annihilation. Nevertheless, it created a scare. The resulting wave of general hysteria, with civilians buying up gas masks and ciprofloxacin as if there were no tomorrow, established beyond a doubt that these microorganisms are today remarkably successful as instruments of mass terror [199]. Their potential as weapons of mass annihilation, however, was not confirmed by these attacks. Thus, the potential threat of anthrax as a bioweapon was greatly exaggerated. But the cost for decontamination of the U.S. Senate office building was $42 million and the prospective cost for the decontamination of the three most effected U.S. postal facilities is now estimated at over $150 million [203].

This confusing situation foretold, for instance, by studying any popular book about Robert Koch's life in medicine and bacteriology. Since 1869 Dr. Koch served as Medical Officer for Rackwitz, Wollstein district, Germany. Anthrax was, at that time, prevalent among the farm animals in the district and Koch embarked, in spite of the demands made on him by his busy practice, on a study of this disease. He confirmed the work of others who had shown that the disease can be transmitted by means of the blood of animals suffering from anthrax.

The Koch family lived on the upper floor of a two-story house. The living quarters consisted of four large rooms and a kitchen. In addition to the three front rooms, in the rear of the left was a larger room and on the right the kitchen . The large room in the left rear served as Koch clinic, the patients waiting on the landing outside until called to be examined. It was here (Figure 9) that Koch carried out the epoch-making researches on anthrax which placed him in the front rank of world scientists.

Figure 9: Dr. Robert Koch at his anthrax workplace.

The patients from farms have provided him with flesh of animals diseased by anthrax. By means of microscope Robert Koch can confirm the presence of appropriate bacillus in these objects (Figure 9). Here Dr. Koch inoculated mice with blood taken from the spleens of farm animals that had died of anthrax. When Koch's research on anthrax began to become ever more dominant, his wife divided the room into two parts with a curtain. Only wife and daughter permitted by Koch to enter the workroom behind the curtain. The patients were examined before the curtain [204].

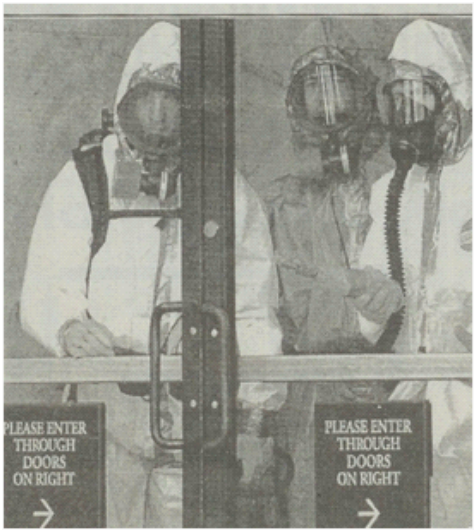

Figure 10: Routine equipment of today's investigators of anthrax.

Undoubtedly, the workers of today's anthrax laboratories (Figure 10) should be embarrassed by absolutely insecure conditions existed in and around the Koch's work place. However, nobody

has been diseased by anthrax among Koch family and numerous patients of this country physician.

The Smallpox Bioweapon. Unlike anthrax and botulism, smallpox is a contagious disease. It is able to transmit from a diseased person to surrounding healthy people, thus forming chains of secondary infections. The ease of transmission of this agent and rapidity of its spreading in a sensitive population all promise significant advantages for its exploitation. Among those agents included by the Center for Disease Control and Prevention in the "Class A Bioterrorist Threats" (Table 4), smallpox is placed among the most dangerous. Accordingly, every scenario of smallpox bioweapon attacks includes gradual accumulation of' diseased humans leading to a subsequent catastrophe. For example, according to a scenario of a terrorist attack [205] during a meeting of some hundred people took place in a city of 2.5 million people, the first dozens of diseased people begin to appear at the end of smallpox incubation period, i.e. two weeks after the attack. Two weeks later, hundreds of secondary smallpox cases appear. Third wave of secondary cases will consist of thousands of infected people. The fourth wave will account for dozens of thousands of people and so on. The process escalates from a local outbreak to a national epidemic and finally to a global pandemic. Because most of the world's population has not been vaccinated and is considered as susceptible to smallpox infection, we are all ultimately at risk [206].

According to Johnson, 2004 [207], in the beginning of 1970, near a small atoll in the south Pacific, a thousand miles southwest of Hawaii, American forces performed a highly secretive test of biological warfare and weapons. A small amount of smallpox powder was released in the few minutes a plane shot across the several miles of barges carrying hundreds of rhesus monkeys. A thin, long curtain of powder swept past first one barge loaded with monkeys, then, at increasing intervals, another and another, finally passing the most distant barge nearly fifty miles away. Over the next few days, half of the monkeys died. Even those positioned fifty miles away from the lay down were not protected by distance. Anyone watching the test that day knew beyond any doubt that smallpox biological weapons really worked and it used to kill millions of people. As for my opinion, the test showed beyond any doubt that this kind of bioweapon can kill half of the blighted rhesus monkeys. A very important question arose immediately, why could the other half of the exposed rhesus monkeys resist the lethal attack?

In reality, the deliberate testing of military weapons-grade smallpox in July 1971 caused an outbreak of small pox in Aralsk, Kazakhstan, U.S.S.R. The incident was recently confirmed by academician P.N. Burgasov, a former chief sanitary physician of the Soviet Union and for many decades, one of the leading specialists in the development of defenses against bioweapons. Aralsk, a city of approximately 50,000 people is located on the northern shore of the Aral Sea in Kazakhstan. From 1936 to 1992, the top-secret Soviet testing ground for the open-air testing of bioweapons, was located in the midwestern part of the Aral Sea, on the Vozrozhdeniye Island. In November 2001, Dr. P.N. Burgasov was interviewed by the Moscow News newspaper [208].

According to the interview, just before the time the outbreak in Aralsk, 400 grams of the strongest formulations of the smallpox weapon were exploded on Vozrozhdeniye Island. A

research ship of the Aral Sea fleet with a crew of twelve came within fifteen kilometers of the island. A young woman, the laboratory technician aboard the ship, took samples of plankton twice a day from the top deck. The ship was clouded by aerosolized smallpox carried by winds from the rest site, located nine miles away from the ship. The woman become ill despite having been vaccinated against smallpox, yet eleven other members of the ship crew were apparently not made ill. One can account that the weaponized smallpox aerosol covered the ship and its concentration was undoubtedly injuring, but only for one of twelve members of the crew.

After returning home to Aralsk, the women infected several people, including children. In addition to the initial case, nine more people contracted the secondary infection and three of them died (the three who died were all unvaccinated). Seven of the ten people who became ill had signs of previous vaccination against smallpox. Another 50,000 citizens escaped the danger. The incidence of infection in the city was 0.02 percent.

Botulinum Toxin Bioweapon. Botulinus toxin is the most poisonous substance known and is considered potential biological weapon. The Aum Shinrikyo cult disseminated the botulinum toxin in Japan, yet, all the attacks failed in the sense that mass annihilation did not occur [209]. A lack of information does not allow a definitive statement concerning the probable causes of the failure to cause casualties. Some experts propose that due to the complicated nature of production and dissemination of botulinum toxin it is inherently a poor weapon of mass annihilation [209,210]. They invoke technical, technological and meteorological influences, as well as chance to explain the small number of casualties in the cases where these three kinds of bioweapons used. As for my opinion, there are more important reasons why botulinum toxin is a weak weapon. Natural biological reasons should also be taken into consideration.

When a Soviet medical military institute began an elaborate defense against botulism, the investigators faced a need to know from which type of botulism (A, B, C, D, E, or F) the defenses should be developed. Extrapolation from animal studies was uncertain. The investigators performed the dangerous, difficult but extraordinary precise work on themselves and demonstrated that although botulism type A is more dangerous for men then types B, E and especially C and D are, humans seem over 500-1000 times more resistant to type A botulism than horses, rabbits and guinea pigs are. This data interred the idea to use the botulinum toxins as a bioweapon of mass annihilation. Also, for botulinum toxins, dogs are the animal model most relevant to humans [47,27]. Meanwhile, only horses were used before for trial of botulinum bioweapons that have been performed for many years on the top secret Soviet testing ground for the open-air testing of bioweapons located in the midwestem part of the Aral Sea, on the Vozrozhdeniye Island, Kazakhstan, U.S.S.R.

The Emperor Has Nothing on at All! The data considered above shatters the myth of the highest annihilating capability of the bioweapon. The conclusion is also confirmed by the row of the recent extraordinary political events, for instance by the collapse of the Soviet Union and the

Soviet bioweapon disarmament. In the light of above information, the fear of bioweapon seems extraordinarily exaggerated and inflated.

Quite naturally, the idea has come to reconsider the present grandiose but doubtless superfluous efforts undertaken everywhere in the world. The healthcare system should return its paramount attention to the prevention of regular epidemics. But, before this opinion can be accepted, we must make clear the reasons of the profound, worldwide delusion about the mass annihilating capability of the bioweapon. We must argue our interpretation of the above observations, taking in our hands the light of modern knowledge, first of all the modern achievements of epidemiology, immunology, genetics, and evolutionary theory: What were the reasons of so profound delusion?

Bioweapon has been proclaimed as an extraordinary means for the mass annihilation of humans able to rival thermonuclear weapons-possibly producing hundreds of thousands to several millions of casualties in a single incident. Meanwhile all arguments for its highest annihilation capability are based on some of the most impressive data selected from the ancient history of epidemics and on the speculative supposition that all people without any exception are susceptible to any bioweapons infectious agents. But this supposition is a result of a profound worldwide delusion, falsehood or ill-intentioned fear, supported presumably by deficits of our knowledge or terroristic organizations like Al Qaeda.

The data of the history of epidemics, clinical and genetic observations, as well as data from experimental investigations and recent results of some accidental, experimental and real exploitation of bioweapons, interpreted from the point of view of recent achievements in discovery of hereditary imminity, does not confirm them as having mass annihilating capabilities. Moreover, their ecological and evolutionary analysis shatters the myth of their extraordinary annihilating capability as bioweapons.

Thus, evolutionary and ecological analysis of botulism, anthrax and smallpox epidemiology foretells that this kind of bioweapon, unlike nuclear weapons, cannot be a means of total or even mass annihilation of humans. The relevant data concerning the evaluation of anthrax, smallpox and botulinus bioweapons confirmed the foretelling. Hereditary immunity constitutes our best line of defense against epidemics as well as bioweapons too. This kind of individual and population defense against mass annihilation by bioweapons and epidemics has already been invented by the previous evolution of humankind [9].

There are reasons to account that, in relation to any epidemics, the susceptible part of worldwide population accounts to no more than 10 percent, whereas over 90 percent are saved from illness by their inherent constitutional features. In the case of anthrax and smallpox the number of defenseless people should be estimated approximately to 1 percent.

Taken together, the above data provides strong evidence for a profound delusion about the real potency of bioweapon. The availability of constitutional genetic immunity significantly removes any major threat of bioweapon exploitation both by terrorists and aggressors. The only way to

provide the battle efficacy of bioweapons is to identify and attack the genetically defenseless. Really, in the case of individual terror, a terrorist should know to which one of over 80 bioagents the target person is susceptible. In the case of mass terror, a terrorist organization should know to which one of over 80 bioweapon agents the target population is most susceptible. Could anybody get a victory by means of a bioweapon based on the Spanish influenza virus that was able to kill, in 1918-1919, an estimated 1 percent of worldwide population [211]. Only a mad general will risk a victory using a weapon that is able to destroy nearly 1 percent of his enemies [9,12-14].

One can suppose that some experts are considering the danger of bioterrorists using genetic engineering to make viruses or bacteria more deadly or contagious. There will be the constant danger that newly engineered pathogens could escape from the lab. Our experience allows us to be skeptical about the prospect of genetically altered superbugs. Extraordinary diversity in the molecular constitution of people will restrict the injurious effect of genetically modified agents of bioweapons too [14]. The barriers will act beginning with intra-laboratorious stage of the modification. The effect cannot be provided by any modification but only by change of injurious effect of infectious agent. The modification must present to the consumer evidence of the efficacy of proposed agents against a population that is planned to be terrorized.

Why all the hysteria about biological weapons in the first place? And why is America spending billions to defend against a large-scale bioattack that will almost certainly never come? All of this for a threat that is more psychological than real. We don't understand why they do this, but should we trust them? That's not a scientifically addressable topic.

The Soviet government was probably the first to understand the impotence of infectious agents as a weapon of mass annihilation and decide to close the programs of bioweapon development and production. Despite previous extensive efforts, it radically discontinued their bioweapon program. As a result all the top-secret centers and facilities for development and production of bioweapons as well as the testing ground for the open-air testing of bioweapon (Vozrozhdeniye Island, Aral Sea), do not exist anymore. Many former Russian bioweapon specialists are now out of work or toiling of menial jobs. Two leading agents of "Biopreparat," the giant Soviet system for development and production of bioweapons arrived in England (V.A Pasechnik, 1989) and the U.S.A. (K. Alibekov, 1992) together with relevant technical documentation and began to proclaim the danger of biological weapon. Nobody tried to hinder them [14].

Unfortunately, so many people and authorities continue to be hypnotized by misinformation distributed by victims of scientific delusion as well as by para-scientific swindlers and apologists of worldwide terror. But Saddam Hussein did not trust the information. He did not try to produce or use bioweapons. One should think he had very competent advisors [13,14].

We should admit the reality too. We should admit it the sooner, the better. One can worry that admission of the real situation will lead to radical change in many biodefense programs. That it is now time to rein in the horses. The new knowledge requires new decisions. According to

President Bush's proposal, Project BioShield will have many applications beyond its immediate goals. As scientists work to defeat the weapons of bioterror, they will gain new insights into the workings of other diseases. This will also break new ground in the search for treatments and cures for other illnesses. This could bring great benefits for all of humanity, especially in developing countries where infectious diseases often go uncontrolled [212].

Debunking the Myth of Bioterrorism

Biological weapon can be planned by terrorist to be used against some individual, a group of individuals, or apopulation of a city, a region or a country. Like any other weapon, they planned to use both in the battlefield and in local terrorist attacks (diversions, individual terror). Potential routes of bioattack include inhalation of aerosols, aquatic contamination, food adulteration and terrorist-to-victim contact, including injection by parasol. The availability in humankind of hereditary immunity significantly removes any major threat of bioweapon exploitation both by bioterrorists.

In these circumstances, the impact of bioterrorism on a community cannot be economically, medically and culturally devastating. Bioterrorism requires control of morbidity and/or mortality after an exposure to a potentially harmful agent or toxin. This situation cannot be changed by worldwide diffusion of biotechnology and the accelerating pace of scientific progress in microbial genomics and genetic engineering that could be misdirected to develop novel pathogens which are not only deadlier than natural strains, but could defeat standard vaccines, antibiotics and other countermeasures. In these circumstances, bioterrorism idea can only become a political skillful swindling [13,14].

Infectious agents might be successful as instruments of psychological terror against uninformed contingents and populations. The main force of bioterror today is fear of the unknown. This kind of danger is real but minimized by the spread of relevant knowledge. The danger of being injured by artificially induced infection still exists theoretically for a small portion of the modern world populations too. To be able to counteract the danger, society needs to know which member can be infected and which will not [13,14].

Don't Cry Wolf on Every Sneeze

Since 1976 a sequence of frightening epidemic forecasts began to shake deeply the health systems of nations and emotional wellbeing of the people. The unprecedented 1976 worldwide campaign to protect the nations against the H1N1 flu pandemic has been induced by unsubstantiated prediction. Near 43 million Americans were vaccinated against epidemics that never materialized for the nation. Analogous programs performed in many developed countries. Nobody was able at that time to prognosticate the further development of an army base small influenza incident.

Regretfully, nothing was done over past three decades to launch the ability. What is more, the

goal was out of the scope of WHO and all national health authorities. Meantime, the lack of WHO ability to prognosticate pandemics has been demonstrated also with HIV, SARS, anthrax letter attacks of 2001, avian influenza H5N1 and "swine" influenza H1N1 2009 as well.

Modern humankind has periodically experienced small outbreaks of infectious diseases that were unknown before and have threatened public health security: mad cow disease, AIDS, Salmonella DT 104, Lame disease, hantavirus and the West Nile virus, severe acute respiratory syndrome (SARS), as well as avian influenza, the so-called "bird flu," Ebola fever, the Marburg virus, Lassa fever and Nipah, a henipavirus. Each of them has been immediately proclaimed as a modern "Plague" and prospective agent of bioweapon. For instance, the forecasted SARS pandemic often referred to as a global public-health catastrophe. This ominous forecast induced a relevant preparedness. In response to each of these episodes, the World Health Organization has updated its guidelines and governments worldwide have pushed relevant plan of bioterrorism preparedness to the tops of their political agendas.

Despite the omninous forecast, none of these bugs did quite make the proclaimed devastation. For instance, SARS caused about 700 deaths in different ends of the world and was a serious illness for about 8,000 people that had also been affected. But it was a far from a global public-health catastrophe. Analogous events were observed in the cases of mad cow disease, Salmonella DT 104, Lyme disease, hantavirus, the West Nile virus, avian influenza, Ebola fever, the Marburg virus, Lassa fever and Nipah, a henipavirus [13].

All the announced calamities challenged profoundly the health economy and people's emotional wellbeing but never have materialized. All the frightening forecasts were not supported by scientific evidence. What is more, such insubstantial prognoses destroyed the people's trust in the plausibility of epidemiologist's declarations: remember the Aesop fable "The Shepherd Boy and the Wolf". Meanwhile, the lonely realistic votes could not be heard.

The confusions arose for the reason that foretellers based their forecasts presumably on the structural "novelty" of the discussed infectious agents whereas the real ability of any bug to induce infectious disease is determined in equal range by mutual chemical, stereo-chemical and biochemical complementariness of both infectious agent and the victim of its aggression.

Why all the hysteria about another next pandemy is in the first place? Why does America spending billions to defend against a large-scale globall epidemics that will almost certainly never come? All of this for a threat that is more psychological than real. However, president Obama put the danger of local Ebola epidemics over any other issues threaten humankind at 2014 and allowed the spend of 5.5 billion for the fight against it.

It is a time now to break the sequence of such humiliating impotencies and begin to launch the substantiated forecasts. The goal is achievable now. Some basic approaches to the problem have been presented since 1976 in dozens of scientific articles but especially in recent book entitled

"Hereditary Immunity: Fundamental Principles and Exploitation in Life Study and Health Care". New York: Nova Science Publishers, 2008. Special chapter of this book is devoted to the forecast of epidemics.

Super-Excessiveness of Total Prophylaxis

The fear of epidemics both reemerged and discovered just recently continues to be a permanent high-priority concern for humankind. This old fear is now extraordinary aggravated by reemerged threat of bioterrorism. To counteract the threat the USA and some other countries are undertaking many extraordinary efforts to develop, improve, produce and distribute many vaccines. But the exploited principle of total vaccination, main principle of traditional strategy of vaccination, has not been planned to be modernized. Meanwhile, there are many reasons for optimization. Human population is very diverse in terms of genetic susceptibility to any infectious disease. Over 90% of World-wide population possess inherent immunity to all known infections and thus do not need to be vaccinated. Far less than 10% of any populations do not possess hereditary immunity. The morbidity and mortality conditioned by infections is predestined by existent minority of genetically defenseless individuals and isolated ethnic groups. That means the principle of total vaccination is at least 10-fold more excessive then real necessity.

According to the CDC's recommended immunization schedule, every child must receive 36 shots containing a total of 126 vaccines from birth through six years of age (Figure 11). This is quadruple the number of vaccines a kid received in the 1980's. In 1983 a child received only 10 shots containing 30 vaccines. Beside, this quadrupling of the vaccination schedule does not guarantee ultimate decrease of childhood morbidity and mortality.

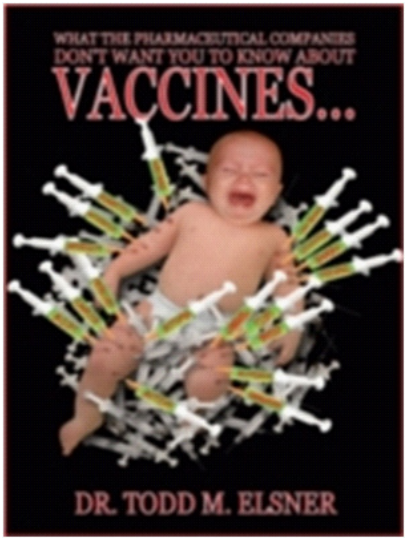

Figure 11: The cover of the book "What pharmaceutical companies don't want you to know about vaccines.

The total mandatory vaccination reveals its 5-10-fold excessiveness especially in early childhood and over school years. For instance, the hepatitis B vaccine is given immediately after birth for the prevention of hepatitis B—which is transmitted by either intravenous drug use or sexual intercourse. At the same time the adult vaccination against hepatitis B is not mandatory.

Vaccination against pneumonia is far more excessive. For some years anti- pneumonia prophylaxis is performed by a vaccine named Prevnar 7 which contains the antigens of seven different serotypes of Streptococcus pneumoniae. The complex vaccine was thought to be able to protect against these serotypes. By the way, every person needs to be protected only against one of seven strains. Other are expensive for them.

Meanwhile, in 2000, researchers have found that nearly two thirds of invasive pneumococcal disease cases in young children caused by six other serotypes not included in that vaccine. Those serotypes, along with the original seven, incorporated into Prevnar-13 intended for children aged 6 weeks through 5 years. Now these days every healthy child will be injected with 13 antigenic complexes instead of one that he/her is possibly in need.

A proposed FDA formulation of next year's seasonal 2010-2011 flu vaccine will be built to protect against three strains of flu, that will be circulating next fall and winter. Swine flu is to be one of the strains incorporated into the vaccine.

Besides, total prophylactic of infectious diseases, a traditional kind of biodefense, is extraordinarily expensive but greatly unsuccessful. For instance, despite the mass vaccination performed yearly, it appears to be unable to protect neither the population nor individual from seasonal influenza. According to the CDC claim, the seasonal flu takes 36,000 lives every year. What is more, it is extraordinarily excessive.

Defend the Defenseless

In the relation to any infection, we need to know who is at risk today. In order to realize the vision, everyone would have to be tested for his/her constitutional immune status. Anyone who might be exposed to infection should be offered information relevant to their constitutional immune status. Individuals identified in order to determine who does not possess genetic immunity and therefore, requires vaccination or other prophylactic measures. Informed people should have the choice of getting a vaccine or not. Those who are naturally immune should not be subject to these procedures, which are not always harmless and society should be spared the considerable expense of carrying them out on a population-wide basis. We must change the mentality about vaccination and begin to defend only the defenseless. Both the necessity and permissibility of each vaccine inoculation should be motivated individually by testing for constitutional defenses. The final decision concerning vaccination could then be well-founded and made for each individual case. The principle of total vaccination exploited today should and can be changed by the principle of individually motivated immunization based on genetic indications. The plans of anti-infectious prophylaxis must be strongly individualized.

Sensitive and rapid tests to identify constitutionally susceptible individuals could allow the targeting of prophylaxis only to those in need. Today's medicine must and can be able to perform this new approach to disease prophylaxis. Special means must be developed to assess constitutional mechanisms of genetic protection. Thus the prevention strategies should be focused on vulnerable members of a population. The main goal of modern prophylactic medicine should be the identification and defense of the defenseless ones. Vaccination strategy should evolve given the changing dynamics of infectious diseases. Should we vaccinate all of our country's inhabitants without exceptions? Who should be vaccinated? Who should be spared from the procedure?

Hereditary immunity has played a major role in the history of mankind over the hundred centuries and millennia. Today its protective capability is able to defend the majority of humanity from mass annihilation both by epidemics and bioweapons. Given these circumstances, the main goal of modem prophylactic medicine is to identify and defend the defenseless ones. The danger of any pandemic's attack should be faced with open eyes.

Before the beginning of a comprehensive vaccination plan, we need to know who is at risk and who is not. That means that everyone should be tested for his/her immune status ahead of time. Special attention must be devoted to constitutional mechanisms of genetic protection. At first, we must identify susceptible individuals, in order to determine in advance which members of a community do not possess genetic immunity and therefore require vaccination or other prophylactic measures. Sensitive and rapid tests to identify genetically susceptible individuals could allow for the targeting of prophylaxis only to those in need.

The progress in the knowledge and exploitation of genetic immunity will doubtless change the strategy and tactics of the fight against epidemics. It is becoming clear that the best way to counteract natural epidemics is to identify and defend the defenseless minority. At the present time we can assess the proportion of constitutionally susceptible members in a population only by the registration of diseased persons. For many years constitutional immunity has been considered beyond both comprehension and exploitation. The defective knowledge of this front line of anti-epidemic defense formed the source of the existed delusion about bioweapons. The situation is beginning to change, [4,24,25] for example, as a gene conferring constitutional immunity to HIV was found in representatives of the Euro-Asian population, in contrast to that of the native inhabitants of sub-Saharan West Africa [80,213].

Testing for Individual Risk

To be able to counteract and minimize the danger of epidemics, society needs to know which member infected and which will not. The growing knowledge about individual genetic immunity inspires the development of methods that allow a more precise delivery of prophylaxis - including vaccination - to those who need it. Recent successes of immunology suggest that it will be possible to identify susceptible individuals without waiting for them to be infected. The state genetic resistance to an infection can be revealed by the lot of methods (Table 5), approved, for instance,

in the cases of HIV/AIDS, malaria, influenza, tuberculosis, botulism, salmonelloses, meningococcal infection and many others.

Table 5: Principles, methods and means for diagnosis of hereditary immunity [5].

Principles	Methods	Means		Results
		Agents	Objects	
Integral	Epidemiological Observations	Natural microbe population	Species, Populations and persons	Integral (hereditary and reactive) immunity of species, populations and persons
	Clinical	Natural microbe population	Persons, organs, tissues	Integral (hereditary and reactive)immunity of persons, organs and tissues
Analytical	Experimental	Cultivated microbes or their molecules	Cultures of organs or tissues	Integral (hereditary and reactive) immunity of persons, organs or tissues
	Histological	Cultivated microbes or their molecules	Cultures of cells; organoids	Hereditary immunity of cells or organoids
	Cytological	Cultivated microbes or their molecules	Cells of potential victim	Hereditary immunity of cells
	Cytological			
	Cytological			Hereditary immunity of cells
	Molecular ecological	Microbial molecules	Molecules of the organism	Hereditary immunity of molecules
	Molecular anatomical		Molecules of the organism tested	Hereditary immunity of molecules
	Molecular genetic		The genome of the organism tested	Genes of hereditary immunity

For a long time, we were able to assess the rate of a population's constitutional predisposition to infection only by registration of diseased persons. For many years constitutional immunity was out of the mainstream of immunology. It considered as being beyond both comprehension and utilization. Now the situation has begun to change, especially after the gene of constitutional immunity to AIDS found in representatives of the Euro-Asian population, in contrast to that of the native inhabitants of sub-Saharan West Africa. The states of genetic immunity/susceptibility to an infection can be revealed individually in advance by *in vitro* tests.

Today, the recent successes of immunology can make it possible to identify susceptible individuals. This could be achieved without waiting for individuals to be affected, but by observing *in vitro* the interaction of infectious agents or their molecular/ecological factors with relevant cellular, subcellular or molecular structures extracted, for instance, from a drop of blood of an individual in question (Table 5).

Hereditary immunity of a body is conditioned by immunogenic properties of its cells and subcellular structures. The testing of the body's components reveals differences in the sensitivity of various species and individuals. For example, in the case of infection with various Salmonella species, the testing the cells response revealed a very high susceptibility of herbivorous but constitutional immunity in representatives of omnivorous and carnivorous species. Individual susceptibility can be assessed *in vitro* by the interaction of infectious agents or their molecular

factors with relevant cellular, subcellular, or molecular components extracted, for instance, from a drop of blood [25,60,202].

We are today at the end of the era of total vaccination and at the edge of selective vaccination based on individual immunogenetic indications. We should accelerate the move to this priority goal. Many experimental prerequisites for developing such tests are presented in scientific literature. One can believe that the means for revealing genetically susceptible individuals may be presented to the market during the next decade.

New Branch of Immune Biotechnology

The exploitation of constitutional genetic immunity should' become a new branch of biotechnology and the production of diagnostic tools for genetic immunity will be able to be predicted by the end of this decade. But before this can be done, we should state the goal as a priority and begin to move toward it.

The tests for a population genetic immunity can provide public health institutions with information about the real danger of both emerged and re-emerged infections i.e. their epidemic ferocity and how it can spread around the world via intercontinental travelers in the search of susceptible individuals and groups. The principles of testing for constitutional immunity that discussed above, allow for the avoidance of those confusions. They allow for the assessment of the grade of natural resistance to any infectious agents on the level of both individuals and populations.

The best way to counteract epidemics is to identify and defend the defenseless minority. The exploitation of hereditary immunity on the field of infectious prophylaxis should become a new branch of biotechnology. Its first goal should be the production of tools for diagnostic of individual genetic immunity. But before this can be done, we should state the goal as a priority and begin to move toward it. The testing for genetic immunity of a population, groups or individuals will provide public health institutions and families with information about the real danger of both emerged and re-emerged infections i.e. their epidemic ferocity. The principles of testing for hereditary immunity were discussed above. Their use will allow for the assessment of the grade of natural resistance to any infectious agents on the level individuals, groups and populations and thus allow for the avoidance of current confusions.

CONCLUSION

The chapter presented most exhausted review of main achievements in more recent trend of future immunology, in the discovery and exploitation of hereditary immunity, what they have mainly accomplished and published over the beginning of 21th century. It contains short synopsis concerning fundamental principles and origin of hereditary immunity. The main focus has been made on the moving function of contra-infectious hereditary immunity in the curse of slow evolution of human predecessors, followed by the spurt descent of early humans over African

Pleistocene and in consequent evolution of modern races over dispersion of humankind around the world. The chapter concluded with exploitation of hereditary immunity in the dating of first emergency of human epidemics, which was performed at very different time and far earlier that thought before. The exploitation of immune heritage of humankind is present from the viewpoint of optimized strategy and genetically individualized tactics of contra-infectious health care. The performed integration of previously separated results and their re-sense in the light of recent discoveries allowed approximate the vision of the topic to fare more important entire picture.

References

1. Boyd WC. Fundamentals of immunology. 4th edition. New York: Interscience publishers. 1996.
2. Metchnikoff E. L'Immunite dans les Maladies Infectieuses. Paris: Paris Masson. 1901.
3. Metchnikoff E. Immunity in infective diseases. New York: Johnson Reprint Corp. 1968.
4. Rumyantsev SN. Constitutional immunity and its molecular-ecological principles [in Russian]. Leningrad: Nauka. 1983.
5. Rumyantsev SN. Hereditary Immunity: Fundamental Principles and Exploitation in Life Study and Health Care. New York: Nova Biomedical Books. 2008.
6. Paul WE. Fundamental immunology. 5th edition. Philadelphia: Lippincott Williams & Wilkins. 2003.
7. Rumyantsev SN. Microbes, evolution, immunity. Leningrad: Nauka, The USSR Academy of Sciences. 1984.
8. Rumyantsev SN. Observations on constitutional resistance to infection. Immunol Today. 1992; 13: 184-187.
9. Rumyantsev SN. The best defence against bioweapons has already been invented by evolution. Infect Genet Evol. 2004; 4: 159-166.
10. Rumyantsev SN. Constitutional and non-specific immunity to infection. Rev Sci Tech. 1998; 17: 26-42.
11. Rumyantsev SN, Shabalov NP, Pyasetskaya MF, Rogacheva NM, Bardakova LI. Species, population and age diversity in cell resistance to adhesion of Neisseria meningitidis serogroups A, B and C. Microbes Infect. 2000; 2: 447-453.
12. Rumyantsev SN. Bioweapon: The Emperor's New Suit! Science dvisory Board. 2004.
13. Rumyantsev SN. Biological Weapon. A Terrible Reality? Profound Delusion? Skillful Swindling? New York: Vantage Press. 2006.
14. Rumyantsev SN. Is Bioterrorism Idea a Delusion or Skillful Swindling? 2nd edition. Belgium: UniBook. 2010.
15. Rumyantsev SN, Gerasimov VK. The Origin and Functions of Biodiversity in Infectious and Non-Infectious Diseases. In: Schwartz J, editor. Focus on Biodiversity Research. New York: Nova Science Publishers. 2007; 199-300.
16. Rumyantsev SN. Deadly Microbes Turned Some Apes into Humans. Virginia: Science Advisory Board. 2007.
17. Rumyantsev SN. Infections, Immunity and Anthropogenesis. Research & Reviews in BioSciences. 2007; 1: 189-202.
18. Rumyantsev SN. Bioecology of pleistocenic spurt in anthropogenesis. Int J Integ Biol. 2010; 10: 14-21.
19. Montague CT, Farooqi IS, Whitehead JP, Soos MA, Rau H. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature. 1997; 387: 903-908.
20. Stunkard AJ, Harris JR, Pedersen NL, McClean GE. The body-mass index of twins who have been reared apart. N Engl J Med. 1990; 322: 1483-1487.
21. Wan W, Farboud B, Privalsky ML. Pituitary resistance to thyroid hormone syndrome is associated with T3 receptor mutants that selectively impair beta2 isoform function. Mol Endocrinol. 2005; 19: 1529-1542.
22. Rumyantsev SN, Bobrakova LV, Gordeeva LV. Four Innate Systems of Immunogenesis. In: Durant M, Morel CV, editors. New Research on Innate Immunity. New York: Nova science publishers. 2008; 73-92.
23. Rumyantsev SN. Structural predestination of individual diversity in the course and severity of infectious diseases. ScientificWorldJournal. 2002; 2: 205-216.
24. Bieniasz PD. Intrinsic immunity: a front-line defense against viral attack. Nat Immunol. 2004; 5: 1109-1115.
25. Wigley P, Hulme SD, Bumstead N, Barrow PA. *In vivo* and *in vitro* studies of genetic resistance to systemic salmonellosis in the chicken encoded by the SAL1 locus. Microbes Infect. 2002; 4: 1111-1120.

26. Rumyantsev S. Selection for hereditary immunity to infections during the evolution of humankind. Webmed Central HUMAN BIOLOGY. 2010; 2: 12.

27. Burgasov PN, Rumyantsev SN. Evolution of Clostridiosis [in Russian]. Moscow: Meditsine. 1974.

28. Burgasov PN, Rumyantsev SN. Antimicrobial Constitutional Immunity. [in Russian]. Moscow: Meditsina. 1985.

29. Rumyantsev SN. Chemical ecology and biomolecular evolution. Acta Biotheor. 1997; 45: 65-80.

30. Rumyantsev SN. Genetic immunity and influenza pandemics. FEMS Immunol Med Microbiol. 2006; 48: 1-10.

31. Rumyantsev SN. What Stops the Spread of Influenza. RAMA J. 2005; 2: 21.

32. Rumyantsev SN, Belyacova IV. L'Immunite constitutionnelle envers les virus de la grippe. Cooperation Franco-Sovietique. 2 eme Colloque sur la Grippe. Paris: INSERM. 1977; 331-335.

33. Webster RG, Bean WJ, Gorman OT, Chambers TM, Kawaoka Y. Evolution and ecology of influenza A viruses. Microbiol Rev. 1992; 56: 152-179.

34. Casanova JL, Abel L. Genetic dissection of immunity to mycobacteria: the human model. Annu Rev Immunol. 2002; 20: 581-620.

35. Kalmann F, Reisner D. Twin studies on genetic variations in resistance to tuberculoses. J Hered. 1943; 34: 269-276.

36. Russell DG. Who puts the tubercle in tuberculosis? Nat Rev Microbiol. 2007; 5: 39-47.

37. Koehler TM. Anthrax. Berlin: Springer. 2002.

38. Kohout E, Sehat A, Ashraf M. Anthrax: A continous problem in southwest iran. Am J Med Sci. 1964; 247: 565-575.

39. Brachman PS. Inhalation anthrax. In: Kundsir RB, editor. Airborn contagion. New York: New York Academy of Sciences. 1980; 83-93.

40. Pang T, Levine MM, Ivanoff B, Wain J, Finlay BB. Typhoid fever--important issues still remain. Trends Microbiol. 1998; 6: 131-133.

41. Hoffman SL, Punjabi NH, Kumala S, Moechtar MA, Pulungsih SP. Reduction of mortality in chloramphenicol-treated severe typhoid fever by high-dose dexamethasone. N Engl J Med. 1984; 310: 82-88.

42. Rogerson SJ, Spooner VJ, Smith TA, Richens J. Hydrocortisone in chloramphenicol-treated severe typhoid fever in Papua New Guinea. Trans R Soc Trop Med Hyg. 1991; 85: 113-116.

43. Hornick RB, Griesman SE, Woodward TE, Dupon HL, Dawkins AT, et al. Typhoid fever: pathogenesis and immunologic control. N Engl J Med. 1970; 283:686-739.

44. Greene CM, Reefhuis J, Tan C, Fiore AE, Goldstein S. Epidemiologic investigations of bioterrorism-related anthrax, New Jersey, 2001. Emerg Infect Dis. 2002; 8: 1048-1055.

45. Hughes JM, Gerberding JL. Anthrax bioterrorism: lessons learned and future directions. Emerg Infect Dis. 2002; 8: 1013-1014.

46. Lincoln RE, Walker JS, Klein F, Rosenwald AJ, Jones WI Jr. Value of field data for extrapolation in anthrax. Fed Proc. 1967; 26: 1558-1562.

47. Burgasov PN. I have believed [in Russian]. Moscow. 2000.

48. Christie AB. Infectious disease: epidemiology and clinical practice. Fourth Edition. Edinburgh: Churchill Livingstone. 1987.

49. Ricketts TF. The diagnosis of small pox. New York: Funk and Wagnalls. 1966.

50. Vavilov NI. Immunity of plants to infectious diseases (In Russian). Moscow: Nauka. 1964.

51. Rumyantsev SN. The origin of individual differences in the course and severity of diseases. ScientificWorldJournal. 2006; 6: 1674-1704.

52. Lew D. Bacillus anthracis (anthrax); In: Mandell GL BJDR, editor. New York: Churchill Living stone Inc. 1995; 1885-1889.

53. Mwenye KS, Siziya S, Peterson D. Factors associated with human anthrax outbreak in the Chikupo and Ngandu villages of Murewa district in Mashonaland East Province, Zimbabwe. Cent Afr J Med. 1996; 42: 312-315.

54. Carr EA Jr, Rew RR. Recovery of Bacillus anthracis from the nose and throat of apparently healthy workers. J Infect Dis. 1957; 100: 169-171.

55. Sweany HC, Cook CE, Kegerreis R. A study of the position of primary cavities in pulmonary tuberculosis. Am Rev Tuberc. 1931; 24: 558-582.

56. Rumyantsev SN. The origin of individual differences in the course and severity of diseases. ScientificWorldJournal. 2006; 6: 1674-1704.

57. Gabliks J, Falconer M. Interaction of diphtheria toxin with cell cultures from susceptibile and resistant animals. J Exp Med. 1966; 123: 723-732.

58. Moehring JM, Moehring TJ. Comparison of diphtheria intoxication in human and nonhuman cell lines and their resistant variants. Infect Immun. 1976; 13: 221-228.

59. Bobrakova LV. Epidemiological aspects of the populations heterogeneity in the resistance of erythrocytes to Salmonella haemolysines.[in Russian]. Central Scientific Research Institute of Epidemiology. 1986; 1-24.

60. Rumiantsev SN, Bobrakova LV, Perkus LV. [Genetic limitations of erythrocyte lysis by bacteria of the genus Salmonella]. Genetika. 1978; 14: 2037-2042.

61. Rumyantsev SN. Toward molecular level of the “Salmonella-victim” ecology, genetics, and evolution. ScientificWorldJournal. 2004; 4: 193-199.

62. Halonen PE, Murphy FA, Fields BN, Reese DR. Hemagglutinin of rabies and some other bullet-shaped viruses. Proc Soc Exp Biol Med. 1968; 127: 1037-1042.

63. Foster JW, Kinney DM. ADP-ribosylating microbial toxins. Crit Rev Microbiol. 1985; 11: 273-298.

64. Matrosovich M, Tuzikov A, Bovin N, Gambaryan A, Klimov A, et al. Early alterations of the receptor-binding properties of H, H2, and H3 avian influenza virus hemagglutinins after their introduction into mammals. J Virol; 2000; 74: 8502-8512.

65. Haywood AM. Characteristics of Sendai virus receptors in a model membrane. J Mol Biol. 1974; 83: 427-436.

66. Carrington M, Dean M, Martin MP, O’Brien SJ. Genetics of HIV-1 infection: chemokine receptor CCR5 polymorphism and its consequences. Hum Mol Genet. 1999; 8: 1939-1945.

67. Samson M, Soularue P, Vassart G, Parmentier M. The genes encoding the human CC-chemokine receptors CC-CKR1 to CC-CKR5 (CMKBR1-CMKBR5) are clustered in the p21.3-p24 region of chromosome 3. Genomics. 1996; 36: 522-526.

68. Morishima T, McClintock PR, Aulakh GS, Billups LC, Notkins AL. Genomic and receptor attachment differences between mengovirus and encephalomyocarditis virus. Virology. 1982; 122: 461-465.

69. Swann AI. The relationship of erythrocyte age and parasitization with Plasmodium gallinaceum in chickens. Can J Comp Med. 1974; 38: 391-397.

70. Allison AC. Coevolution between hosts and infectious disease agents and its effects on virulence. In: Anderson RM, May RM, editors. Population biology of infectious diseases. Heidelberg: Springer Verlag. 1982; 245-267.

71. Burrows TW, Gillett WA. Host specificity of Brazilian strains of Pasteurella pestis. Nature. 1971; 229: 51-52.

72. Gibbons RJ, van Houte J. Bacterial adherence and the formation of dental plaques. In: Beachey EH, editor. Bacterial adherence. New York: Chapman and Hall. 1980; 62-104.

73. Takeda Y, Takeda T, Honda T, Miwatani T. Inactivation of the biological activities of the thermostable direct hemolysin of Vibrio parahaemolyticus by ganglioside Gt1. Infect Immun. 1976; 14: 1-5.

74. Rumiantsev SN, Avrova NF, Pospelov VF, Denisova NA. [The effect of gangliosides on the adhesive interaction of Neisseria meningitidis with human cells]. Zh Mikrobiol Epidemiol Immunobiol. 1990; : 29-32.

75. Abel L, Dessein AJ. The impact of host genetics on susceptibility to human infectious diseases. Curr Opin Immunol. 1997; 9: 509-516.

76. Cheever AW. Predisposition to helminth infection in man. Nature. 1986; 320: 195-196.

77. Hill AV. Genetics of infectious disease resistance. Curr Opin Genet Dev. 1996; 6: 348-353.

78. Hormaeche CE. Natural resistance to Salmonella typhimurium in different inbred mouse strains. Immunology. 1979; 37: 311-318.

79. Koike S, Ise I, Nomoto A. Functional domains of the poliovirus receptor. Proc Natl Acad Sci U S A. 1991; 88: 4104-4108.

80. O’Brien SJ, Dean M. In search of AIDS-resistance genes. Sci Am. 1997; 277: 44-51.

81. Paxton WA, Martin SR, Tse D, O’Brien TR, Skurnick J. Relative resistance to HIV-1 infection of CD4 lymphocytes from persons who remain uninfected despite multiple high-risk sexual exposure. Nat Med. 1996; 2: 412-417.

82. Kaslow RA, Dorak T, Tang JJ. Influence of host genetic variation on susceptibility to HIV type 1 infection. J Infect Dis. 2005; 191 Suppl 1: S68-77.

83. Haldane JBS. Disease and evolution. La Riserca Sci. 1949; 19: 68-76.

84. O’Brien SJ, Evermann JF. Interactive influence of infectious disease and genetic diversity in natural populations. Trends Ecol Evol. 1988; 3: 254-259.

85. Varki A, Altheide TK. Comparing the human and chimpanzee genomes: searching for needles in a haystack. Genome Res. 2005; 15: 1746-1758.

86. Centers for Disease Control and Prevention. Bioterrorism Agents/Diseases. 2010.

87. Rumiantsev SN. [Immunity and molecular constitution]. Zh Obshch Biol. 1977; 38: 500-511.

88. Smith H. The state and future of studies on bacterial pathogenicity. In: Roth JA, editor. Virulence mechanisms of bacterial pathogens. Washington DC, American Society for Microbiology. 1988; 365-382.

89. Smith H. The Leeuwenhoek Lecture, 1991. The influence of the host on microbes that cause disease. Proc Biol Sci. 1991; 246: 97-105.

90. Achtman M, Gibbons RJ, Gotschlich EC, et al. Contact and entry described in terms of a sea voyage. In: Smith H, Skehel JJ, Turner MJ, editors. The molecular basis of microbialpathogenicity. Weinheim: Verlag Chemie GmbH. 1980; 69-86.

91. Smith H. The effect of enviromental conditions *in vivo* and *in vitro* on the determinants of microbial pathogenicity. In: Smith H, Skehel JJ, Turner MJ, editors. Molecular basis of microbial pathogenicity. Weinheim: Verlag Chemie GmbH. 1980.

92. Cox JH, Dietzschold B, Weiland F, Schneider LG. Preparation and characterization of rabies virus hemagglutinin. Infect Immun. 1980; 30: 572-577.

93. Roberts DJ, Biggs BA, Brown G, Newbold CI. Protection, pathogenesis and phenotypic plasticity in Plasmodium falciparum malaria. Parasitol Today. 1993; 9: 281-286.

94. Anstee DJ. The blood group MNSs-active sialoglycoproteins. Semin Hematol. 1981; 18: 13-31.

95. McDougal JS, Kennedy MS, Sligh JM, Cort SP, Mawle A. Binding of HTLV-III/LAV to T4+ T cells by a complex of the 110K viral protein and the T4 molecule. Science. 1986; 231: 382-385.

96. Dalgleish AG, Beverley PC, Clapham PR, Crawford DH, Greaves MF. The CD4 (T4) antigen is an essential component of the receptor for the AIDS retrovirus. Nature. 1984; 312: 763-767.

97. Ramm LE, Winkler HH. Identification of cholesterol in the receptor site for rickettsiae on sheep erythrocyte membranes. Infect Immun. 1976; 13: 120-126.

98. Littleton J, Frohlich B. Fish-eaters and farmers: dental pathology in the Arabian Gulf. Am J Phys Anthropol. 1993; 92: 427-447.

99. Davis CD, Kuhn RE. Selective binding of Trypanosome cruzi to host cell. Infect Immun. 1990; 58: 1-6.

100. Donovan JJ, Simon MI, Montal M. Insertion of diphtheria toxin into and across membranes: role of phosphoinositide asymmetry. Nature. 1982; 298: 669-672.

101. Moehring JM, Moehring TJ. Strains of CHO-K1 cells resistant to Pseudomonas exotoxin A and cross-resistant to diphtheria toxin and viruses. Infect Immun. 1983; 41: 998-1009.

102. Mikula I, Toth L. Adherence of uropathogenic E.Coli to uroepithelial cells. Folia Veter. 1986; 30: 9-24.

103. Lingwood CA, Law H, Richardson S, Petric M, Brunton JL. Glycolipid binding of purified and recombinant Escherichia coli produced verotoxin *in vitro*. J Biol Chem. 1987; 262: 8834-8839.

104. Fujikawa A, Shirasaka D, Yamamoto S, Ota H, Yahiro K. Mice deficient in protein tyrosine phosphatase receptor type Z are resistant to gastric ulcer induction by VacA of Helicobacter pylori. Nat Genet. 2003; 33: 375-381.

105. Hakomori S. Glycosphingolipids in cellular interaction, differentiation, and oncogenesis. Annu Rev Biochem. 1981; 50: 733-764.

106. Strömberg N, Ryd M, Lindberg AA, Karlsson KA. Studies on the binding of bacteria to glycolipids. Two species of Propionibacterium apparently recognize separate epitopes on lactose of lactosylceramide. FEBS Lett. 1988; 232: 193-198.

107. Boyd B, Lingwood C. Verotoxin receptor glycolipid in human renal tissue. Nephron. 1989; 51: 207-210.

108. Igarashi K, Ogasawara T, Ito K, et al. Inhibition of mutant streptococci by the hematin formed on blood-containingmedia by proteolytic enterococci. FEMS Microbiol Lett. 1987; 44: 91-94.

109. Beachey EH. Bacterial adherence: adhesin-receptor interactions mediating the attachment of bacteria to mucosal surface. J Infect Dis. 1981; 143: 325-345.

110. Morishima T, McClintock PR, Aulakh GS, Billups LC, Notkins AL. Genomic and receptor attachment differences between mengovirus and encephalomyocarditis virus. Virology. 1982; 122: 461-465.

111. Petri WA, Mann BJ. Microbial adherence; Principle and practice of infectious diseases. Churchill Livingston. 1995; 11-19.

112. McClintock PR, Notkins AL. Viral receptors: expression, regulation and relationship to infectivity. In: Notkins AL, Oldstone MBA, editors. Concepts in viral pathogenesis. New York: Springer. 1984; 97-101.

113. McClintock PR, Morishima T, Notkins AL. Expression and modulation of virus receptors: relationship to infectivity. In: Scolnick EM, Levine AJ, editors. Tumor viruses and differentiation. UCLA Symposium on Molecular and Cellular Biology 5. 1983; 299-308.

114. Altrock BW, Arthur LO, Massey RJ, Schochetman G. Common surface receptors on both mouse and rat cells distinguish different classes of mouse mammary tumor viruses. Virology. 1981; 109: 257-266.

115. Mogensen SC. Role of macrophages in natural resistance to virus infections. Microbiol Rev. 1979; 43: 1-26.

116. Chesebro B, Buller R, Portis J, Wehrly K. Failure of human immunodeficiency virus entry and infection in CD4-positive human brain and skin cells. J Virol. 1990; 64: 215-221.

117. McLaren LC, Holland JJ, Syverton JT. The mammalian cell-virus relationship. I. Attachment of poliovirus to cultivated cells of primate and non-primate origin. J Exp Med. 1959; 109: 475-485.

118. Middlebrook JL, Dorland RB. Responce of cultured mammalian cells to the exotoxins of Pseudomonas aeruginosa and Corinebacterium diphtheriae: differential cytotoxocity. Canad J Microbiol. 1977; 23:183-189.

119. Cheney CP, Schad PA, Formal SB, Boedeker EC. Species specificity of *in vitro* Escherichia coli adherence to host intestinal cell membranes and its correlation with *in vivo* colonization and infectivity. Infect Immun. 1980; 28: 1019-1027.

120. Brooks DE, Cavanagh J, Jayroe D, Janzen J, Snoek R, et al. Involvement of the MN blood group antigen in shear-enhanced hemagglutination induced by the Escherichia coli F41 adhesin. Infect Immun. 1989; 57: 377-383.

121. Rutter JM, Burrows MR, Sellwood R, Gibbons RA. A genetic basis for resistance to enteric disease caused by E. coli. Nature. 1975; 257: 135-136.

122. Mourant AE, Kopek AK, Domaniewska-Sobszak K. Blood groups and diseases. Oxford: Oxford Univ Press. 1979.

123. Miller LH, Aikawa M, Johnson JG, Shiroishi T. Interaction between cytochalasin B-treated malarial parasites and erythrocytes. Attachment and junction formation. J Exp Med. 1979; 149: 172-184.

124. Strobel GA. A mechanism of disease resistance in plants. Sci Am. 1975; 232: 81-88.

125. Rowland MW. Fitness of insecticide resistance. Nature. 1987; 327: 194.

126. Currier WW. Molecular controls in the resistance ofpotato to late blight. TIBS. 1981; 6: 191-194.

127. Nishimura H, Sugawara K, Kitame F, Nakamura K. Attachment of influenza C virus to human erythrocytes. J Gen Virol. 1988; 69 : 2545-2553.

128. Foster JW, Kinney DM. ADP-ribosylating microbial toxins. Crit Rev Microbiol. 1985; 11: 273-298.

129. King CA, Van Heyningen WE. Deactivation of cholera toxin by a sialidase-resistant monosialosylganglioside. J Infect Dis. 1973; 127: 639-647.

130. Strobel GA. A mechanism of disease resistance in plants. Sci Amer. 1975; 232: 81-88.

131. Eiklid K, Olsnes S. Interaction of Shigella shigae cytotoxin with receptors on sensitive and insensitive cells. J Recept Res. 1980; 1: 199-213.

132. Middlebrook JL, Dorland RB. Protection of mammalian cells from diphtheria toxin by exogenous nucleotides. Can J Microbiol. 1979; 25: 285-290.

133. Pappenheimer AM, Moynihan MR. Diphtheria toxin: a model for translocation of polypeptides across the plasma membrane. Receptor mediated binding and internalization of toxins and hormones. New York: Academic Press. 1981; 31-51.

134. Pellizzari A, Pang H, Lingwood CA. Binding of verocytotoxin 1 to its receptor is influenced by differences in receptor fatty acid content. Biochemistry. 1992; 31: 1363-1370.

135. Cohen A, Hannigan GE, Williams BR, Lingwood CA. Roles of globotriosyl- and galabiosylceramide in verotoxin binding and high affinity interferon receptor. J Biol Chem. 1987; 262: 17088-17091.

136. Pudymaitis A, Armstrong G, Lingwood CA. Verotoxin-resistant cell clones are deficient in the glycolipid globotriosylceramide: differential basis of phenotype. Arch Biochem Biophys. 1991; 286: 448-452.

137. Waddell T, Cohen A, Lingwood CA. Induction of verotoxin sensitivity in receptor-deficient cell lines using the receptor glycolipid globotriosylceramide. Proc Natl Acad Sci U S A. 1990; 87: 7898-7901.

138. Kannagi R, Nudelman E, Hakomori S. Possible role of ceramide in defining structure and function of membrane glycolipids. Proc Natl Acad Sci U S A. 1982; 79: 3470-3474.

139. Segal R, Milo-Goldzweig I. The susceptibility of cholesterol-depleted erythrocytes to saponin and sapogenin hemolysis. Biochim Biophys Acta. 1978; 512: 223-226.

140. Friedman MJ, Trager W. The biochemistry of resistance to malaria. Sci Am. 1981; 244: 154-155, 158-64.

141. Eaton JW, Eckman JR, Berger E, Jacob HS. Suppression of malaria infection by oxidant-sensitive host erythrocytes. Nature. 1976; 264: 758-760.

142. KasÄƒrov LB. Degradiation of the erythrocyte phospholipids and haemolysis of the erythrocytes of different animal species by leptospirae. J Med Microbiol. 1970; 3: 29-37.

143. Kuge O, Akamatsu Y, Nishijima M. Abortive infection with Sindbis virus of a Chinese hamsters ovary cell mutantdefective in phosphatidylserine and phosphatidylethanolamine biosynthesis. Biochimica and biophysica acta. 1989; 986: 61-69.

144. Spoerel N, Herrlich P, Bickle TA. A novel bacteriophage defence mechanism: the anti-restriction protein. Nature. 1979; 278: 30-34.

145. Bickle TA, Krüger DH. Biology of DNA restriction. Microbiol Rev. 1993; 57: 434-450.

146. Krüger DH, Bickle TA. Bacteriophage survival: multiple mechanisms for avoiding the deoxyribonucleic acid restriction systems of their hosts. Microbiol Rev. 1983; 47: 345-360.

147. Tomasz A. The mechanism of the irreversibleantimicrobial effects of penicillins: how the beta-lactam antibiotics kill and lyse bacteria. Ann Rev Microbiol. 1979; 33: 1134-1137.

148. Manners JM. Hidden weapons of microbial destruction in plant genomes. Genome Biol. 2007; 8: 225.

149. Becker EL, Landau SI, Manuila A. International dictionary of medicine and biology. New York: Wiley. 1986.

150. Hedin PA, Jenkins JN, Collum DH, et al. Multiple factors in cotton contributing to resistance to the tobacco budworm. In: Hedin PA, editor. Plant resistance to insects. Washington DC: American Chemical Society. 1983; 347-365.

151. Ryan MF, Byrne O. Plant-insect coevolution and inhibition of acetylcholinesterase. J Chem Ecol. 1988; 14: 1965-1975.

152. Corbett JR, Wright R, Baillie AC. The biochemical mode of action of pesticides. New York: Academic Press. 1984.

153. Jones DA. Cyanogenesis in animal-plant interactions. Ciba Found Symp. 1988; 140: 151-170.

154. Pavlovic J, Haller O, Staeheli P. Human and mouse Mx proteins inhibit different steps of the influenza virus multiplication cycle. J Virol. 1992; 66: 2564-2569.

155. Pavlovic J, Zürcher T, Haller O, Staeheli P. Resistance to influenza virus and vesicular stomatitis virus conferred by expression of human MxA protein. J Virol. 1990; 64: 3370-3375.

156. Johnson AP, Taylor-Robinson D, McGee ZA. Species specificity of attachment and damage to oviduct mucosa by Neisseria gonorrhoeae. Infect Immun. 1977; 18: 833-839.

157. Brown WJ, Lucas CT, Kuhn US. Gonorrhoea in the chimpanzee. Infection with laboratory-passed gonococci and by natural transmission. Br J Vener Dis. 1972; 48: 177-178.

158. Refsnes K, Olsnes S, Pihl A. On the toxic proteins abrin and ricin. Studies of their binding to and entry into Ehrlich ascites cells. J Biol Chem. 1974; 249: 3557-3562.

159. Holmgren J, Fredman P, Lindblad M, Svennerholm AM. Rabbit intestinal glycoprotein receptor for Escherichia coli heat-labile enterotoxin lacking affinity for cholera toxin. Infect and Immun. 1982; 38: 424-433.

160. Pappenheimer AM Jr. Diphtheria toxin. Annu Rev Biochem. 1977; 46: 69-94.

161. Lonberg-Holm K, Crowell RL, Philipson L. Unrelated animal viruses share receptors. Nature. 1976; 259: 679-681.

162. Pauling L. Molecular complementariness and serological specificity. Immunochemistry. 1975; 12: 445-447.

163. Neiburger EJ. Syphilis in a Pleistocene bear? Nature. 1988; 333: 603.

164. Morgan C, Rose HM. Structure and development of viruses as observed in the electron microscope. 8. Entry of influenza virus. J Virol. 1968; 2: 925-936.

165. Birdwell CR, Strauss JH. Distribution of the receptor sites for Sindbis virus on the surface of chicken and BHK cells. J Virol. 1974; 14: 672-678.

166. Rosenblith JZ, Uhera TE, Yiss HH, Berlin RD, Karnovsky MJ. A comparative evaluation of the distribution of concanavalin A-binding sites on the surface ofnormal, virally transformed, and protease-treated fibroblasts. Proc Nat Acad Sci USA. 1973; 70: 1625-1629.

167. Koike S, Taya C, Kurata T, Abe S, Ise I. Transgenic mice susceptible to poliovirus. Proc Natl Acad Sci U S A. 1991; 88: 951-955.

168. Smith DW, Wiegeshaus EH, Edwards MS. The protective effects of BCG vaccination against tuberculosis. In: Bendelli M, Friedman H, editors. Mycobacterium tuberculosis. New York: Plenum Publishing Corp. 1988; 341-370.

169. Smith DW, Wiegeshaus EH. What animal models can teach us about the pathogenesis of tuberculosis in humans. Rev Infect Dis. 1989; 11 Suppl 2: S385-393.

170. Wiegeshaus E, Balasubramanian V, Smith DW. Immunity to tuberculosis from the perspective of pathogenesis. Infect Immun. 1989; 57: 3671-3676.

171. Harding GE, Smith DW. Host-parasite relationships in experimental airborne tuberculosis. VI. Influence of vaccination with bacille Calmette-Guerin on the onset and/or extent of hematogenous dissemination of virulent Mycobacterium tuberculosis of the lungs. J Inf Dis 1982; 156: 439-443.

172. Fok JS, Ho RS, Arora PK, Harding GE, Smith DW. Host-parasite relationships in experimental airborne tuberculosis. V. Lack of hematogenous dissemination of Mycobacterium tuberculosis to the lungs in animals vaccinated with bacille Calmette-Guerin. J Infect Dis. 1976; 133: 137-144.

173. Bodian D, Horstman DM. Poliovirus. In: Horsfall FL, Tamm I, editors. Viral and ricketsial infections of man. London: Pitman. 1965.

174. Raoult D. Host factors in the severity of Q fever. Ann N Y Acad Sci. 1990; 590: 33-38.

175. Clark HF, Lunger PD. Viruses. In: Cooper JE, Jackson OF, editors. Diseases of reptilia. New York: Acad Press. 1981; 135-164.

176. Russel CE. Plant breeding for pest and disease resistance. London, Butterworth. 1978.

177. Vavilov NI. Immunity of plants to infectious diseases (In Russian). Moscow. 1918.

178. Moehring JM, Moehring TJ. Characterization of the diphtheria toxin-resistance system in Chinese hamster ovary cells. Somatic Cell Genet. 1979; 5: 453-468.

179. Moehring TJ, Moehring JM. Responce of cultured mammalian cells to diphteria toxin. Infection and Immunity. 1972; 64: 487-492.

180. Reid G, Brooks HJ, Bacon DF. *In vitro* attachment of Escherichia coli to human uroepithelial cells: variation in receptivity during the menstrual cycle and pregnancy. J Infect Dis. 1983; 148: 412-421.

181. Thomas GA, Williams D, Williams ED. The demonstration of tissue clonality by X-linked enzyme histochemistry. J Pathol. 1988; 155: 101-108.

182. Rasmussen M, Guo X, Wang Y, Lohmueller KE, Rasmussen S. An Aboriginal Australian genome reveals separate human dispersals into Asia. Science. 2011; 334: 94-98.

183. Gazzaniga MS. The Science Behind What Makes Us Unique. New York: Ecco (HarperCollins). 2008.

184. Rumyantsev SN. Dating of First Emergence of Human Infections. Journal of Medicine and Medical Sciences. 2012; 3: 423-433.

185. Rumyantsev SN. Where and When Human Viral Epidemics First Emerged. British Journal of Medicine & Medical Research. 2012; 2: 647-661.

186. Rumyantsev SN. The HIV age ad location of origin. British Journal of Medical and Health Sciences. 2013; 1: 16-31.

187. Wang S, Lewis CM, Jakobsson M, Ramachandran S, Ray N. Genetic variation and population structure in native Americans. PLoS Genet. 2007; 3: e185.

188. Hasenauer H. Anthrax update. Soldier. 1998; 53: 16-17.

189. World Health Organization. Health Aspects of Chemical and Biological Weapons. Geneva: World Health Organization. 1970.

190. Office of Technology Assessment UC. Proliferation of Weapons of Mass Destruction 53-55. Washington DC: US Government Printing Office. 1993.

191. Cole LA. The specter of biological weapons. Sci Am. 1996; 275: 60-65.

192. Central Intelligence Agency. The Darker Bioweapons Future. Directorate of Intelligence, Office of Transnational Issues. 2003.

193. Bioterrorism and biocrimes: the illicit use of biological agents in the 20th Century. Washington DC: Center for Counter Proliferation Research, National Defence University. 1998.

194. Ford C. Testimony to the US Senate, Committee on Foreign Relations. Washington. 2002.

195. Mintz J, Warrick J. U.S. Unprepared Despite Progress, Experts Say. Washington Post. 2004.

196. Wein LM, Craft DL, Kaplan EH. Emergency response to an anthrax attack. Proc Natl Acad Sci U S A. 2003; 100: 4346-4351.

197. Misawa A. Aum bio-attacks opened Pandora's box. Yomiuri Shimbun. 2001.

198. Keim P, Smith KL, Keys C, Takahashi H, Kurata T. Molecular investigation of the Aum Shinrikyo anthrax release in Kameido, Japan. J Clin Microbiol. 2001; 39: 4566-4567.

199. Regis E. Evaluating the threat. Does mass biopanic portend mass destruction? Sci Am. 2001.

200. Guillemin J. Anthrax. The investigation of a deadly outbreak. Berkeley: University of California Press. 1999.

201. Meselson M, Guillemin J, Hugh-Jones M, Langmuir A, Popova I. The Sverdlovsk anthrax outbreak of 1979. Science. 1994; 266: 1202-1208.

202. Rumyantsev SN, Shabalov NP, Pyasetskaya MF, Rogacheva NM, Bardakova LI. Species, population and age diversity in cell resistance to adhesion of Neisseria meningitidis serogroups A, B and C. Microbes Infect. 2000; 2: 447-453.

203. Leitenberg M. Biological Weapons and "Bioterrorism" in the First Years of the 21st Century. Rome: ICGEB, Landau Network, Ministry of Foreign Affairs, Italy. 2003.

204. Brock TD. Robert Koch. A life in medicine and bacteriology. Washington DC: ASM Press. 1999.

205. O'Toole T1. Smallpox: An attack scenario. Emerg Infect Dis. 1999; 5: 540-546.

206. Tucker JB. Scourge: the once and future threat of smallpox. New York: Atlantic Monthly Press. 2001.

207. Johnson GB. Smallpox: Is This Once-Vanquished Killer a Threat Again? 2004.

208. Kvitko E. Smallpox: as bad as a weapon. An interview with general Pyotr Burgasov. Moscow News. 2001.

209. Beardsley T. Facing an ill wind. The U.S. gears up to deal with biological terrorism. Sci Am. 1999.

210. Ewan SG. Bioweapons: The silent assassins. HMS Beagle. 2001; 107.

211. Epidemiology & Prevention of Vaccine-Preventable Diseases. 7th edition. Atlanta: Dept. of Health & Human Services, Centers for Disease Control and Prevention. 2002.

212. Agres T. Funding 2004: President's budget request disappoints biology community. The Scientist. 2003.

213. Rumyantsev SN. AIDS: Fears are exaggerated. Moscow News. 1992.