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ARTICLE

Nanomedicine for SARS-CoV-2: Therapeutic and Prophylactic Approach in Immunocompromised Individuals

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ABSTRACT

SARS-CoV-2 is a novel coronavirus that first appeared in Wuhan, China in December 2019 and then spread all over the world, causing a global respiratory epidemic COVID-19 illness. Certain health conditions can increase your exposure to COVID-19, such as chronic obstructive lung disease, high blood pressure, cardiovascular disease, and diabetes. The immune system of the host is severely compromised in the event of a respiratory viral infection. Immunocompromised patients have a more difficult time avoiding respiratory viral infections, making them more vulnerable to COVID-19 pneumonia and increasing the death rate to 19%. The ability of SARS-CoV-2 to damage the host cell by modifying its own DNA or RNA and proliferating inside the host cell, with antiviral treatments and prophylactic vaccinations being tested. In recent years, numerous innovative technologies have been examined to diagnose, prevent and treat viral infections. Nano technology opens the way to distinguish the living cell mechanisms and develop new technologies that make it possible to diagnose and cure various viral infections in the early stage. The therapeutic and preventative approaches of nanomedicine are essential factors for curing SARS-CoV-2. The delivery of antiviral drugs based on nanocarrier, changes in pharmacokinetic/pharmacodynamic properties, leading in dose reduction, reductions in toxicity, increased bioavailability, and the prevention of the virus. The overall efficiency and safety of vaccinated adjuvant vaccine nanoparticles (VANs) helps enhance the immune response of older, immunocompromised persons with the greatest death rate of SARS-CoV-2. The review focuses on recent advancements in nanomedicine treatments and prevention strategies for SARS-CoV-2.

1. Introduction

The world has advanced in many areas, but there are still viral diseases that contribute to human death and their social and economic manifestations. Corona virus, nipa virus, Ebola virus, Zika virus, Dengue virus, Chikungunya virus, and various influenza virus strains - H5N1 (Avian influenza), H1N1 and H3N2 (Swine flu) causes numerous viral infections [1]. Environmental hazards, as well as water supply, sanitation facilities, climate, lifestyle smoking, alcoholism, a specific geological area, and various medical procedures such as body fluid transfusion, surgery, and vector broadcast, have all been identified as risk factors for viral infection [2]. While some of these factors can be predicted and precautions taken to avoid them, others can be targeted for a positive response [3].

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A severe pandemic caused by the new corona virus (nCoV) recently killed nearly 2.1 thousand people [4]. It originally surfaced in China, then spread rapidly to other countries around the globe as a new Coronavirus-2019 (COVID-19) [5]. The virus's emergence and rapid spread of infection has resulted in a worldwide respiratory epidemic disease Covid-19 [6]. The major symptoms are fever, muscle suffering, weariness, headache, and bleeding [7]. While 5% of infected persons are in critical condition and 14% are in severe condition, most infected people have relatively minor symptoms like mild pneumonia [8]. The elderly and those with comorbidities such as anorexia, pharyngeal soreness, diabetes, and hypertension are the most likely to require the intensive care unit (ICU) [9]. COVID-19 susceptibility can be increased by certain health problems such as pulmonary obstruction, hypertension, cardiovascular and diabetes health difficulties [10].

Immunocompromised patients have a more difficult time avoiding respiratory viruses, rendering them more receptive to nCoV. In immunocompromised patients, 19% of deaths were caused by viral lung infection [8]. Pneumonia caused by the Coronavirus was responsible for 24% of deaths, with the viruses spread more commonly in cancer patients than in non-cancer individuals (3%) [11]. Conventional corona viruses have been linked to a high degree of oxygen use and mortality in individuals with malignant hematomas [12]. COVID-19 hospitalized patients have severed lymphopenia with time [9], which, in turn, causes pneumonia in patients with malignant hematomas who also have respiratory virus infections [13]. Up until now, Coronavirus infection had no vaccinations or antivirals [5]. In the case of viral infection, the host's immune system is greatly compromised, and relapses are common. The ability of a virus to destroy a host cell by editing its own DNA or RNA and multiply within the host cell presents difficulties in developing antiviral therapies [14]. Because of prior exposure, viral antibodies may be triggered in the host, making symptomatic infection harder to detect [15].

2. SARS-CoV-2

The new coronavirus has been named severe acute respiratory syndrome-2 (SARS-CoV-2) by the International Committee on Virus Taxonomy [16]. On February 11, 2020, the World Health Organization designated the nCoV as COVID-19, and the outbreak quickly grew in scale [15]. "COVID- 19" was the name of the new virus. The ICRC Virus Classification (ICTV) has updated this to "SARS-CoV-2," indicating an 80 percent similarity to the sequence of SARS-like coronaviruses (SARS-CoV) and a 50 percent similarity to the sequence of Coronavirus-like virus (MERS-CoV) [17]. Corona viruses have caused three epidemic diseases in the last two decades: COVID-19, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS) [18]. Coronaviruses (CoVs) are enveloped viruses from the family Coronaviridae (Coronavirinae subfamily), with a single-tagged RNA genome (26-32 kb) and positive viruses that infect the host widely, multiply in the affected cytoplasm, and cause diseases ranging from the common cold to death [19]. COVID-19 cases have been discovered in several nations throughout the world, and the World Health Organization (WHO) has declared COVID-19 a Public Health Emergency of International Concern (PHEIC) [20]. A large range of possible vaccine candidates, including live-attenuated, inactivated, viral-vectored based, sub-unit vaccines, DNA, mRNA, peptide, adjuvant, plant, and nanoparticle-based vaccines, are undergoing several clinical trials to treat COVID-19 disease [21]. Antiviral drug development requires an understanding of the pathogenesis of molecular immune dysfunction and the identification of COVID-19 [16].

3. Genome and Proteins of SARS-CoV-2

Human coronaviruses (HCoVs) have a positive RNA genome that is single-stranded encased within them (26-32 kb) [22]. SARS-CoV-2 has a genome like that of other CoVs, with up to ten open frames for reading (ORFs). Almost two-thirds of the viral RNA are translated into two large proteins by the first ORFs (ORF1a/b). In SARS-CoV-2 and MERS-CoV, two multiple proteins, pp1a and pp1ab, were converted into 16 non-structural proteins (nsp1-nsp16)., which make up the viral replication complex [23].

Viral replication and transcription are carried out in double-membrane vesicles from the rough endoplasmic reticulum (RER) [24]. Other SARS-CoV-2 ORFs found inside the genome's four primary structural proteins are spike (S), envelope (E), nucleocapsid (N), and membrane (M), as well as several unknown functionally complementary auxiliary proteins that aren't involved in viral replication [16]. To enter cells, SARS-CoV-2 requires angiotensin converting enzyme 2 (ACE2) as a receptor [25]. Because it crossed species to infect humans, the SARS virus ACE2 most likely evolved in bats [26] and adapted to species other than bats [27].

4. Mechanisms SARS-CoV-2 Pathogenesis

COVID-19 patients demonstrate clinical symptoms, such as fever, non-productive cough, respiratory shortness, muscle discomfort, exhaustion, normal or low white cell numbers, and radiological pneumonia [28], that are like symptoms of SARS and MERS infection [29]. Different

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stages of pathogenesis are followed: (1) viral attachment at the entry point, (2) host cell infiltration, (3) the removal of the virus cover, (4) transcriptive replication and translation leading to virus-specific protein synthesis, (5) nude capsid accumulation through nucleocapsid, and (6) viral release that causes infection spread [30]. Many factors affect pathogenic pathways such as tissue access to causative viruses, vulnerability of virus cells, and virus host protection. The affinity of the virus to specific tissues is determined by multiple elements, amongst them, the existence of cell transcriptions for virus-specific receiver, the cell's cell transcription factors, the local pH, temperature, and the presence of viral enzymes, which can hinder activity [31]. The host's defenses may interact with the virus by inhibiting its growth or by stimulating the immune response in infected tissues [32].

5. Viral Entry and Replication

The essential component of SARS-CoV-2 input into host cells has been identified as the spike protein (protein S) [18]. SARS-CoV-2 entrance into cells was originally considered to occur by means of direct membrane fusion between the S protein virus and the receptor Angiotensin-Converting Enzyme 2 (ACE2) [33]. SARS-CoV-2 is similarly mediated through membrane fusion, clathrin-dependent and clathrin-dependent endocytoses [34]. After entering the virus, the virus RNA genome is released into the cytoplasm and converted to two numerous proteins and structural proteins, which lead to the virus multiplication of the genome [35]. The newly created glycoprotein envelopes are introduced into the reticulum membrane or Golgi and a mixture of genomic RNA and nucleoside proteins is formed from the nuclear plug. In the endoplasmic reticulum - Golgi medium chamber, the viral particles germinate. Finally, the plasma membrane fuses with the virus-containing vesicles, which releases it [18].

6. Immune Response to the SARS-CoV-2

After the virus enters the cells, its antigenic peptides are presented by antigen-presenting cells (APC), major histocompatibility complex (MHC), or human leukocyte antigen (HLA), and are then recognized by the virus's cytotoxic T lymphocytes (CTLs). SARS-CoV-2 antigen presentation depends mostly on the MHC I molecules, but MHC II plays a role as well [36]. Previous research has linked several types of HLA to SARS-CoV-2 exposure, including HLA-B 4601, HLA-B 0703, HLA-DR B1 1202, and HLA-Cw 0801 [37], while alleles for HLA-DR0301, HLA-Cw1502, and HLA-A 0201 are linked to protection against SARS infection [9]. MHC II molecules, such as HLA-DRB1 11:01 and HLA-DQB1 02: 0 in MERS-CoV infection, are associated with MERS-CoV infection [38]. In addition, several genotypes of antigen presentation are related to a higher risk of SARS infection [39].

The antibody form against SARS-CoV-2 is immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies, as with common acute viral infections. The IgM antibody for SARS disappears by the end of week 12, however the IgG antibody can last for months, indicating that the IgG antibody may be the primary protective factor [40]. SARS IgG antibodies are made up predominantly with S and N specific antibodies [18]. The number of $CD4^+$ and $CD8^+$ T cells in the peripheral blood of patients infected with SARS-CoV-2 was significantly reduced, indicating hyperactivation, as indicated by high levels of HLA-DR (CD4 3.47%). And double positive fractions of CD38 (CD8 39.4 %) [43]. CD4+ and CD8+ memory cells can survive for four years in a subset of SARS-CoV-2 patients if no antigen is present and perform T cell proliferation and interferon (IFN) production if no antigen is present [11].

During SARS virus infection, a cytokine storm is induced by uncontrolled systemic synthesis of pro-inflammatory cytokines, and other chemokines and cytokines are produced by immune cells. Individuals with SARS-CoV-2 and MERS-CoV had higher levels of IL-6, IFN-, CCL5, CXCL8, and CXCL-10 in their serum than those with mild to moderate disease [41]. In severe cases of emerging coronavirus infection, a cytokine storm will cause a violent immune system attack, acute respiratory distress syndrome, and organ failure, ultimately leading to death [40].

7. SARS-CoV-2 Therapeutics Approach

Many viral infections remain dormant for long periods of time, posing diagnostic and treatment challenges [42]. Antiviral selectivity toward the virus on the host cell and the identification of a unique target for the virus's life cycle are two other challenges in the virus's evolution [43]. It's difficult to develop a broad-spectrum antiviral agent because each virus has its own structure and function [44]. Many antivirals have a short half-life, resulting in increased treatment frequency and poor patient compliance [45]. Reduced bioavailability due to restricted solubility or permeability could result in greater doses and consequently in hazardous effects [46]. The development of medication resistance is probably owing to extended drug exposure, especially to immunocompromised patients [47].

8. Nanomedicine Approach for SARS-CoV-2 Therapeutics

The cellular mechanics of living cells are being devel-

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oped by nanotechnology and similar technologies which help to diagnose and treat diverse viral diseases in the early stages [50]. Nanotechnology Some of its uses include medicinal products and genes. Use of biological fluorescent labels and protein, pathogens, and tumor screening; biological molecules and cells separation and purification; fabric engineering; increased RMI contrast and Pharmacokinetic study [49]. It has since opened the door to a wide range of research and application with the ability to effectively treat viral disorders while also dealing with traditional anti-viral medications [50].

The nanomedicine method is an effective tool for improving COVID-19 treatment and renovating antiviral medicines [51]. Current antiviral therapies' limitations, such as impaired aqueous solubility and reduced bioavailability of antiviral drug sub-concentrations at reserve sites, can be overcome by nano transmitter-based antiviral drug delivery, resulting in dose reduction and reduced toxicity [52]. Specific organ, cell, and intra-cellular vectors engaged in pathophysiology of SARS-CoV-2 may also be targeted by targeting nanoscale vectors and reaching therapeutic concentrations in protective virus reservoirs, likely ACE2-expressing cells, and cathepsin-binding sites [53]. The supply of nanometer-based pharmaceuticals (including primary biological medications) ensures better biological half-life by preventing early dropping and degradation and avoiding renal or hepatic clearance [54].

Several nanoparticle strategies for co-encapsulating hydrophobic and hydrophobic drugs [55] have been described. To overcome lymph node drug deficiency in the oral synthesis of these drugs, lipid nanoparticles (LNPs) loaded with three antiretroviral drugs (ARVs) (two hydrophobic: lopinavir and ritonavir and one hydrophilic: tenofovir) were formulated, which demonstrated a long-term effect of plasma drug profiles and levels. In an in vivo model, a lymph node drug performs better in macaques [56]. This multifunctional nano therapy can be used to target SARS-CoV-2 in the central nervous system [57].

9. Nanomedicine Approach for SARS-CoV-2 Prophylactic

Most preventive techniques are designed to cause a strong neutralizing impact of the surface-exposed S protein, which produces specific T-cell response and neutralizes antibodies [58]. The fundamental achievement for protection against viral infection is the neutralization of antiviral antibodies. In US vaccine trials the nanoparticles of lipid-coated mRNA that cover the encoding of spike protein and recombinant adenovirus are used. Most coronavirus neutral antibodies are directed at RBD [59]. As a result, preventing viral attachment to ACE2 is the key immunological mechanism for avoiding infection, and most vaccine candidates adopt the technique of developing vaccine-inducing antibodies against RBD [60]. Nanoparticle delivery techniques can deliver antigens and adjuvants in the same particle carrier [61]. Reduced particle size, high loading efficiency, surface charge, increased bio-penetration across the mucosal barrier, and appropriate protection from intestinal fluids are all features of nanoparticles that promote their immunity [62].

Adjuvants that promote safety convey a counter-regulatory signal to the immune system, telling it to develop tolerance to incoming antigens. Vaccine auxiliary nanoparticles (VANs) are required to reduce the required antigen dose (dose sparing), allowing more units to be produced, made available to a larger population, and they improve the overall efficacy and safety of the generated immune response, particularly in the case of the COVID-19 pandemic [60]. Antigen and cyclic dinucleotide (adjuvant; agonist of interferon gene stimulator that produces type I interferon when cells are infected with intracellular viruses to protect the infected cells and nearby cells from local infection) co-loaded liposomal nanoparticles showed a dose-sparing effect, resulting in safe and uncompromised immune responses [63]. VANs designed to improve potency (by acting as immune booster signals, also known as "risk signals") work by informing certain immune cells to mount a protective immune response against a specific antigen [64]. VANs can operate as molecular adjuvant nanocarriers or have a physio-chemical property that stimulates or inhibits the immunological or anti-immunomodulatory pathway [65].

VANs have been used to improve vaccine efficacy and antibody responses in the elderly, who have the highest SARS-CoV-2 fatality rate [8]. Aging is linked to chronic subclinical systemic inflammation (inflammatory ageing) and acquired immune system impairment, also known as immune ageing [66]. Immune ageing is characterized by a significant decrease in immunoglobulin M, interferon levels, T cell number, rate of cell division and proliferation, neutrophil chemical concentration, and phagocytosis [67]. Many adjuvant technologies have been developed to improve influenza vaccination in the elderly, including cationic and anionic liposomes, viruses, and fine particles [68]. Adjuvant drugs have been shown in clinical trials to reduce the risk of developing pneumonia and influenza, and they play an important role in stimulating the immune system [69].

10. Conclusions

A Novel nanotechnology is one of the most imperative fields of science, that proposition incomes from the use

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of nano systems, like metallic nanoparticles, polymeric, liposomes, micelles, and lipid nanoparticles for drug encapsulation, improvement of its pharmacological properties, and drug delivery for effective target drug release. Nanomedicine and its components exert an imperative role in different stages of diagnosis, prevention, treatment, vaccination, and scientific research related to SARS-CoV-2 disease. Nanoparticles possess antiviral effects, as it can target the binding, entry, replication, and budding of SARS-CoV-2. As a result, nanomedicine-based therapeutic and preventive strategies are key assets for the curative management of SARS-CoV-2 disease, particularly in elderly immunocompromised patients, who have the highest SARS-CoV-2 fatality rate.

Consent for Publication

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Abbreviations

ACE2	Angiotensin converting enzyme 2
ARDS	Acute respiratory disease syndrome
ARVS	Anti-retroviral drugs
APC	Antigen-presenting cell
COVID-19	Coronavirus-2019
CTLs	cytotoxic T lymphocytes
E	Envelop protein
HCoVs	Human coronaviruses
HLA	Human leukocyte antigen
IFN	Interferon
IgG	Immunoglobulin G
IgM	Immunoglobulin M
LNPs	Liposomal nanoparticles
MHC	Major histocompatibility complex
nCoV	Novel corona virus
N	Nucleocapsid
PHEIC	Public health emergency international concern
RBD	Receptor binding domain
S	Spike protein
SARS-CoV	SARS- Like corona virus
VANs	Vaccine adjuvant nanoparticles
VLP	Virus like particles
WHO	World health organization

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ARTICLE

Tick-borne Diseases, Transmission, Host Immune Responses, Diagnosis and Control

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ABSTRACT

Present review article explains tick-borne diseases, transmission, host immune responses, diagnosis and control in relation to climatic variations. Ticks are hematophagous ectoparasites which suck large volumes of blood from livestock and humans. They release large numbers of protozoans, bacteria, rickettsia and viral pathogens during blood feeding and transmit disease pathogens through saliva. Due to heavy blood sucking by ticks animals face significant blood and weight loss that affect their overall health. Due to more severe illness, high economic losses were noted in livestock. This article highlights medically important tick borne diseases in man and livestock, its pathogenesis, diagnosis and treatment methods. The present article emphasizes invasion of hosts, host-pathogen interactions, tick saliva toxin induced host immune responses and biological effects. This article highlighted various tick control methods i.e. physical killing, acaricidal, biological, hormonal, genetic and immunological methods such as administration of protective antibody and vaccines for disease control in human being and his livestock. The authors suggest non-chemical environmentally safe methods for successful control of tick borne diseases to kill cattle, bird and canine invading ticks.

1. Introduction

Ticks rely on host blood, and live as ectoparasites of so many terrestrial vertebrates mainly mammals, birds, reptiles and amphibians. Due to blood sucking behaviours, ticks are capable of transmitting numerous human and animal bacterial, viral or parasitic diseases. Ticks are the most important vectors of human pathogens, leading to increased public health problems worldwide. Ticks are arachnids, having a body length of 3 to 5 mm in size. Along with mites, they constitute the subclass Acari. There are a number of medically important arthropods including vespids, ticks, mosquitoes, flies, and fleas mites and ticks. These small sized or tiny animals produce deadly toxins and cause lethal allergic reactions.They are major vectors of arthropod-borne pathogens in the both tropical and sub-tropical and even in temperate countries [1-3]. Few wild animals mainly veretebrates are reservoir hosts of ticks. Ticks are vectors of a number of pathogenic viruses, bacteria, fungi, protozoa, and filarial nematodes. These were evolved during a million of years of long evolutionary period over millions of years [4]. Ticks as ectoparasites always rely on blood feeding and its all feeding stages pass their life cycle pass in different hosts and generate morbidities of medical and veterinary importance [5]. (Table 1). Ticks maintain enzootic cycles and make continuous transmission of pathogens among livestock and

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wild animal hosts. All these tick-borne pathogens show severe consequences in man and his livestock. Tick borne disease largely affects livestock and cause economic harms to dairy farming industry and veterinary medicine [6] (Photograph 1).

Photograph 1. 1a hard tick parasite on cattle skin, 1b-1c soft ticks, 1d-1i tick infestation on dairy cow and buffalo skin.

There are two big families of ticks i.e. Argasidae and Ixodidae. Among them Ixodes genus, contain highly infectious tick species which transmit a range of pathogens and give rise diseases in livestock [7]. Hard ticks bear a beak-shaped structure in their mouthparts; while soft ticks have their mouthparts on the underside of their bodies (Photograh 1). Adult ticks are either ovoid or possess pear-shaped bodies, which remain engorged with blood. They found tightly stick over host skin by using its eight legs and continuously remain involved in blood feeding. Hard ticks are characterized by hard shield or scutum on their dorsal surfaces [8-11]. Soft ticks do not possess hard shield hence kept in Family Argasidae. Ixodidae is the family of hard ticks or scale ticks one of the two big families of ticks. It consists of over 700 species [12,13]. At present more than 904 various tick species have been listed throughout the world [14-19] .(Table 1).

Ticks are transmission vectors of numerous pathogens which are particularly sensitive to climatic changes and spread due to anthropogenic behaviour Both affect complexity of their cycle, parasites-host relationships and emergence of zoonotic diseases in live stock and wild animals.. More specifically tick borne pathogens spread due to variation in vector to host ratio, intensity of pathogen, ecological factors of that area [20]. Terminal point of epizootic never comes and diseases spread among mammals, including livestock and humans.

Ticks continuously feed on blood, for which remain attach to the host skin for days to weeks. These secrete anticoagulants and toxin in saliva to neutralize the host defenses. Ticks salivary glands secrete toxins, and passed into the blood through feeding, make livestock anemic and cause great economic losses to them worldwide [21]. Tick saliva is used as an invading liquid that imposes multiple severities in host and do impairment of physiological health [22]. Ticks for blood feeding puncture the host skin, damage it, and transmit various categories of dreadful infectious agents into host blood which cause serious diseases in host animals. Few newly emerged tick-borne infectious diseases are Lyme borreliosis, ehrlichiosis, and babesiosis [23]. Babesiosis and anaplasmosis are dreadful tick-borne diseases, these are spread by *R. microplus and R. annulatus* in bovine cattle herds. Ticks also transmit encephalitis virus [24] Rickettsia and other protozoa cattle parasites [6], Mediterranean Spotted Fever, Turalemia (human and animal) are emerging diseases [25]. There are no prophylactic therapies are available to control bovine babesiosis and anaplasmosis [26].

Due to their worldwide distribution, ticks usually found in all types of climates from hottest to coldest climates, and show worldwide distribution. But these are widely distributed especially in warm, humid climates. *Hyalomma anatolicum* and *Haemaphysalis bispinosa* was observed inside the cattle sheds. ixodid ticks in Maharashtra, India, was undertaken during 1976 to 1978 [27]. Both show their presence throughout India, but *H. spinigera* is confined in Southern Indian states, central zones, Orissa and Meghalaya [27]. From Kerala State 23 ticks species of domestic and wild animals have reported so far [28,29].

Both *Borrelia burgdorferi sensulato* and tick-borne encephalitis virus (TBEV) are transmitted by Ixodes ricinus tick.This tick species also *perform* transmission of *Anaplasma phagocytophilum, Babesia divergens, Babesia microti, Babesia venatorum, Borrelia miyamotoi, Neoehrlichia mikurensis, Rickettsia helvetica and Rickettsia monacensis* [30]. *Anaplasma phagocytophilum* live inside ticks and various wild and domestic animals It causes human granulocytic anaplasmosis (HGA) [31]. Few tick borne diseases caused by members of Rickettsiales and Legionellales remain asymptomatic in nature and spread by silent transmission to humans [32]. Rickettsia species initiate unknown pathogenicity to vertebrate hosts during tick blood meal acquisition [33]. Both the large and small forms of *Babesia species* (*B. canis, B. vogeli, B. gibsoni,* and *B. microti*-like isolates also referred to as "*B.vulpes*"

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Table 1. important bacterial diseases transmitted by various tick species

S.No.	Disease	Organism	Vector	Geographical distribution	Symptom	Treatment
1	Lyme borreoliosis disease	*Borrelia burgodorferi*	*Ixodes scapularis* *Ixodespacificus* *Ixodesricinus*	North east,Midwest and west coast states, Europe, south central U.S.	Erythema migrans, Fatigue, erythema migrans , malaise myalgias,arthralgias,headache, fever chills	Amoxicillin) or cefuroxime Doxycycline (Vibramycin, non-steroidal anti-inflammatory drugs
2	Anaplasmosis	*Anaplasmaphagocytophilum*	*Ixodesscapularis* *Ixodespacificus*	North east,Midwest and west coast states	Myalgias,headache, fever chills	Doxycycline Chloramphenicol (Chloromycetin) Rifampin (Rifadin)
3	Anaplasmosis	*Anaplasma platys*	*Rhipicephalussanguineus*	South central south western, U.S.	Myalgias, headache, fever chills	Doxycycline Chloramphenicol (Chloromycetin) Rifampin (Rifadin)
4	Ehrlichiosis	*Ehrlichiacanis*	*Rhipicephalussanguineus*	South central south western, U.S	myalgias,headache, fever chills	Doxycycline Chloramphenicol (Chloromycetin) Rifampin (Rifadin)
5	Ehrlichiosis	*Ehrlichiaewingii* *Ehrlichiachaffeensispanola mountain* *Ehrlichiasp*	*Amblyommaamericanum*	Cental and south eastern U.S. Extending northward along the atlantic coast	myalgias, headache,fever chills	Doxycycline Chloramphenicol (Chloromycetin) Rifampin (Rifadin)
6	Ehrlichiosis	*Ehrlichiamuris*	*Ixodesscapularis*	Upper Midwest(minnesota and Wisconsin)	myalgias, headache, fever chills	Chloramphenicol (Chloromycetin) Rifampin (Rifadin)
7	Rocky mountain spotted fever	*Rickettsia ricketsii*	*Dermacentorvariabilis* *Rhipicephalussanguineus*	South central and south westerna and eastern U.S.	myalgias, ,headache,fever ,malaise,vomiting , rash	Chloramphenicol tetracyclin Doxycycline
8	Tularemia	*Francisellatularensis*	*Ixodesscapularis* *Amblyommaamericanum* *Dermacentorvariabilis*	South and Midwest	myalgias, headache,fever chills vomiting fatigue, sore throat, abdominal pain , skin ulcers, diarrhea, lymphadenopathy	Chloramphenicol Streptomycin Gentamicin ,Tetracyclin, Fluroquinolones

and "*Theileria annae*") infect dogs in Europe, [34]. The most abundant and widespread tick species in Great Britain, in human relapsing fever (HRF) and African swine fever (ASF) are spread by *Ornithodoros moubata* argasid tick [35].

Ticks are responsible for the spread of diseases like Anaplasmosis, Babesiosis and Ehrlichiosis (Table 1). So far 19 tick borne diseases have been reported in animals and men, involving four protozoa (babesiosis, theileriosis, cytauxzoonosis, hepatozoonosis), one filarial nematode (acanthocheilonemasis), ten bacterial agents (anaplasmosis, ehrlichiosis, aegyptianellosis, tick-borne typhus, Candidatus Rickettsia vini, Lyme borreliosis, tick-borne relapsing fever [TBRF], tularaemia, bartonellosis, and hemoplasmosis), and four viral infections i.e. tick-borne encephalitis [TBE], Crimean-Congo Haemorrhagic Fever [CCHF], louping-ill [LI], and lumpy skin disease [LSD]) [36]. TBE virus is the most frequent virus associated with potentially severe neurological lesions. No treatment is available so far for this disease. The most frequent bacterial diseases cause neurological complications due to occurrence of Lyme borreliosis, Q fever and some rickettsial infections. In present review article we have critically *evaluated* the disease transmission by different tick species, disease causing pathogens, host immune responses, biological damages generated. This article also has *demarcated* important diagnosis methods, ticks prevention and various control programs.

2. Source of Information

For writing present comprehensive review article on tick-borne diseases, transmission, host immune responses, diagnosis, and control various databases were searched exhaustively. For finding and collection of relevant information on present topic specific terms such as medical subject headings (MeSH) and key words “tick borne diseases”, “pathogens”, tick control methods” and “biological effects” were used in MEDLINE to fetch out research publications published till 2021. Most specially for re-

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trieving all articles pertaining to the use of VIT for tick borne diseases, electronic bibliographic databases were searched and abstracts of published studies with relevant information on the tick borne diseases and transmission were collected. Furthermore, additional references were included through searching the references cited by the studies done on the present topic. For an extensive literature search most relevant terms were used individually and in combination to other key words. Efforts have been made to collect most recent information available on present subject. From database important abstracts, available on relevant research articles, books, conferences proceedings and public health organization survey reports were searched, downloaded and collated based on the broader objective of the review. For writing this review important research articles, its findings available from databases, including SCOPUS, Web of Science, and EMBASE, Pubmed, PMC, Publon, Swissprot, Google searches"were read well and tried to summarize the conceptual notings. By applying common methodology, important discoveries, findings and outcomes were identified and summarized in this final review.

3. Tick Habitat

Ticks are slow moving tiny creatures incapable of flying or jumping. These usually live in sandy soil, hardwood trees, and rivers, with an overt story of trees or at least shrubs. These also live in narrow spaces near animal houses, cattle yards, grassy mats, nests, found inside human dwellings in dark and very silently attacks roosting birds. All tick species rely on blood feeding from vertebrate hosts. For extensive blood feeding ticks apply all counteractive measures to weaken their hosts' immune and homeostatic mechanisms. They move by sensing carbon dioxide released in the breath of their hosts [37]. Ticks give eggs in dark places, mainly in narrow spaces or hole in the spring season. After embryonic development tiny larvae can emerge, which are seen crawling on to grass weds found in low-lying vegetation field. Ticks live on side lawn's edge where they crawl swiftly are a tick migration zone. More than 82% of tick nymphs reside inside grass fields and lawns [38]. Ixodid ticks also found in the vegetation grounds where antelopes and other herbivores come to forage in closed enclosures; where ticks show free-living intensively in large numbers. Ticks found in open grasslands to urban woody material, carpets, doormats and cloth seats. They also found in Antarctica, where they found stuck on penguins and feed upon their blood [28].

4. Tick Life Cycle

Ticks complete their life cycle in four i.e. egg, larva, nymph, and adult. Ixodid ticks pass their life cycle among three hosts, and complete single their life cycle in one year. Argasid ticks develop in consecutive seven nymphal stages (instars). Each one requires a blood for feeding. Tick's early larva just after hatching bears six legs, and it develops two more legs after a blood meal and *moulting* into the nymph stage [26]. Both nymphal and adult stages, possess seven segments and a pair of claws and possess eight legs. Tick's soft very small legs have sensory or tactile hairs which help them to find a suitable site on host skin [39] (Photograph 1). Ticks attach to a host bite. They remain engorge deep into skin and regularly suck blood this process may take days or weeks. Due to strong hematophagous nature all life stages of ticks are highly destructive and suck blood in groups. These lacerate host tissue and secrete a variety of biologically active substances which assist them in invasion of hosts and for enabling the uptake of a blood meal [40] (Photograph 1).

Ticks detect animal host by breathing carbon dioxide and body odors. They also sense through body heat, moisture, and vibrations [41]. For blood sucking ticks grasp the host skin by legs and puncture or cuts into the surface of the host's skin [42] (Photograph 1). They make tiny holes in the host's epidermis, into which insert their hypostome, and suck blood with the help of anticoagulants secreted in saliva that acts as platelet aggregation inhibitor [43,44]. Ticks mostly target marsupial and placental mammals, birds, reptiles (snakes, iguanas, and lizards), and amphibians for blood feeding [45]. Because ingestion blood, ticks are vectors of so many diseases that affect health of humans and other animals. Ticks harm largely domestic animals by making them anemic and damaging wool and hides [46] (Table 1) (Photograph 1).

4.1 One-host Ticks

Both ixodid and argasid ticks pass their life cycle in egg, larva, nymph, and adult in single host [47]. It starts with egg laying by females which after 4-5 days hatch and larvae emerge, just after eclosion they need a host for blood meal. After blood feeding larvae moult into unfed nymphs which also need host blood for their nourishment. After engorging on the host's blood, the nymphs moult into sexually mature adults that remain on the host in order to feed and mate. Other example of one host tick life cycle is Winter tick *Dermacentor albipictus* and the cattle tick *Boophilus microplus* [48]. *Dermacentor variabilis and D. anderson* (Ixodidae) also pass on their life cycle in four consequent life stages [49]. Ticks show a complex epidemiology but are of great ecological significance. They generate larger impact on clinical and socio-economic status of man due to occurrence of the pathogenic diseases [50].

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(Table 1) (Figure 1).

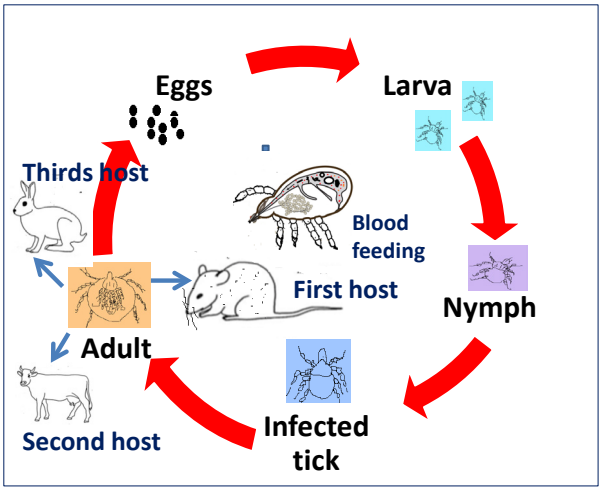

Figure 1. various stages of tick life cycle completed in different hosts

4.2 Two-host Ticks

There are few ticks species like *Hyalomma anatolicum excavatum*which complete their life cycle between two-host ticks [51]. From eggs laid by female ticks, after hatching tiny size larvae emerge, which crawl and attach to a host skin for sucking blood. They remain attached on the host after developing into nymphs which also reattach to the host for blood feeding. Once engorged, they drop off the host and find a safe area in the natural environment in which to molt into adults. Both male and female adults seek out a host on which to attach, which may be the same body that served as host during their early development. Once attached, they feed and mate. After mating tick females lay eggs and oviposit them in crevices, leaves, clothe and vegetation cover (Table 1) (Figure 1).

4.3 Three-host Ticks

Most ixodid ticks for completion of their life cycle need three hosts. For establishing parasitism their females lay eggs thousands in number on the ground/garden soil. After hatching larvae emerge, which attach themselves for feeding blood primarily on small mammals and birds. After feeding, they detach from their hosts and molt to nymphs on the ground, which then attach and feed on larger hosts before dropping off yet again in order to molt into adults. Adults seek out a third host on which to feed and mate. Female adults engorge on blood and prepare to drop off to lay her eggs on the ground, while males feed very little and remain on the host in order to continue mating with other females [51]. (Table 1) (Figure 1)

5. Transmission of Diseases

Ticks as ectoparasites of livestock in tropical and sub-tropical areas tramsmit wideranges of pathogens and cause severe economic losses. Ticks transmit a wide range of viral, bacterial and protozoan pathogens; many of them establish persistent infections of lifelong duration in the vector tick. Ticks also spread pathogens through transovarially to the next generation, these pathogens are *Borrelia spp., Babesia spp., Anaplasma, Rickettsia/ Coxiella, and tick-borne encephalitis virus and Theileria parva.* Ticks also transmit protozoan, rickettsial, Ehrlichiacasis and viral diseases of livestock, which are of great economic importance world-wide [52]. Ticks and tick-borne diseases (TBDs) affect the productivity of bovines in tropical and subtropical regions of the world. Most of the poor countries have cattle farming is main economic source, leading to a significant adverse impact on the livelihoods of resource-poor farming communities [52] (Table 2).

Ticks suck blood regularly from vertebrate hosts for nutrients, survival, oviposition and developmental stage for completion of their life cycle. Blood feeding by ticks severely impacts animal health, results in *reduction weight* and induce anemia among domestic animals. Ticks suck blood and feed on birds, mainly on migratory birds (Table 2). Migrating birds carry ticks with them. Thus ticks population spread through cattle trade, bird homing and trans-national trans-human movements.

The castor bean tick, *Ixodes ricinus*, transmit *Borrelia burgdorferi, s, Anaplasma phagocytophilum, Rickettsia helvetica, Francisella tularensis, Neoehrlichia mikurensis, Bartonella spp., Borrelia miyamotoi and Babesia spp [53]. However, Babesia microti, Borrelia miyamotoi (another spirochete), Anaplasma phagocytophilum, and Powassan virus* also transmitted by ticks [54]. Ticks transmit potential tick-borne pathogens that affect human health that results in severe pathogenesis and mortality [30]. Babesial vector tick synthesize defensin against *Babesia sp*. Ticks also transmit *Borrelia sp* and viral pathogens among wild canines, and white-tailed deer (Table 2). Tick borne diseases are also spread by birds which feed on *Borrelia burgdorferi Sensu Lato*-infected blacklegged mites.

Distribution of population of various tick species depends on regional ecology and climatic situation. Climatic situations also support vertebrate population growth, survival and reproduction. Ticks also feed blood on ro dents and wild and domestic animals mostly mammals and infect them with various disease pathogens. Mostly domestic and wild mammals are reservoir hosts of tick transmistted pathogens mainly protozoans, bacteria, viruses, rickettsia, fungi and others during their feeding process

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Table 2. important protozoan diseases transmitted by various tick species

S. No.	Disease	Organism	Vector	Symptom	Treatment
1	Babesiosis	*Babesia vogal*	*Rhipicephalus sanguineus*	Severe headache, nausea, abdominal pain, hemolytic anemia, fever, chills, sweats	Atovaquone PLUS azithromycin, Clindamycin PLUS quinine
2	Babesiosis	*Babesia gibsoni*	*Rhipicephalus sanguineus*	Severe headache, nausea, abdominal pain, hemolytic anemia, fever, chills, sweats	Atovaquone PLUS azithromycin, Clindamycin PLUS quinine
3	Babesiosis	*Other Babesiasp*	*Rhipicephalus sp.*	Flu like symptoms, body aches, loss of appetite, nausea, or fatigue	Antiparasitic drugs,
4	Hepatozoonosis	*Hepatozoon americanum*	*Amblyomma maculatum*	fever, lethargy, decreased appetite, weight loss, muscle pain/weakness, reluctance to move, and discharge from the eyes and nose	Trimethoprim-sulfa, clindamycin, and pyrimethamine.
5	Hepatozoon canis	*Hepatozoon americanum*	*Rhipicephalus sanguineus*	haemolymphatic tissues and causes anaemia and lethargy.	Imidocarb dipropionate at 5-6 mg/kg IM and Tab. Doxycycline
6	Tularemia	*Francisella tularensis*	*Ixodesscapularis Amblyommaamericanum Dermacentorvariabilis*	cough, chest pain, and difficulty breathing, swollen lymph nodes near the skin ulcer	Streptomycin, gentamicin, doxycycline, and ciprofloxacin
7	Rocky mountain spotted fever	*Rickettsia ricketsii*	*Dermacentorvariabilis Dermacentorandersoni Rhipicephalussanguineus*	Fever, chills, or loss of appetite, nausea or vomiting, skin rashes or red spots, eye redness, headache, rash on the palms and soles, or sensitivity to light	Doxycycline , Monodox, Vibramycin,
8	Q Fever	*Coxiella brunette*	*Dermacentor andersoni*	Pain in the abdomen or muscles, fatigue, high fever, malaise, chills, or night sweats, coughing, headache, nausea, or shortness of breath	Antibiotic doxycycline
9	Ehrlichiosis	*Ehrlichia chaffeensis*	*Amblyomma americanum, Ixodes scapularis*	Human Monocytic plasmolysis, fever, chills, malaise, nausea, diarrhoea	Doxycycline
10	Anaplasmosis	*Anaplasma phagocytophilum*	*Ixodes scapularis Ixodes pacificus*	Human Granulocytic plasmolysis, fever, headache, chills, and muscle aches.	Doxycycline, single IM injection of long-acting oxytetracycline at a dosage of 20 mg/kg.

on the hosts [55]. After mosquitoes *ticks* are second vector group that transmit large number of pathogens to humans [56]. Blood feeding by ticks is the most prevalent modes of transmission as they infect human and his pets. Due to easy dissemination of highly infectious pathogens which cause multiple infection, ticks are proved most dangerous vectors worldwide. Tularemia is a dreadful zoonotic disease caused by the *Francisella tularensis*, a highly infectious Gram-negative *Cocco-bacillus.* This is also used as biological weapons for generating potential bioterrorism threat and classified in category A of warfare agents by the CDC [57]. *Rickettsia parkeri Luckman* (Rickettsiales: Rickettsiaceae), is the tick-borne causative agent causes a more sever fatal disease rickettsiosis [58].

Tick-borne diseases are expanding regularly and these are reaching to new geographical locations in northern part of the world. This isdue *international* trade of animals and food and clothes. Recent surveys indicate tick-borne diseases like rickettsioses, Lyme borreliosis, tularemia, are transferring from *non-endemic* areas due to transmission favorable climatic conditions. Lyme disease and human ehrlichiosis have been spread in geographical locations because of increased movements of *Ixodes scapularis* and *Amblyomma americanum* [59]. Tick have saliva toxins cause paralysis in human hosts [60].

There are very few tick vectors which tansmit arboviruses [61] but these more frequently transmit obligate intracellular bacteria belong genus Rickettsia [62]. Ixodes ticks are commonly infected with both *B. microti* and *B. burgdorferi*, and transmit these pathogens together into hosts. Lyme disease-causing spirochete, *Borrelia burgdorferi.* And *B. microti* are also transmitted through transfusion of blood products A. [63]. Various species of genus Ixodes infest livestock, mainly spread diseases in grazers [64]. Tick infestation is directly occur due to increase in outdoor activities and movement of man and his pets in orchards, grassy vegetation and lawn. Dogs exposed to ticks and tick borne diseases by living with infected dogs and cattle [65].

Ixodid ticks *Ixodes pacificus, Ixodes persulcatus, Ix-*

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odes ricinus and Ixodes scapularis, are major vectors which transmit tick-borne pathogens. For taking a regular blood meal ticks remain attached to their hosts for almost 1-2 weeks to obtain blood meals (Table 2). *Ixodes ricinus* a mediclly important free living tick transmit disease pathogens i.e. *Amblyomma spp, Anomalohimalaya spp, Bothrio crotons spp, Cosmiomma sp, Dermacentorspp, Haemaphysalisspp, Hyalomma spp, Ixodes spp, Margaropusspp, Nosomma sp, Rhipicentorspp, and Rhipicephalusspp* in man and other mammalian hosts [66]. The Lyme disease spirochete *(Borrelia burgdorferi)* to humans is transmitted by western black-legged tick *(Ixodes pacificus)* [67,68]. Ixodes pacificus (Acriixodidae) nymphs do make horizontal and vertical movements in hardwood forest for searching hosts. *Ixodes hexagons* or brown Ixodid ticks parasitze domestic and wild animals (Table 2).

6. Major Tick Borne Diseases

Tick-borne diseases are transmitted through the bite of an infected tick. These include Lyme disease, Anaplasmosis, Ehrlichiosis, Babesiosis, Powassan (POW), Rocky Mountain Spotted Fever, and Tularemia. Ticks can be infected with bacteria, viruses, or parasites. Tick-borne diseases are those spread by the bite of an infected tick (Table 3). Most of the tick-borne diseases are caused by saliva secreted toxins during blood feeding on hosts, parasite spreads through blood supply in various body parts after its entry. Tick borne diseases are also spread through blood products and blood transfusion. The transmission of tick-borne pathogens via blood transfusion is of global concern [69]. (Table 3) (Figure 2). Few important tick brone diseases which are responsible for illness and severely affect public health are following:

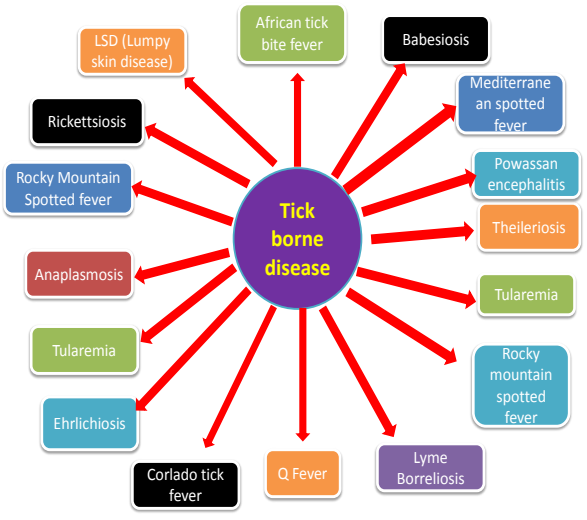

Figure 2. various tick borne diseases

6.1 Lyme Disease

Ixodid ticks are notorious bloodsucking ectoparasites and are completely dependent on blood-meals from the hosts. Lyme disease, is an infectious, inflammatory disease, this is caused by *Borrelia burgdorferi,* parasite a spirochete consulate bacteria. This pathogen is transmitted to humans by the bite of blacklegged tick *(Ixodes scapularis)* [70]. *Borrelia burgdorferi* parasite contains membrane protein antigens which are differentially regulated during its life cycle. During blood feeding tick also release anticoagulants, anti-inflammatory and antihemostatic compounds in saliva with this parasite [71]. (Table 2). This disease is a potential health threat to the Canines mainly dogs, and lives stocksriti. Important symptoms of Lyme disease are fever, chills, headache, joint and muscular pain, fatigue, and a skin rashes with erythema migrants. It manifests with lameness, anorexia, fever, lethargy, lymph adenopathy and, in some cases, fatal glomerulo-nephritis. Lyme disease patient display erythema migrans, and bullseye-like rash. It also causes long term complications in untreated cases, it imposes arthritis, facial palsies, meningitis, and carditis. The vaccine could be an efficient approach to decrease. For treatment of Lyme disease oral antibiotics are provided, but few patients (10 to 20%) suffer from persistent, non-specific symptoms and identified post-treatment they display Lyme disease syndrome (PTLDS). Lyme disease is treated by vaccination of healthcare providers and public health practitioners**.** It also needs public awareness and tick control [72] (Figure 2).

Lyme disease is also caused by multi-system bacterial infection that cause relapsing fever [73]. Important symptoms of this disease are red signs over skin, mild fever, and influenza-like symptoms with ocular manifestations [74]. Some patients also show neuro-meningeal complications and severe neurological lesions [75]. At earlier satge diagnosis remains difficult because of nonspecific symptoms [76] in endemic areas [72]. Borrelia causes Tick-borne relapsing fever (TBRF), it is transmitted spread by Ornithodoros tick vectors [77].

6.2 Anapalsmosis

Anaplasmosis is spread by a bite of *Anaplasma phagocytophilum and Anaplasma marginale* a highly infectious hard tick. This disease is prevalent in northeastern and upper midwestern U.S. and Pacific coast. Its large numbers of cases have been reported worldwide also occurs worldwide during last two decades. Anaplasmosis is caused by the bites and blood feeding of infected Ixodes scapularis, known as deer tick *(Ixodes scapularis)*. Anaplasmosis is hemolytic disease and its main symptoms are

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Table 3. Important tick borne diseases in man and livestock

S.No.	TBDs	Species	Host	Vector Tick species	Symptoms
1	Rocky Mountain Spotted fever	*Rickettsia rickettsia (Dermacentor variabilis, Dermacentorandersoni)*	Man, Dog, small mammals are the natural reservoirs in the wild	*Dermacentor variabilis and Dermacentor andersoni.*	Subclinical infection to severe or fatal multiorgan collapse. Blackened or crusted skin at the site of a tick bite.
2	Rickettsiosis	*Rickettsia parker (Amblyommamaculatum)*	Small mammals, and humans	*Dermacentor variabilis Dermacentor andersoni Rhipicephalus sanguine*	Rickettsial vasculitis, vascular inflammation
3	Pacific Coast tick fever	Rickettsia philipii (Dermacentoroccidentalis)	Horses, deer, cattle, lagomorphs, peccaries, porcupines, tapirs, desert bighorn sheep, and humans	*Dermacentor* species	Eschar or tissue necrosis
4	Mediterranean spotted fever	Rickettsia philipii (Dermacentoroccidentalis)	Man	*Dog tick Rhipicephalus sanguineus*	Headache, fever andmaculopapular rash
5	African tick bite fever	Rickettsia philipii (Dermacentoroccidentalis)	Ruminants , equids, candis, felids, rodents, human	*Rhipicephalusannulatus,Rhi. Bursa, Rhituranicus, Rh isanguineus,Hyalomma excavatum, H rufipes, H marginatum,H.dromedarii, Haemaphysalis punctate, Haeparva , Hae.sulcata, Dermacentormarginatus, D. reticulatus, Ixodesricinus*	Severe headache, nausea, abdominal pain, hemolytic anemia, fever, chills, sweats
6	Theileriosis	Rickettsia philipii (Dermacentoroccidentalis)	Ruminantsequid	*H. marginatum, H.anato licum,Hexcavatum,Hdetr itum, Haemaphysalisspp, Rhipicephalus*	Anemia and, in some cases, jaundice or hemoglobinuria.
7	Cytauxzoonosis	*Cytauxzoonfelis*	Domestic cat	*star tick, Amblyomma americanum*	Necropsy, splenomegaly, hepatomegaly, enlarged lymph nodes, and renal edema
8	Hepatozoonosis	*Hepatozooncanis*	Candis felids	*Rhi. Sanguineus*	Fever, lethargy, decreased appetite, weight loss, muscle pain/weakness, reluctance to move, and discharge from the eyes and nose
9	Canine filariosis	*Acanthocheione-mareconditum*	Dogs	?	Weight loss, cough,fatigue
10	Anaplasmosis	*Anaplasmaphag-ocytophilum, A. platys, A. marginale, Abovis, A ovis, A central*	Ruminants dogs, human	*Ixodespp, Dermacentorspp, Rhi picephalusspp,Haemaphysaliss pp,Hyalommaspp,Ornithodoru sspp*	Human Granulocytic plasmolysis, fever, headache, chills, and muscle aches
11	Ehrlichiosis	*Ehrlichiacanis*	Dogs	*Rhi. Sanguineus?*	Human Monocytic plasmolysis, fever, chills, malaise, nausea, diarrhoea
12	Aegypti anellosis	*Aegyptianellapullorum*	Duck	?	Parasitize the erythrocytes, infectious anemia".
13	Tick borne typhus	*R. hoogstraali, R. aeschlimanni, R. slovaca*	Human Dogs	*H. marginatum, H. aegyptium, H excavatum, D. marginatus, Haeparva*	High fever, nausea, malaise, diarrhea, and vomiting.

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14	*Candidatus R. vini*	*R. vini*	Birds	*Ixodesarboricola, Haemaphysalis longicornis ticks*	Leukopenia and elevated hepatic enzyme levels
15	Lyme Borreliosis	*Borreliaburgdorferi, Bor. Turcica sp.* Nov	Human, dogs, horses	*I .ricinus, H. aegyptium, H excavatum, D. marginatus, Haeparva*	Circular rash with red oval or bull's-eye marks appear anywhere on body, fatigue, joint pain and swelling, fever, swollen lymph nodes
16	TBRF	*Bor. Crocidurae*	Rodents	*Ornithodoroserraticus*	Fatigue, fever, loss of appetite, malaise, night sweats, or sweating, loss of muscle, phlegm, severe unintentional weight loss, shortness of breath, or swollen lymph nodes
17	Tularemia	*Francisella tularensis*	Human	?	cough, chest pain, and difficulty breathing, swollen lymph nodes near the skin ulcer
	Bartonelliosis (Cat scratch fever)	*Bartonellahenselae*	Cat	?	Fever, headaches, fatigue, poor appetite, brain fog, muscle pain, and swollen glands around the head, neck, and arms.
18	Hemoplasmosis	*Mycoplasma haemofelis*	Cat	?	Lethargy, weakness, reduced appetite, dehydration, weight loss and intermittent pyrexia
19	CCHF	CCHF virus	Human	*H. marginatum, haemaphysalisspp, Rhipicephalusspp, I .ricinus*	Stomach pain, and vomiting. Red eyes, a flushed face, a red throat, and petechiae
20	LI	LI Virus	Sheep	?	
21	LSD (Lumpy skin disease)	LSD Virus	Cattle	?	Skin nodules and oedema, enlarged lymph nodes, nasal discharge
22	Tick borne encephalitis	*TBE virus complex Ixodusricinus, Ixodus persulcatus*	Europe Asia, Middle East	Common and widespread	Swelling of the brain and/or spinal cord, confusion, and sensory disturbances
23	Powassan encephalitis	*POW virus (Ixodesscapularis, Ixodes cookie)*	Nortthern US / adjacent Canada far eastern Russia	Rare increasing	Swelling of the membranes surrounding the brain and spinal cord
24	Other TBEsOmsk hemorrhagic fever (OHF), Kyasanur Forest Disease(KFD) Louping ill virus, others	*OHF virus KFD Louping ill virus (IxodesDermacentor, Haemophysalis*	Europe , Russia, China, Japan , India , Southeast Asia, Middle East	Rare to common within localized range some increasiing	High-grade fever with chills, intense frontal headache, severe myalgia and body aches
Bunyavirales /Orthonairovirus					
25	Crimean - Congohemorrhagic fever (CCHF)	(CCHF) virus *(Hyalommamarginatum* other tick species	Europe Central Asia, India , Africa	Common and widespread increasing	Headache, high fever, back pain, joint pain, stomach pain, and vomiting.
	Bunyavirales /Phelbovirus				
26	Severe fever with thrombocytopenia syndrome (SFTS)	SFTS virus *(Haemophysalislongicornis , Rhipicephalusmicroplus*	China Korea Japan	Uncommon increasig	Thrombocytopenia, leukopenia, nausea, and vomiting

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27	Heartland virus disease	Heartland virus *(Amblyammaamericanum)*	Midwestern and Southwestern US	Rare	Fever, fatigue (feeling tired), decreased appetite, headache, nausea, diarrhea, and muscle or joint pain
28	Bhanja virus disease	*Dermacentor, Haemophysalis*	Africa Central Asia Southern Europe	Rare	
	Reovirdae/ Coltvirus				
29	Corlado tick fever	CTF virus *(Dermacentorandersoni)*		Rare	Photophobia, vomiting, meningoencephalitis, and slight or partial paralysis.
30	Eyach virus disease	Eyach virus *(Ixodusricinus)*		Rare	Biphasic fever, chills, headache, generalized musculoskeletal aches, and malaise.
	Orthomyxovir Idea / Thogotovirus				
31	Thogotovirus (THOV) disease, Dhori virus (DHOV)disease Bourborn virus disease	(THOV) (DHOV) disease *Bourborn virus (HyalommaAmblyomma , Rhipicephalus)*	Africa, Asia Europe, (THOV) (DHOV) USA, (Bourborn)	Rare , Bourborn virus isolated from *Amblomma americanum*	Meningitis and neuromyelitis optica

chills, fever, body and headache, fatigue, nausea, vomiting, and diarrhea. patient also feel loss of appetite, chills, abdominal pain and muscle aches [78,79]. Its asymptomatic coinfection show plus *anaplasmosis* SFG rickettsiosis. Anaplasma phagocytophilum harbors inside patient erythrocytes and was identified by cell sorting assay [80]. Parasites house inside ticks show regional climatic induced variations in genospecies and strain frequencies differing in pathogenicity [81]. For its identification DNA tests are performed [80]. For human granulocytic anaplasmosis diagnosis is important to identify *Ixodes scapularis* ticks and zoonotic amplification of *Anaplasma phagocytophilum* [82]. (Figure 2)

6.3 Tick-borne Babesiosis

Babesiosis is a zoonotic, disease that is caused by a tick-borne intra-erythrocytic hemoprotozoan parasites of genus Babesia. Disease provokes due to climate changes and rising vector population of Ixodes ticks and presence of human and other mammalian hosts in plenty [83]. Babesiosis is a major threat to human health [84]. Both dirofilariosis and babesiosis in was spread in central Europe, it was reirted in microfilaraemic dogs [85]. Babesiosis is transmitted through blood transfusion or congenitally [86]. Its pathogen mainly invade human erythrocytes and lyse red blood cells that results in febrile hemolytic anemia much similar to human malaria [87]. Disease also occurs in dogs in tropical regions [88].

Besides, human babesiosis canine babesiosis is spread by a tick species *Dermacentor reticulatus* [89]. Canine babesiosis is caused by many species of Babesia. Babesiosis disease level is ascertained by a ICD-9-CM diagnosis code [90]. This disease is also reported in canines that is caused by Babesia canis, B. vogeli, B. gibsoni, and B. microti from infect dogs in Europe [91]. *Bovine babesiosis* is caused by several species of *Babesia spp.,* including *B.bovis, B. bigemina, and B. divergens Human babesiosis* is caused by *Babesia microti* and it is endemic in the northeastern and the upper Midwestern United States(Figure 2).

Human babesiosis is caused by intraerythrocytic protozoan parasites the *Babesia microti*. This disease remains asymptomatic in beginning and patenint feel high fever, sweats, chills, nausea, headaches and fatigue after 4-5 days of infection. Babesiosis patient loss appetite, fatigue, urine color become dark due to jaundice and anemia. Babesiosis patients also show few clinical symptoms like anorexia, dehydration, temperature, dullness/depression, diarrhea /constipation, pale mucosa, hepatomegaly, vomiting/nausea, splenomegaly, distended abdomen/ascites, yellow coloured urine, emaciation/weight loss, and ocular discharge [92]. Extracellular phosphorylated proteins found in serum of *infected* patient are used for diagnosis [93]. Disease is also transmitted by blood transfusion and causes heavy mortality in high risk populations in spite of anti-biotic therapy [94]. (Table 2) (Figure 2) Few broad spectrum antibiotics such as atovaquone plus azithromycin or clindamycin and quinine are prescribed for the treatment of babesiosis patients.

6.4 Tick-borne Encephalitis

Ticks are important vectors of encephalitis virus (TBEV) and Omsk hemorrhagic fever virus (OHFV). These are highly pathogenic ticked-borne flaviviruses. These are leading cause of encephalitis that is an emerging disease, spreading in many regions in Eurasia in dogs. Tick-borne encephalitis virus is a dreadful pathogen. It is transmitted from nymph-to-larva and in small mammals [95]. Ticks infect domestic and wild dogs and accidental

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and during extensive search of vertebrate hosts. TBEV infect neural tissues in humans, while OHFV causes lysis of blood cells and evoke hemorrhagic fever [96]. Tick secrete neurotoxins HT-1, saliva ticks during blood feeding it causes paralysis in man and animals [97]. Tick bites during blood feeding transfer pathogens of Lyme disease, human granulocytic anaplasmosis and human babesiosis [98]. Powassan virus causes meningoencephalitis in North America. This is a neurovirulent flavivirus [99]. (Table 2) (Figure 2)

Tick also harbors endogenous viruses and modulation tick-borne pathogen growth. Ticks also transmit viruses with diverse genetic attributes, these are placed in two orders, nine families, and at least 12 genera. Tick-borne encephalitis virus (TBEV) evokes severe neurological diseases in humans in different parts of world [100]. The salivary gland secretions in the hematophagous parasites, blood sucking arthropods such as ticks have a greater role to counteract their vertebrate host's homeostasis, inflammation, and immunity [101]. Tick saliva contains microbiome communities of microorganisms, including viruses, bacteria and eukaryotes [102]. Both *Ehrlichia ruminantium* (ER) and *Ehrlichia chaffeensis* obligate intracellular pathogenic bacteria, and fatal tick-borne disease like hot water and monocytic ehrlichiosis in livestock [103] and man [104]. (Table 2) (Figure 2).

6.5 Powassan Encephalitis

Powassan encephalitis is spread by woodchuck tick *(Ixodes cookei)*, deer tick (*Ixodes scapularis* and squirrel tick *(Ixodes marxi)*. This is a fatal neuroinvasive disease first reported in Powassan, Ontario in 1958. Its major symptoms are mild fever, head and body pain, vomiting, aphasia, muscle weakness, seizures, confusion, loss of coordination and slurred speech. Due virus invasion on brain patient under go dementia and death. No established and effective treatment of disease is available. Its early treatment of tick-borne disease is critical and in later stage it causes severe health issues in affected patients.

6.6 Lumpy Skin Disease

Lumpy skin disease is caused by *Borrelia burgdorferi* into the mammalian hosts by an infected-tick bite of various species of Ixodid ticks belong to genera Rhipicephalus (i.e., brown dog tick), Dermacentor (i.e., American dog tick), Amblyomma (black-legged tick, Lone Star tick), and Haemophysalis yellow dog ticks in various parts of wolrd (Table 2). *B.* h*ermsii* and *B. turicatae* (in the southwest) cause infantile tick paralysis [60]. (Figure 2)

6.7 *Borrelia miyamotoi* Disease

Borrelia miyamotoi infection is spread by the black-legged tick *(Ixodes scapularis)*. It was detected in deer ticks in the eastern United States and Russia. This is a spirochete bacterium resembles with *Borrelia species*. It also spread tick-borne relapsing fever. It was first identified and isolated from ticks in Japan in 1995. Infected female ticks lay eggs, and its larval offsprings get natural infection and become an important participant in the transmission cycle. Important symptoms of *Borrelia miyamotoi* disease are fever, chills, fatigue, severe headache, muscle/joint pain.

6.8 *Borrelia mayonii*

Borrelia mayonii is Gram negative spirochete that causes Lyme disease in North America and midwestern United States. *Borrelia mayonii* infect humans and ticks, and Blacklegged ticks *(Ixodes scapularis)*. *I. scapularis* is a transmission vector. The major symptoms of the disease are fever, chills, headache, fatigue, body and joint pain and cardiac, neurologic and arthritic problems.

6.9 Alpha-Gal (Red Meat) Allergy

Alpha-gal allergy is a severe food allergy that is caused by the bite of a lone star tick. Alpha-gal allergy is caused by transfer of Alpha-gal (galactose-alpha-1,3-galactose) a sugar molecule found in red meat by the star tick to humans. Sugar molecule triggers delayed allergic reaction that persists for three to six hours. The other symptoms which are noted in patients are hives and/or severe itching, swelling of the lips, face, throat, or other body parts, shortness of breath, nausea, vomiting, diarrhea, abdominal pain, sneezing, headaches, anaphylaxis (Figure 2).

6. 10 Bourbon Virus

Bourbon virus infection was first identified in Midwest and southern United States mainly in in Kansas and Oklahoma states. This is very rare infectious disease and its patients show mild symptoms like fever, fatigue, rash, muscle and joint pain.

6.11 Colorado Tick Fever

Colorado tick fever (CTF) is a viral infection (Coltivirus) that is caused after bites made by an infected Rocky Mountain wood tick i.e. *Dermacentor andersoni*. Its patient shows important features like fever, rash, low white blood cell counts, heart problems and severe bleeding.

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6.12 Ehrlichiosis

Human ehrlichiosis starts with mild fever associated with lymphoadenopathy. It is caused by several bacterial species *Ehrlichia chaffeensis, E. ewingii, Ehrlichia* muris-like agent, Panola Mountain *Ehrlichia species*, and Anaplasma phagocytophilum [105]. This disease is transmitted to humans by star tick *Ambylomma americanum*. Disease is noted in the southcentral and eastern U.S. More recently ehrlichiosis have emerged as new infections that may be associated with neuro-meningeal complications. Borad spectrum antibiotics are prescribed for the treatment of ehrlichiosis, till the date no suitable vaccine is available so far [106].

6.13 Mycoplasma

Mycoplasma fermentans is also transferred with Borrelia bacterium via an infected tick the Lyme disease causative agent. This is smaller than bacteria, it invade body cells disrupt the immune system, causing severe fatigue, joint pain, nausea and neuropsychiatric problems (Figure 2).

6.14 Rocky Mountain Spotted Fever (RMSF)

This is spread by the American dog tick (*Dercacentor variabilis*), Rocky Mountain Wood Tick (*Dermacentor andersoni*), and Brown Dog tick (*Rhipicephalus sanguineus*).The brown dog tick also transmit bacterium Rickettsia rickettsii. This disease more predominantly outbreak in the summer season. RMSF shows unique illness features like fever, paralysis, sequel, chronic arthritis, and also impose neurologic or cardiac problems (Maureen McCollough) [107].

6.15 Tick Borne Paralysis

Ticks transmit pathogens through bite which causes loss of motor function and induce paralysis. Mainly few toxins are secreted by female ticks of *Amblyomma aculatum* which react with host's tissues and cells and generate toxicoses [108]. *Ixodes holocyclus* also generate same morbidity and induce paralysis [109]. Toxins secreted by these tick species generate positive inotropic responses in rat left ventricular papillary muscles and positive contractile responses in rat thoracic aortic rings [109]. Spirochetes are blood-borne pathogens transmitted through the saliva of soft ticks but they never evoke paralysis in host [110]. Destruxin A secreted by *Rhipicephalus (Boophilus) microplus* ticks (Acari:Ixodidae) causes tetanic paralysis [111] (Table 2) (Figure 2).

6.16 Rickettsioses

Rickettsiosis diseases is caused by an obligate intracellular bacteria belong to the genus Rickettsia. Two species *Rickettsia phillipi* and *Rickettsia parkeri* cause rickettsiosis. This disease is transmitted to humans by the Gulf Coast tick *Amblyomm amaculatum* and Pacific Coast tick Dermacentor occidentalis ticks. Rickettsia conorii, pathogen causes Mediterranean spotted fever while Rickettsia *parkeri, and Rickettsia akari* causes rickettsioses in United States [112]. Rickettsioses in this region is transmitted by dog tick *Rhipicephalus sanguineus* and the camel ticks *Hyalomma dromedarii*. These are important vectors and reservoirs of Rickettsiae. Disease is spread by infected male ticks through sexual transmission. Rickettsiae have been detected in spermatogonia, spermatocytes, and maturing spermatids [70] (Table 3) (Figure 2).

6.17 Tularemia

Tularemia is also known as rabbit fever, it is a dreadful zoonotic disease caused by the *Francisella tularensis*, a highly infectious Gram-negative coccobacillus. In man tularemia is also caused due to direct contact. The main vectors of tularemia pathogen are dog tick (*Dermacentor variabilis*), the wood tick (*Dermacentor andersoni*), and the star tick (*Amblyomma americanum*). Pateint feel fever and face skin ulcer at the site of tick bites.

Tularemia is spread in humans by the dog tick (*Dermacentorvariabilis*), the wood tick (*Dermacentorandersoni*), and the lone star tick (*Amblyommaamericanum*). Tularemia is bacterial infection sometimes it is also called rabbit fever, and development of an ulcer at the site of infection also seen. This disease is also spread by inhalation of contaminated dust or through contaminated food and water [114]. Disease shows important clinical symptoms including spiking fevers, inflamed lymph nodes and eyes, pneumonia and weight loss. This is also used as biological weapons for generating potential bioterrorism threat and classified in category A of warfare agents by the CDC [57,115]. (Figure 2). Parasite is detected in wild species, of animals lagomorphs, rodents, carnivores, fish and invertebrate arthropods [116]. *Francisella tularensis* is also detected in large number of animal species. [117]. *F. tularensis* holarctica, biovar I is also found in common marmosets (*Callithrix jacchus*) [118] Few broad spectrum antibiotic aminoglycosides, the fluoroquinolones and the tetracyclines are recommended for the treatment of this diseases [119]. The macrolides found highly effective against *F. tularensis* grown in phagocytic cells than in acellular media [120]. Important tools which are used for diagnosis of tularemia are PCR, ELISAs, MAT and IFA [121] (Figure 2).

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7. Immune Responses

For control of ticks there is immense need to study tick life cycle, tick-borne pathogens, and tick-host interactions. There are so many control methods which have been used to control ticks in various parts of world. These are based on biomacromolecular repository and its enzyme inhibitors by using genomes, transcriptomes, and proteomes. Most of the methods are mechanical, chemical, genetic, repellents, pesticides, toxic baths, and environmental and community based control mechanism. During blood feeding ticks secrete plethora of biomolcules in saliva which directly responsible for inflammation, vasoconstriction and the modulation of host defense mechanisms. Saliva secreted rerine protease inhibitors are used to prepare innate immune defense. Saliva secreted molecules do hemolymph coagulation and induce egg development. Till the date so many enzyme inhibitors like serine protease inhibitors (SPIs), which inhibit various tick biological processes found more appropriate. These will become effective tick control agents in future [122].

Salivary secretions in ticks are responsible for transmission of pathogens to the various animal hosts including man. Tick saliva is a complex mixture of various peptides mainly toxins and non-peptides. These substances strongly counteract hosts' homeostasis, immunity, and inhibit tissue-repair and wound healing. The ixodid ticks salivary glands (SG) secreted saliva contains a rich mixture of anti-hemostatic, anti-inflammatory, and immune modulatoranti-coagulatory, anti- vasoconstrictory, and anti-platelet aggregation factors. Tick saliva produces itching or pain and initiate blood feeding by making incision in skin cells. Ticks inject toxins which generate cellular and humoral responses. Tick brone pathogens affect immune system of other invertebrates, and induce humoral and cellular immune responses and affect signaling pathways in higher vertebrates mainly mammals. These pathogens also affect redox metabolism, complement-like molecules and action of regulatory biomolecules [123]. Ticks bear antigen families evasions, Isac, DAP36, and many others on their surface. Sialostatin L (SialoL) is cysteine protease inhibitor identified in the salivary glands of the Lyme disease vector *Ixodes scapularis*. Tick salivary glands secrete cystatin sialostatin L2 which suppresses Type I interferon responses in mouse dendritic cells. Dendritic cells (DCs) secrete IFN in response to tick saliva proteins. Sialostatin L also shows immunomodulatory action on dendritic cells and obstruct autoimmunity. SialoL significantly decrease LPS-induced maturation of dendritic cells in C57BL/6 mice [124].(Table 2).

Tick salivary gland secreted bio-molecules ticks induce immunomodulation in hosts. These also obstruct innate immunity and inhibit the generation of adaptive immune responses. The only way to stop feeding in ticks are antigen evoked acquired immune responses in immunologically-strong animal hosts. Tick saliva toxins also act as allergens these induce severe IgE-associated allergic reactions. These also cause fatal anaphylaxis, after subsequent saliva toxin exposure to the skin cells [125]. Borrelia species affect differentiation of THP-1 Cells while *Ehrlichia chaffeensis* causes monocytic ehrlichiosis in man [93,126]. Tick saliva more specifically salivary cystatins secreted by hard tick Ixodes scapularis, sialostatin L (Sialo L) and sialostatin L2 (Sialo L2) in saliva inhibits differentiation, maturation and function of murine bone-marrow-derived dendritic cells. *Borrelia burgdorferi* pathogen interact with Toll-like receptors and evoke immune responses (Table 2).

Ticks as vectors secrete immunosuppressant peptide, and, immunoreactive proteins and antimicrobial peptides which also used in host defense. Few non-coding small RNAs regulate synthesis of these peptides at post-transcriptional level [127]. Tick harbor rickettsiae that spread spot fever in cattle and human [128]. Rickettsiae produce two immune dominant outer membrane proteins; rickettsial, Omp A (rOmp A) and rOmpB which are strong antigen and could be used for vaccine production.Besides this, ticks secrete hundreds to thousands of proteins into the feeding site in saliva. Tick salivary gland secreted natural substances play an important role in modulation of host defense mechanisms [129]. Few of them neutralize innate immune functions and inhibit the formation of adaptive immunity. Similar Australian tick *Ixodes holocyclus* secrete toxins and other active components which show immunomodulatory effects.Tick salivary products exposed to *Borrelia burgdorferi, Anaplasma phagocytophilum* dihydrolipoamide dehydrogenase 1 affect host-derived immunopathology during microbial growth inside hosts [129]. Similar immunomodulation is also seen in other blood sucking arthropod vectors mainly mosquitoes, tse-tse flies and sand flies which also transmit pathogens during blood feeding [130]. For treatment of neurologic diseases immunoglobulin therapy is provided [131]. (Table 2).

For therapeutics of tick-borne encephalitis a thiomersal-free and albumin-free (TBE-vaccine) was developed in Australia 2000 [132]. For neutralizing paralysis causing toxins secreted by *Rhipicephalus evertsi evertsi, Rhipicephalus appendiculatus, Boophilus microplus and Ixodes holocyclus ticks monoclonal antibodies* are used *[133]. A recombinant* veterinary vaccine is also developed to neutralize effect of tick neurotoxin peptide. Though, this vaccine is successful, cost-effective, and provides long-term protective immunity against tick-induced paralysis [134]. Simi-

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larly, a vaccine is also administered to decrease the Lyme disease incidences [135]. Moreover, for seeking protection against Anaplasma marginale VirB2, VirB7, VirB11, and VirD4 proteins are adminsitered as immunogenic components. These show effective serological responses in man [136]. Similarly, few outer membranes (OM) proteins are used for immunization of cattle to defend from *Anaplasma marginale* tick infestation. These provide complete protection against disease and persistent infection. Polyclonal dog antiserum is also used for treatment of tick paralysis (Table 2).Other approaches are also tried for development of tick vaccines for prophylactic use [137].

However, for preparation of an appropriate vaccine complete genome sequencing of bacterial parasites of ticks and its antigens is must be identified and charecterized [138]. This highly distinctive type IV secretion system stays as neurotoxins found in tick saliva [139]. More specifically, surface protein with α_3 integrin binding and channel forming activities responsible for *Borrelia burgdorferi* [140]. And a plasminogen receptor BosR (BB0647) released in outer membrane of Borrelia burgdorferi governs virulence expression could be used as antigen [141]. Nitric oxide also function as an antimicrobial effector molecule, it is produced by activating mouse macrophages in response to viral infection. It is implicated in antiviral defense mainly against flaviviruses [142]. Ceftriaxone is recommended when parenteral antibiotic therapy against tick borne microbial pathogens [143]. More specifically, oraldoxycycline,amoxicillin and cefuroxime axetil are used against Lyme disease pathogen.

8. Diagnosis

For diagnosis of tick brone diseases methods are used. Among them most frequently method is enzyme immunoassay (EIA), followed by western blot test(s). For diagnosing blood specimens of HGA and babesiosis patients various microscopy methods [143]. Babesiosis generated plasminogen are tested by using chromogenic assay. Besides this, and concentrations of high mobility group box-1protein (HMGB-1), intercellular adhesive molecule-1 (ICAM-1), vascular adhesive molecule-1 (VCAM-1), soluble urokinase receptor of plasminogen activator (suPAR),thrombin activatable fibrinolysis inhibitor (TAFI), soluble thrombomodulin (TM)and plasminogen activator inhibitor-1 (PAI-1) level is determined by using ELISA [144]. In clinical samples Babesia pathogen is also identified by staining with Giemsa stain in blood smears. Besides this, PCR, and anti-babesia antibody titers are also used for identification of *Babesia* sp.[145]. These is a need for development of diagnostic methods, vaccine development, "omics" analysis, and gene manipulation techniques of local *Babesia* strains [146].

Skin biopsy specimens are diagnosed for lesions by using immunohistochemical stains. For diagnosis of rickettsiae polymerase chain reaction (PCR) is used [147]. For testing samples from asymptomatic anaplasmosis cases PCR and an indirect immunofluorescence assay (IFA) is performed to identify tick-borne infectious diseases [148]. Because serology provides a low specificity and high sensitivity and used for testing acute and convalescent samples. But PCR and immunofluorescence tests were found more apparopriate for anaplasmosis diagnosis as both provide more auathentic results [149].

SDS-PAGE gel electrophoresis is used to identify and chareterize the basic functions of tick saliva proteins. Morespecifically, pathogen specific proteins of Lyme disease are identified by SDS-PAGE gel electrophoresis, ELISA (enzyme- linked immunosorbent assay) and immunoblottin [150]. These are also diagnosed by measuring the level of Immunoglobulin G1 isotype [151]. More specifically spotted fever caused by rickettsiasis can be identified by LPS lipopolysaccharides antigenicity. *Theileria lestoquardi,T. ovis and T. annulata* are detected by using molecular methods in the blood of Goats and Ticks. Mast cells and IgE levels are used to detect tick borne allergy.

9. Effect of Climate on Emergence of Tick-borne Diseases

Tick borne illness found almost in all climatic regions because of wide distribution and occurrence of various ticks species adapted in local environment. Moreoften, climate cycles determine genetics, adaptability, host-parasite interaction and pathogen multiplication. The main endemic areas of tick brone diseases are forest sites, high density urban and rural habitations.. Tick infestation is a major animal health problem world wide, its higher endemicity is noted in Middle East and North Africa, tropical and subtropical countries [152]. The disease prevalence, infestation and invasion accelerates with climatic favourability and tick borne pathogens spread very fast and make heavy economic losses to livestock farming and wild life. Emergence of tick-borne zoonotic diseases also severely effect human health, as both morbidity and deaths are noted higher Northern Hemisphere due to regional variations climatic variations and rising resistance in ticks and tick borne pathogens. Moreoften, hydroclimatic changes occur due to unstable weather conditions which also affect the range of some infectious diseases, including tularemia. Tularemia incidences are directly related to climate variables,and assessment can be done for future disease outbreaks by analyzing these varaibles rainfall, humidity, latitudinal gradient, temperature and photo period [152]. In

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middle east and NorthAfrican countries domestic livestock are more severely attacked by multiple tick species due to harsh environmental conditions. These areas have most suitable climate and vegetation for tick population growth and easy availability of large number mammalian hosts [153]. Hence, there is an immense need in mapping of tick borne diseases based on ecology of area evoked across their geographic distribution to evaluate burden of pathogens transmitted by ticks [154].

Tick infestation is affected by climatic conditions in mountain region and its incidences increase with increase in elevation and latitude. Temperature, rainfall, humidity, day periodicity, landscape and altitude increase risk of tick-borne diseases. Spatiotemporal conditions affect distribution of ticks in temperate climate. In cold countries dogs or cats possess broad range of tick-borne pathogens and easily transmit them and generate important public health issues. Climate mainly temperature and vegetation affect horizontal distribution of ticks and tick borne parasites in all different climatic zones. Tick borne disease mapping shows high to low density of tick and its host population and disease pathogens in agro-ecosystems and forest ecosystem. Ticks from these areas show regional variation in tick-borne disease incidence, vector abundance and pathogen prevalence. Moreoften, environmental changes and unstable climatic conditions affect tick population genetics and give rise isolation among several tick populations.

10. Use of Bioinforamtic Tools for Study of Novel Tick Antigen Proteins

For generating successful anti-tick vaccines, various known antigens from different tick species are compared and suitable gaps are identified to have new novel antigen structures. Moreover, tick aquaporin-1 (AQP1) protein is compared with other antigenic proteins by using multiple sequence alignment (MSA), motif analysis, for finding similarities and differences. Its structure analysis revealed tick-specific AQP1 peptide motifs. Moreover, for finding other identifcial features in antigenic BepiPred, Chou and Fasman-Turn, Karplus and Schulz Flexibility, and Parker-Hydrophilicity prediction models are used to predict these motifs' potential to induce B cell mediated immune responses mainly for production of antibodies for therapeutic purposes [155]. By using transcriptome studies genetically susceptible and resistant bovine hosts and their corresponding proteomes can be obtained. These will help to obstruct or modify of expression of many genes encoding mediators of parasitism in nymphs and larvae of ticks. Besides this, effect of few inhibitory proteins or enzymes can be identified in silico to certain metabolic pathways which restrict developmental stages of the tick. These insight should assist in developing novel, sustainable technologies for tick control [156].

Ticks invade cattle farm yard and severely affect farm production and economy of owners. Most of the under developed and developing countries have cattle yards, which play a paramount role in agriculture production systems, throughout the world. Hence, safety and animal health of cattle tick populations is highly important. For prevention of tick borne diseases in farm animals vaccination is done. Vaccines are also used to prevent the spread and re-introduction of tick brone zoonotic diseases in human beings [157]. *Ixodes scapularis* Tick bites use saliva toxins/proteins for modulation of the feeding site. Fibrinogen, is key protein that participate in blood clotting and wound healing. Ticks salivary secretions are anti-fibrinogen molecule [158]. Host genetics plays important role in immune responsiveness against ticks and tick-borne pathogens. Moreover, susceptible breeds display increased expression of Toll like receptors, MHC Class II, calcium binding proteins, and complement factors. These also show an increased presence of neutrophils in the skin following tick feeding. Resistant breeds had higher levels of T cells present in the skin prior to tick infestation. These also contain higher numbers of eosinophils, mast cells and basophils with up-regulated proteases, cathepsins, keratins, collagens and extracellular matrix proteins in response to feeding ticks [159].

Transmission of various pathogenic microorganisms to vertebrate hosts takes place by tick bites and blood sucking [160]. Tick salivary glands, secrete toxins or proteins which exhibit cytolytic, vasodilator, anticoagulant, anti-inflammatory, and immunosuppressive activity. For their survival ticks parasitize on number of animals as they need blood components for their survival and reproduction mainly completion of their life cycle varying among species [161]. In response to invasion of tick brone pathogens host body make defense by using innate immunity, but tick breach host cutaneous defenses prior to pathogen transmission and suck blood and become give rise infectivity [162]. As protease inhibitors obstruct blood feeding in ticks, these are thought to be good candidates for broad-spectrum anti-tick vaccines [163]. In other approach tick endogenous dsRNA corresponding to potential control targets within midgut and salivary glands are used as main target for obstrtion of tick blood feeding and lower down infectivity [164].

11. Tick Management and Control

11.1 Control of Ticks

Ticks spread various diseases i.e. viruses, bacteria,

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protozoan, in livestock and in man [165]. Because of their complex transmission its control involves multiple vertebrate hosts and variety of parasites, tick prevention is prevention very difficult [166]. Identification of factors responsible for tick survival, spread, and pathogen transmission, design and performance will help in reduction in tick population and the prevalence of tick-borne diseases [167]. In additions, there is a need of rapid diagnosis and clinical management [168]. In addition, for tick control both individual persons and professionally staffed tick-management programs mainly systematic treatment programmes for control of southern cattle fever tick (SCFT), caused by *Rhipicephalus (Boophilus) microplus* [169]. Efforts must be made to control tick populations by using multiple strategies to inhit or breakdown of pathogens transmission cycle [59]. Therefore, for controlling tick population implementation and adoption of integrated program is highly essential [73] (Figure 3). For large scale control both advanced tools and techniques must require to avoid human tick bites, and roll back tickborne diseases. Multiple infection by various fungal spores and necrotic toxins can more quickly control both ticks and tick-borne diseases.

Tick-borne diseases (TBDs) are treated by using antibiotics as prescribed to the livestock for killing ticks. Few tailor-made pesticides could be used by using dsRNAs. These affect P0 gene function in tick, *Rhipicephalus haemaphysaloides*. Use of these pesticides significantly cut down blood feeding, molting or reproduction in ticks [170]. Few noble anti-tick agents could be harvested by maintain laboratory cultures of tick cell lines. Its in vitro culture cell lines could be used for production secretory molecules against tick-borne viral, bacterial and protozoan pathogens [171]. Blood feeding inhibition is also possible by using immunological based inhibitory molecules [172]. Host-targeted new technologies and methods will prove good alternative of conventional pesticide of *Ixodes scapularis* [173]. Ethnobotanical substances were also found effective and affordable products against field and domestic tick. These natural products are highly economically affordable, environmentally safer after use. It could be adopted for community-driven tick control programs [174]. For large and massive control plant origin inhibitors for more innovative tick control [175] (Figure 3).

11.2 Use of Pesticides for Tick Killing

For successful control of tick-borne zoonotic diseases an integrated tick management program must be adopted [73]. For tick control few conventional tick control methods such as spray with chemical acaricides, fluid sprays like Jeyes, engine lubricating oil, pine and tarpene oil, latex are used. Farmers also manually remove ticks by hand picking and put them inside pouricide and ash missed cow dung for their immediate killing. *Aloe ferox* sap and solvent extracts of bark of *Ptaeroxylon obliquum* are used for killing of ticks. Farmers collect ticks by hand picking and kill by dumping them in kerosene oil or in tarpene oil. For tick control of acaricides are used. For regular tick prophylactic treatment DDT, flumethrin, Bayticol® are used at large scale. Though, synthetic pesticides are highly toxic to animals and humans.The synthetic pyrethroid insecticide phenothrin is combination with the hormone analogue methoprene topically applied to flea and ticks. Phenothrin kills adult ticks while Methoprene is used to kill ticks eggs. Flumeltrin B atical ® Peptide toxin and Nitric oxide are effective in tick killing. Bifenthrin and permethrin, both pyrethroids, are also used to control ticks measures.Besides these, few residual insecticides, FenvaStarEcoCap, Bifen IT, or Precor2000 Plus Aerosol are also to kill ticks. For quick killing of ticks' non-residual, contact space sprays that contain pyrethrins are used. These highly toxic synthetic acaricides show several negative side effects because they bio-accumulates at each stage and impose toxicity to non-target organisms/animals.

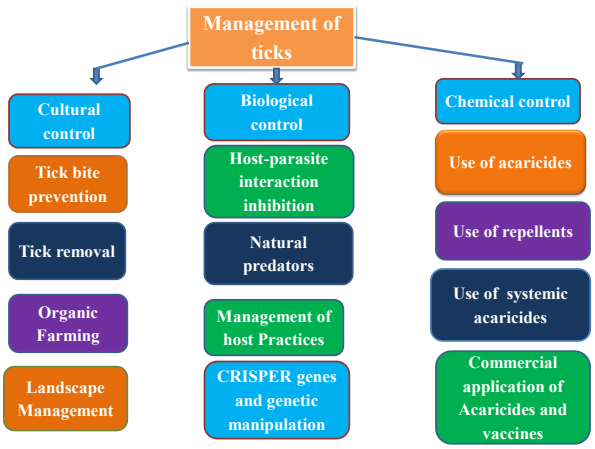

Figure 3. various methods used for management of ticks

Maxforce Tick Management System (TMS), was also used for control of field ticks. In this system bait boxes are prepared by using doxycycline *hyclate*-laden baits to attract and kill ticks. For protection of bait boxes from squirrel depredation galvanized steel shrouds are used [176]. For of flea and tick control in domestic cats fluralaner a novel isoxazoline is used, it works well as systemic ectoparasiticide [177]. For control of ticks traditional pesticides are also sprayed by using portable sprayers [178]. But due to longer exposure of pesticides tick population has developed resistance against these chemicals [179]. Therefore, to avoid harmful effects of highly toxic synthetic acaricides

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various latest eco-friendly strategies must be used and adopted for the prevention of tick and tick-borne illness. However, protection of environment and toxicity in hosts few tick avoidance, vector reduction programs, chemoprophylaxis, and natural repellents should be used for tick control [180]. For control of tick population Tekko Pro IGR is used to stop development in immature ticks. Ticks such as *Rhipicephalus turanicus* are controlled by using acaricidal plant products [181]. Natural tick repellents are also used for cultural management of ticks (Figure 3).

Bacillus thuringiensis (Bt) bio-insecticidal toxins are also used to kill ticks and its associating pathogens. Entomopathogenic fungi spores also control ticks mainly at enzootic or epizootic levels in their host populations. But for the use of bio-insecticides and other chemicals licensed applicators are required [182]. because they show cytotoxicity in human osteosarcoma cells, [183] damage membrane and obstruct organ functions [184]. Efforts should be made for their targeted release, low exposure period and safe use [185]. Ticks possess unique natural compounds which show multiple biological activities [186] much similar to defense molecules found in other animal groups mainly venomous [187,188]. For cultural control of ticks safe land-use pattern must be used, it reduces exposure to tick-borne pathogens and indirectly cutdown infestation (Figure 3).

Various acaricide formulations are used to control *Ixodes scapularis* nymphs a dreadful livestock tick residential areas. It successfully kills nymphal and larval stages if applied on skin topically or sprayed on grassy weds and narrow crevices or whole in doors and under neath of mats and clothes. These cutdown prevalence and intensity of parasitic interaction to small mammals [189]. Morespecifically, for long term killing of tick borne pathogen reservoirs, mild slow acting systemic acaricides must be used in endemic areas. These can do mass mortality of not only adult ticks but also nymphs and larvae successfully. These slow acting posions will prove highly useful tool for disrupting the natural cycle of the vector and pathogen. Besides this, fipronil baits made by using low dose of acracides and organic attractants can be used to control blacklegged ticks and other arthropod vectors [190]. For Lyme disease abatement besides tick control tick bites must be avoided in high risk areas [191]. However, for minimize tick attack and invasion on livestock and farm yard animals various plant orgin active constituents such as oil combinations, crude extracts, and pure compounds were also used. In addition, genetic and molecular methods which might obstruct tick feeding will prove ore safer and effective against different tick species [192]. Few antibiotics were found effective against some ticks, mainly blue ticks. A well practed method i.e. RNAi-mediated gene silencing is also used to inhibit expression of saliva toxin genes. This method genetically regulate the large tick population successfully (Table 3). But both acaricides and antibiotics they were found in milk that is again harmful for human being [193] (Figure 3).

For control of both ticks and pathogenic diseases caused by their field survey, pathogen identicfication and incidence time, status of climatic factors and interaction of host and parasite is highly important. In addition, identification of various tick species in different geographical is highly important. There is a need to use modern surveillance methods and environmental friendly methods to control ticks and tick-borne diseases [194].These must be less toxic, effective environmental friendly in order to reduce its impact on wildlife [195]. For control of ticks carbamates are also used [196]. But its low physiological dose should use because its exposure generates many numerous birth defects [197]. For tick control formamidines, is used, this a new group of acaricide-insecticides, that effectively kill ticks effectively with an uniques mode of action. For effective killing of ticks both structure--activity relations and environmental stability of compounds is very important. In additions, both toxicity and lateral transport of acarcides used for control of ticks must be explored to know its effects on physiology and metabolism on animal hosts. Most of the acaricides activate chlordimeform action by N-demethylation in vivo [198].

Pesticides put adverse effects and many of them detected organochlorine pesticides in serum concentration which lead to development of breast cancer [199]. Hence, there is a need to make and apply alternative methods, strategies and approaches to control tick and tick borne pathogen population in wild and in human surroundings. Farmers must adopt safe animal practices as use acaricides by rotation, and low toxic pesticide mixture formulations for tick killing on body surface of host animals. Manual removal of ticks, nutritional management, use of plant origin natural products, release of sterile male hybrids, are more safer methods to control ticks. Clean cultivation, pasture management, use of slow release posion baits and animal bathing cutdown chances of tick colonization. Use of multiple antigen based vaccines and antibodies obstruct tick feeding that is most safe and successful way to control population of different tick species vaccination. Among all integrated tick management methods, if two methods will be used in systematic combination with modern technological tools will provide much faster control. Such combination of methods will reduce selection pressure in parasites and may provide enlarged protection to acaricide-resistant individuals besides normal population [200] (Figure 3).

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11.3 Use of Repellents

Use of repellents repel ticks to invade wild-animal populations. Pets and wild animals should pass adequate quarantine delivery systems [201]. For protection of clothing and fabric repellents or acaricides are sprayed onto are used to deter ticks' access to human hosts [202].

11.4 Tick Control by Herbal Products

Plant natural products such as oils and other bio-organic compounds are also used for ticks [203]. Most of plant origin bio-organic compounds inhibit blood feeding in ticks [204]. These could be used to develop new highly active anti-tick agents [205]. These bioactive plant constituents need bio-evaluation process for their efficient isolation and identification [203] (Figure 3).

11.5 Natural Predators of Ticks

Red wood ants(Formica polyctena) are natural predators of Ixodes ticks and assist in reducing the local abundance of ticks [206]. Biological control agents are highly beneficial for safety of animals and protection of environment. For control of tick borne parasites and parasitism various biological agents can be employed [207]. One of the important tick controlling agent is an entomopathogenic fungi *Beauveria bassiana (B. bassiana 5197 and B. bassiana Evin)*. This fungal strain can easily grown on specific media and fungal spores are exposed to tick for inducing fungal infection [208]. Another strains of entomopathogenic fungi, the *Metarhizium spp*., also used to control tick population. *M. robertsii microsclerotia* or blastospores-granular formulations are used to control *R. microplus*, and is an important tool for control of field ticks [209] (Figure 3).

11.6 Control by Using Vaccines

For control of tick population various tick vaccines developed against saliva origin antigens have been used. Few of these vaccines have shown very high efficacy agsnat ticks as they obstruct blood feeding in ticks. These are cost-effective, sustainable and environmentally friendly and much safer alternatives of highly toxic acaricides used for tick control. SUB-MSP1vaccine is used for controlling tick population that infest cattle and sheep [210]. This vaccine is made from protective antigen, and its chimeric antigen was prepared from *Escherichia coli* membranes fused to *Anaplasma marginale* Major Surface Protein 1a (MSP1a). This SUB-MSP1a vaccine has low-cost and found highly effective for the control of cattle tick, *Rhipicephalus (Boophilus) microplus and R. annulatus* infestations in pen trials. Similarly, another SUB vaccine was developed by using recombinant subolesin in combination with other antigens for the control of cattle tick infestations [211]. Though, Subolesin (SUB)-based vaccines were found highly effective against so many tick species, but there is a need to mix and multiple antigen vaccine to curb tick infestations caused by various life stages of different tick species [212] (Figure 3).

Because tick salivary glands synthesize and release so many biomolecules which enhance transmission, and pathogenicity [213]. These tick saliva proteins involved in tick-pathogen interactions and are important targets in tick antigen-based vaccines [214]. Best example is tick midgut antigen BM86 that was used to prepare highly effective and promising vaccine for cattle tick control [215]. This Bm86 vaccines was commercialized in the 1990s (GavacTM in Cuba and TickGARDPLUS™ in Australia), only Gavac™ is available [216]. TBEV vaccines molecules from tick saliva mainly toxins are used as antigens [217]. Hence, for development of effective vaccines tick-pathogen-host interface, and identification of effective antigens is highly needful [218]. However, for preparaing development of potential anti-tick vaccines genetically modified pathogens and recombinant tick antigens could be used [219]. For generating live vaccine genetically modified viruses can be used. These may result in control of tick-vertebrate host transmission cycle in nature. But such type of vaccines will need environmental safety [220]. Further, tick-borne parasite released molecules must be identified and used for generation of potential vaccine or therapeutic candidates [221]. Few more recent methods extracellular vesicles (EVs) including exosomes that mediate transmission of flavivirus RNA and proteins to the human cells have been identified [222]. These are also used for development of novel vaccines to control ticks and tick-borne diseases [223].

Few B-cell epitopes in all the amino acid sequences are used to prepare single or arranged peptides to develop new strategies for the control and prevention of bovine anaplasmosis transmitted by ticks [224]. More specifically, after blood-feeding, tick midgut overexpresses proteins that play essential functions in tick survival and disease transmission. If salivary gland proteins/toxins responsible for tick parasitism and host interaction will be traced used for production of vaccine, these might disrupt life-cycle of ticks and eliminate tick harboring pathogens [217] .

The recombinant *B. microplus* Bm86 protective antigen was used to generate new vaccine and administer to protect cattle from tick infestations [225]. Similarly argasid chitinases and RPP0 were also used as protective antigens, for finding new vaccine targets against many tick species [226]. HlFER2 an iron-binding protein ferritin produced and secreted by hard tick *Haemaphysalis longicornis* was used

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to generate anti-tick vaccine antigen against multiple tick species [227]. Besides this, this aquaporin antigen found as an active ingredient in cattle vaccines targeted against infestations of *R. microplus* [228].

For control of ticks parasitize over various rodent species both oral vaccines and antibiotic baits are used [229]. It is also necessary to develop technology and antibiotics and tick controlling agents to cut down tick bites and protection of public health [230]. Though, tick invasion and infestation are regulated by many biotic and abiotic factors, and these could be manipulated to decrease tick bites. Recombinant antigens are used to generate vaccine for its effective and safe control. These vaccines successfully obstruct blood-feeding and ticks remain unfed and go on long-term starvation finally died due to antioxidant response [231]. Different levels of host anti-tick immunity affected gene expression in tick salivary glands. There is also a need to explore new drug targets for eco-friendly acaricide development. These proteins are encoded by certain genes which may be weakly expressed in ticks. These can be used to make tick resistant hosts. It will also reduce parasitism, and naturally infected bovine may develop antibodies prior to tick bites. It will also lower down the host susceptibility both ticks and easily neutralize the invasion of hosts by disease pathogen [232]. For mass vaccination of people there is a need to combine transfection technologies and the in vitro culture system prepare genetically modified live vaccines for mass vaccination [233]. For controlling babesiosis highly efficacious potential vaccine by using recent antigen technologies [234,235] (Figure 3).

11.7 International Tick Control Programs

Fro control of tick population various tick control program were launched at international level. For elimination of Cattle Fever, caused by *R. microplus* and Babesia Tick Eradication Program has been launched in Mexico and the U.S. [236]. Few countries like West Indies have launched identification and characterization of pathogens tick-borne diseases (TBDs) of human and livestock [237]. For tick eradication genetic analysis of tick population will be useful for finding types of pathogen-vector and host interrelationships. By applying genetic and molecular methods a wide array of tick and tick borne pathgen antigens could be searched world wide. These could be used to make vaccines for reduing the tick invasion on host populations [238]. MaxEnt models is best example of prediction for the occurrence of all tick species examined [239]. With this, disease diagnosis, type of invading pathogen, area wise incidence rate and climatic conditions must also study to ascertain efficacy of treatment and control method [240]. In cattle ticks acaricidal resistance is a major inderance in tick control, it could be resolved by using non-chemical methods [241]. In addition for control of ticks, study of host-parsite interactions is highly important at community level, because both community structure and the dynamics interlink ticks and its pathogenic association and host invasion [242]. For control of ticks such as Amblyomma ticks acaricide-impregnated leg-bands are tied on legs of goats [243].

11.8 Precautions

To minimize the tick infestation keep away pets from living sides. Regularly spray hosue beds, clothings curtains, grassy lawns with spray. Under side of doors and holes, crevices must be sprayed to ill tick nymphs. Apply creams to deter termites from feeding and skin penetration by infected tick larvae and nymphs. These risks can be minimized by dusting and spraying regularly the pet rooms and cattle yards with accaricides. Fumigation is also used to kill ticks inside wooden window, door mats, clothings, wooden furniture, and curtains. Regularly treat pets with anti-tick oils, sprays and provide them clean and health by regular bathing. For management of ticks in farm houses shorten and minimize grassy vegetation and use repellents to minimize tick movements.

12. Conclusions

Ticks are major vectors which transmit diverse group of pathogens and evoke diseases in livestock and make huge losses to veterinary, animal farms, pets and wild life animals worldwide. Ticks harbor a wide variety of pathogens in saliva. It is a repository of various disease pathogens including viruses, bacteria, malaria-like protozoan parasites causing babesiosis. Ticks cause direct economic losses; hence, their control is an important issue. For tick control conventional tick control methods such as household disinfectants, sprays, herbal leaf dusts, peptide toxin and Nitric oxide are effective in tick killing. Natural tick repellents are also used for cultural management of ticks. For tick control DDT, flumethrin, Bayticol®Farmers are used at large scale but these are highly toxic to animals and humans and show several negative side effects. For killing of ticks found on body surface of cattle dog, sheep, rabbit and other pats phenothrin a synthetic pyrethroids is applied topically mixed with methoprene a hormone analogue. Besides this, permethrin is also most commonly to control ticks. It is available in the market in different brand names and forms as shampoos, powders, emulsions, sprays, and coated over ribbons. But all these pesticides absorb in the skin and show lateral transport and are quite harmful for cattle. Repititive use of these acaricides against ticks is generating resistance and causing environ-

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mental contamination.

For control strict quarantine measures are enforced to prevent reintroductions of ticks with goods and materials ferried or parceled among countries. For the killing of ticks natural oils, bioinsecticides in form Bt toxins are used. For safety of man and his livestock vaccines are used. For successful control various models of tick population dynamics is required for predicting outcomes of control methods. It also needs better understanding of drivers of distribution, aggregation, stability, and density-dependent mortality. Climate-matching models, geographic information systems, and expert systems mainly subject experts and artificial intelligence are being used to identify unaffected areas in which tick pests could become established if introduced. Due to development of resistance in ticks species against conventional acaricides there is a need to opt immunological methods or vaccines to overcome the problem. Because ticks as ectoparasites suck blood from hosts and release pathogens in their blood supply. If any how blood feeding can obstruct, it will break the transmission cycle between and among hosts. If gut membrane based antigens mainly glycoproteins could be used as protective antigens tick feeding and infestations can be obstructed. Because antibodies raised against these tick antigens antibodies will be synthesized and these bind to receptor sites on the midgut of vector ticks. This close association will block tick-ingested tick-borne pathogens and their transmission. For control of ticks salivary gland extracts and various antigens isolated from tick saliva are injected to produce antibodies to obstruct feeding in ticks. For targeted control recent technologies such as transcriptomics and proteomics could be sued to discover novel genes, make expression libraries of cDNA for immunization. Do genome sequencing of expressed sequence tags, for rapid, systematic and global antigen screening. After comparison of transcriptomes and comprehensive study of various antigen types will assist in generation of more appropriate vaccines for control of ticks.. In addition, for killing of tick transmitted infectious agents broad spectrum antibiotics and vaccine doses are prescribed to control pathogenicity and deaths. There is need to apply integrated control methods and strategies for successful control of ticks.

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ARTICLE

Low Intensity Microwave Fields and Radiation and Their Interaction with the Human Body

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ABSTRACT

Sources of low-intensity microwave signals formation, which affect the metabolism processes when they interact with human body, are considered in the article. It's noticed that increasing intensity level of the technogenic signals in environment significantly exceeds natural electromagnetic fields and radiation (EMR). The peculiarities of the registration and measurement of low-intensity signals parameters of the microwave range are considered. The processes of the interaction of the microwave signals and human organism are analyzed. Formation mechanisms of the positive and negative microwave flows of the electromagnetic radiation are revealed. Particularly, possible formation mechanism of the microwave EMR fluxes of implants in the human body. The results of the experimental study of the EMR signals levels of the objects contacting with human body, partly materials for bone defects replacement and soft tissues regeneration so as materials for physiotherapy, are given. The use of the term "electromagnetic compatibility" for materials which contacting the human body, is proposed. The expediency of its use is proven. Microwave properties of materials for clothes, minerals and building materials, which can affect the human body and environment, have been also studied.

1. Introduction

1.1 Natural and Technogenic Sources of Microwave Radiation

There is a wide range of the electromagnetic signals of the Sun and space at all which irradiate the Earth. This spectrum covers the range from ultraviolet radiation (UV) with a wavelength of 180…400 nm to long-wave signals in the radio frequency range. Most of the signals in the UV range are absorbed by the Earth's atmosphere, and signals with longer wavelengths pass freely through the Earth's atmosphere.

UV signals are characterized by significant quantum energy (3.1…6.2 eV) and can have both a positive effect (bactericidal effect, increase immunity response, stimulation of photochemical synthesis of vitamin D, other therapeutic effects) and negative (burns, stimulation of processes that cause gene mutation and skin cancer, etc.) [1,2].

The visible part of the spectrum covers optical electromagnetic radiation in the range of 400-750 nm, and

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infrared (thermal) with a wavelength greater than 750 nm. The energy of the quanta of this radiation is less (2.95-1.24 eV), but the depth of penetration into the human body increases, which are widely used in various spheres of human life, in particular for the diagnosis and treatment [3,4].

If the protective reaction of the human body from UV radiation is manifested in the form of tanning on the skin surface, the optical signals of the visible and infrared ranges are better absorbed and more affect the deep layers of skin and inner organs, which is typical for the microwave range, too.

Particular attention should be paid to electromagnetic radiation of cosmic origin in the millimeter range (frequency 30…300 GHz), which includes microwave relict radiation with a maximum intensity at a frequency of 160 GHz [5].

The energy of the quantum signals of the mm range is much less than the signals of the optical range (10^{-5}… 10^{-4} eV), so their effect on the human body at equivalent power will be softer. The Earth's atmosphere selectively responds to frequencies in the microwave range, attenuating most of them, and at some frequencies, in the so-called "transparency windows", some microwave signals are transmitting without changes. The main reasons for the mm signals weakening passing through the atmosphere are their absorption, including resonant, by molecules of water, steam and oxygen. Microwave signals of cosmic origin can be characterized as primary. Solar radiation in the infrared range, passing through the atmosphere, gets to various objects on the earth's surface - water, soil, sand, stones, forest and grass cover and heats them.

It is known that any physical body emits electromagnetic waves in a wide range of frequencies when heated. Such thermal radiation is a noise-like, and the distribution of its energy density by frequency is described by Planck's law.

The maximum temperature of the earth's surface objects when heating can reach ≈ 50 °C. This leads to the formation of low-intensity microwave signals, which can be characterized as secondary.

Man-made (technogenic) sources of electromagnetic microwave radiation (EMR) should include generating structures for mobile communications, special military radio systems, generators for microwave therapy, etc.

Such sources create a significant electromagnetic background in the environment. The power level of signals from such sources ranges from tens of mW to 10^{-6} W [6,7]. At the same time, for microwave therapeutic generators, this level can be less than 10^{-6} W [8,9]. Electromagnetic saturation (pollution) of the ether of the environment is carried out mainly by permanent man-made means of communication and will increase in the future, due to the launch of new mobile communication systems 4G and 5G [10].

1.2 Features of Registration and Measurement of Low-intensity Microwave EMR

Primary and secondary microwave radiation are weak natural electromagnetic signals that constantly irradiate living organisms in their area of influence.

The power of such signals can be determined by Rayleigh-Jeans law.

$$P = 2\pi\beta(f,T)\frac{f^2}{c^2}kT_oS_0\Delta f\ , \tag{1}$$

where $k = 1{,}38\cdot10^{-23}$ J/K - Boltzmann constant; T - thermodynamic temperature of the object; f - radiation frequency; $\beta(f,T)$ - the coefficient of emissivity of the object (for grey bodies $\beta < 1$); Δf - the bandwidth of a measuring device, such as a highly sensitive radiometric system, S_0 - the area of the analysis surface, which is limited by the aperture of the receiving antenna.

The integral power *P* for the microwave range is also described by the Nyquist formula:

$$P = kT\Delta f \tag{2}$$

where $G(f,T)$ - spectral density of the noise signal.

The average power of the noise signal can be measured at a fixed frequency using a high-sensitivity radiometer with bandwidth analysis Δf, which is able to record the EMR of a heated body with emissivity β:

$$P = G(f,T)\Delta f = \beta kT\Delta f \tag{3}$$

where $G(f,T)$ - spectral density of the noise signal.

The human body, at its temperature of 36.6 °C, is also a source of weak microwave signals. The integrated power of the microwave signal of the human body or its areas is in the range of 10^{-13}…10^{-14} W, depending on the state of the organism. Studies have shown that the average value of the radiation level of the palm of the majority of respondents was within $(3…6)\cdot10^{-13}$ Вт [11]. The possibility to measure signals of this level is provided by the use of highly sensitive radiometric systems (RS).

Since the RS has its own temperature characteristic, the output signal power is determined by the temperature difference between the object of study and the measuring system, which is described by the formula

$$\Delta P = 2\pi K_1(f)\beta(f,T)\frac{f^2}{c^2}k(T_o - T_R)S_o\Delta f, \tag{4}$$

where $K_1(f)$ - the conversion coefficient of the receiving

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antenna, which also takes into account the influence of the radiation source; T_R - temperature of the radiometric system.

Thus, for the registration of low-intensity microwave electromagnetic fields and radiation, as well as the study of their interaction with the human body, the required sensitivity of radiometric systems must be an order of magnitude higher than the level of measuring signals.

Measurement of low-intensity signals is a rather complex technical problem, which is considered and try to be solved by specialists from different countries [7,12].

The authors of this article (review) have developed such systems in the frequency range 37…53 GHz and 53…78 GHz. These systems have a sensitivity of $3*10^{-14}$ W, which is confirmed by metrological certification by the State Standard of Ukraine. All studies conducted and described by the authors in the article were performed using the developed by their radiometric systems.

1.3 Processes of Interaction of Microwave Signals with Objects of Living Nature and the Human Body

In addition to natural sources of microwave radiation, in the environment there are signals generated by mm-range generators, relay lines, mobile communication systems, and so on. The level of man-made radiation power can significantly exceed the natural microwave background and, accordingly, have a significant impact on highly sensitive biological life forms, such as insects. Some authors note in their studies the harmful effects of a constant man-made electromagnetic background in the environment on the biosphere and living beings [13,14].

At the same time, low-intensity millimeter-wave microwave signals with short-term effects on living beings and the human body can have a therapeutic and stimulating effect, on which microwave therapy is based [15,16]. As noted, millimeter-wave signals are actively absorbed by water and oxygen molecules, which are also present in living organisms. The effect of resonant absorption of millimeter range signals is the basis of millimeter resonance therapy [15].

Millimeter therapy show its efficacy in treatment of gastroenterology problems (peptic ulcer), orthopedic (musculoskeletal disorders), neurologic (neuritis, pain syndromes) and other diseases [17]. The power level of therapeutic signals can be within 10^{-6}…10^{-9} W, and in some cases decrease to 10^{-12} W [18]. Positive changes in human body indexes during the treatment process at the specified power level of signals are fixed laboratory. The extremely low level of signals, which have positive effects on the human body, gave the authors [15] a reason to call this area "quantum medicine". Targets of irradiating microwave signals are biological structures at the cellular level.

Considering the process of interaction of microwave signals of the object of radiation with the human body, it should be noted that, as follows from formulas (1,2), it is determined by the temperature gradient between the human body and the heated object. If the temperature of the object is higher than the temperature of the human body area, $T_o > T_H$, thus a positive irradiating flow of microwave EMR is formed, and if $T_o < T_H$ - flow should be negative. These flows affect human body in different ways [19]. The impact can be spatial (non-contact) or contact.

Positive EMR flows increase the energy of the irradiation area, and negative ones reduce it. The absorption of the energy of the electromagnetic field by the cells of a living organism in the case of a positive flow stimulates biochemical processes and causes a reaction to the radiation in the different levels - cellular, tissue, organ and whole organism. Negative fluxes, on the contrary, due to energy extraction, reduce the excitation of the irradiation area and inhibit biochemical processes in it. It was proven with laboratory tests performed at the Kyiv Oncology Institute of the Ministry of Health of Ukraine on mice irradiated with C37 sarcoma tumor [20]. Positive EMR flows accelerated tumor growth during irradiation by 13.5%, and negative flows during the same time inhibited tumor by 27.4%.

2. Investigation of the Interaction of Low-intensity Microwave Signals of Objects in Contact with the Human Body

The authors studied the emissivity of a number of dielectric objects that come into contact with the human body, including

- materials for medical use (dental materials, implants, physiotherapeutic materials);
- materials for clothing;
- materials for jewelry;
- building materials.

In the course of the research, the emissivity of the material was determined, its power level at the heating temperature of 36.60 was compared with the power of the human body. By the difference between radiation levels of the human body and material the possible impact on the human body was supposed and evaluated.

2.1. Research of EMR of dental filling materials

Different filling materials are used in dentistry for crown restorations and root canals sealing [21]. Since the

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creation of EMR flows of opposite directions is possible, as mentioned above, it is advisable that the materials and tissues of the tooth were compatible.

The electromagnetic parameters of these materials (emissivity, grayness coefficient) must coincide (or differ slightly) with the corresponding parameters of the restored tooth tissues.

10 samples of materials were prepared for research [22], among them №№1-7 filling materials: 1- «Foredent» (SPOFA, Slovenia), 2- Endion (VOCO, Germany), 3- Endomethazone» (Septodont, France), 4-AH Plus (Dentsply, USA), 5-«Spectrum» (shadow A3,5) (Dentsply, USA), 6- «Compolux» (Septodont, France), 7- «Cavitan - plus» (SPOFA, Slovenia); samples №№8 - 10 - natural structures: 8 - enamel and 9 - dentin of the extracted for medical indications tooth, and 10 - spongy bone tissue received in surgical interention for medical indications. Samples 1 - 4 are used for root canals sealing, samples 5 - 7 intended for crown restorations. Emissivity of samples 1 - 4 were compared with emissivity of the sample 9, which them contact in. Electromagnetic radiation of the samples 5 - 7 was compared with sample 8 emissivity.

The study of experimental samples was performed using high-sensitivity RS at frequency 52 GHz. The obtained results of radiation intensity measurements of the studied dental materials are concentrated in the range (1,8-3,1)·10^{-13} W/см^2.

The biocompatibility of tooth materials and tissues was determined by comparing their emissivity coefficients, which was calculated by the formula:

$$\beta_M = Đ_M / P_{cbb} \quad (5)$$

where P_M- radiation power of the material; P*cbb* - the radiation power of an absolutely black body, which is calculated by the formula

$$Đ_{cbb} = \beta (f/c)^2 kT \quad (6)$$

where *f* - signal frequency; c- light speed.

The calculated values of the coefficients of emissivity of materials are given in Table 1:

Table 1. The coefficient β of the material relative to the level of radiation of an absolutely black body

№	1	2	3	4	5	6	7	8	9	10
β	0,71	0,6	0,46	0,41	0,46	0,51	0,48	0,46	0,67	0.58

Comparison of the coefficients of emissivity of filling materials and natural tooth tissues recorded the largest deviation in the pair 4 and 9-38%, then - 10,8% in the pair 6 and 8; the next - 7,8% in the pair 1 and 9 and perfect coincidence in pair 5 and 8. When using, preference should be given to materials with a greater coincidence of emissivity, because the positive and negative flows of the microwave EMR are minimal. Such a verification technique of dental materials compatibility is promising and deserves to be used in the development of new dental materials.

2.2. Microwave Properties of Materials for Incorporation in the Human Body

Modern surgical medical practice widely uses implants to replace separate elements of the bones, vessels, eye and even some entire organs. For these purposes materials of both natural and synthetic origin are used. These can be metals, synthetic polymers, bioceramics, various powdered fillers for bone defects and materials for soft tissue regeneration in some injuries. Widely used biotissues of animal origin, hybrid and composite materials, such as metal, as a base, coated with a dielectric, the characteristics of which are close to human biotissue [22]. Recently, research has been conducted using promising nanomaterials [23].

The use of biomaterials is associated with long-term research and testing for compatibility with human biotissues. The main indicators to which attention is paid are biological tolerance, resistance to biocorrosion, chemical stability, antimicrobial activity. This fully applies to all types of implant materials (Figure 1).

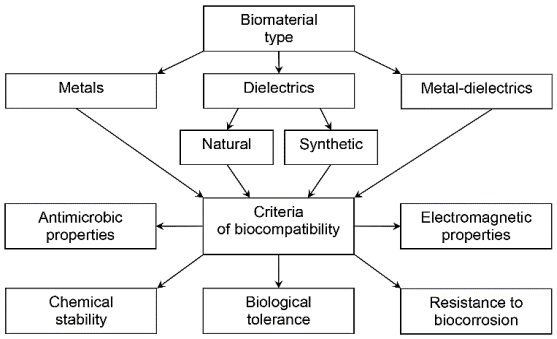

Figure 1. Classification of biomaterials and criteria for their compatibility

When implants made of foreign materials are introduced into the body, a biophysical interaction occurs between them and the biotissue, including through electromagnetic radiation. The electromagnetic properties of biomaterials have not yet been studied, although they can significantly affect the processes of their interaction with living organisms. The study of dielectric and combined materials for low-intensity fields and EMR has revealed another important criterion to pay attention to: the electromagnetic compatibility of the biomaterial with the biotissues of the human body.

The flows of electromagnetic energy generated by the implants with respect to the biotissue can be neutral, pos-

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itive or negative. It's especially important for biotissues cells, which are able to respond to EMR of the low intensity. Irradiating (electromagnetic) parameters of implants can significantly differ from the same characteristics of the alive tissues. When the flows of the implant and the biotissue are equal, full electromagnetic compatibility occurs. Significant deviation from it, in one direction or another, for a long time can lead to a violation of the electromagnetic state (homeostasis) of adjacent cells and the appearance of complications in the area of implant placement.

Figure 2 shows the scheme of formation and interaction of electromagnetic flows of positive (Figure 2a) and negative (Figure 2b) directioncreatedby installed bone implant 3 with in contact nearby biotissues of the human body - bone 1 and soft tissues 2. Symbols in the figure: P_1, P_2 - - radiation power per unit area of bone and soft tissue, P_3 - radiation power per unit of implant surface.

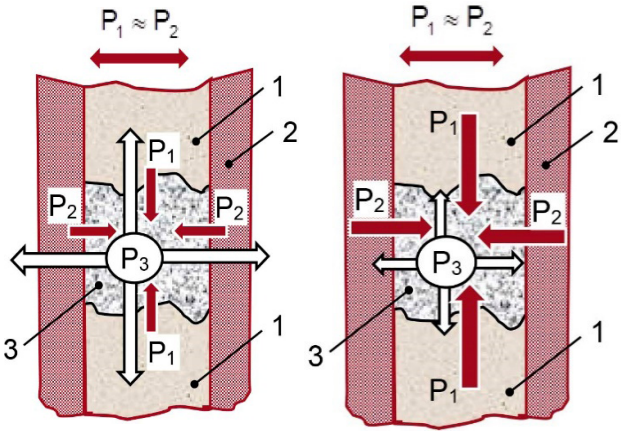

Figure 2. Schemes of Formation: a) positive flow when $P_3 > P_1 \approx P_2$ and b) negative flow when $P_3 > P_1 \approx P_2$

EMR power of bone P_1 and neighboring soft tissues P_2 physiologically consistent with each other in natural way, and the radiation level of the implant P_3 in the variant of Figure 2a is increased, so the surrounding biotissues receive constant additional irradiation. In the variant of Figure 2b, in contrast, the implant absorbs EMR of the surrounding tissue because its radiation level is lower.

The specified energy transfer in the form of a microwave EMR from an object with higher emissivity β*1* to an object with a lower level of parameter β*2*, at certain values and with prolonged action can both improve and worsen the conditions and course of reparative processes in the body. This process thus determines the clinical effectiveness of the study materials. The increase in microwave radiation is equivalent to the appearance of an inflammatory process, due to excess energy at the site of implant placement. If they should know researched electromagnetic interaction of material and biotissue, choice of implant become more effective.

The authors [24] conducted research of the EMR of some biomaterials used to replace bone defects in dental implantation. Value of the EMR of these materials was measured and compared to the radiation level of the human body. Studied materials were heated to the temperature 36,6 °C (equivalent human body temperature) and measurements of the EMR at the frequency 52 GHz were conducted.

Designation of research objects (Table 2): 1- the average value of human EMR (H - human): before each study of materials, measurements of the respondents' own radiation (study participants) were performed under the same conditions for comparison; 2 - Osteoplast K; 3 - Bone powder - (ground tubular bone of animal origin); 4 - Osteoplast T; 5 - Polihemostat - powder; 6 - Calcium salt of orthophosphoric acid $Ca_3(PO_4)_2$; 7 - Calcium salt of orthophosphoric acid with the addition of silver ions $Ca_3(PO_4)_{2+}Ag$; 8,9 - Bioactive glass (500-1000 microns), Bioactive glass (500-1000 microns) ; 10 - Biomin GT -700; 11 - Biomin GT-500.

According to the determined levels of EMR materials, the relative coefficient of emissivity have been calculated by the formula

$$K_1 = P_M / P_H , \quad (7)$$

where P_M - EMR power of the studied material, and P_H - the average level of human radiation power. The results of the experiment for indicated parameters are presented in Table 2.

Table 2. The coefficient K1 of the material relative to the level of human radiation

№	1	2	3	4	5	6	7	8,9	10	11
K_1	1,0	0,98	0,95	0,92	0,90	0,14	0,13	0,13	<0,01	<0,01

In the process of radiometric studies of these biomaterials revealed a number of features related to the human body and the properties of some materials. A number of materials have a emissivity of approximately the same (difference within 10%) with the human body. This probably causes a very small transfer of energy in the form of microwave radiation from a body with a higher level to a body with a lower level power of the EMR. Thus, materials that have a relative emissivity slightly lower than the level of human emissivity (Osteoplast K, Osteoplast M, Osteoplast T, Polyhemostat) are likely to interact more physiologically with the tissues of the human body. Using of such materials in dental implantation create almost identical positive flows of EMR from implants to body tissues, and this can lead to increased treatment efficiency.

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Other materials (calcium salt of orthophosphoric acid with the addition of silver in various quantities, Biomin GT - 500, Biomin GT - 700, bioactive glass) - on the contrary, have a low relative coefficient of emissivity (the difference from the human body by one or two orders of magnitude), may cause the formation of a negative microwave flow. The presence of a negative microwave flow from alive tissues to the implanted material can, in turn, lead to chronic inflammation, pain, and so on.

Thus, to improve the prognosis of engraftment and long-term successful use of implants, increase the effectiveness of treatment in general, it is necessary to take into account the level of microwave EMR flows of materials and the possible impact on the patient's body.

2.3 Electromagnetic Microwave Properties of Materials for Physiotherapy

Heat treatment is one of the most common procedures in physiotherapy, which uses a variety of dielectric materials, including minerals, peat, sand, mud and some materials of oil fields - naphthalene, ozokerite and paraffin. Among these materials, ozokerite and paraffin should be singled out. Each of them, alone or in a mixture, are most often used in physiotherapy treatment technologies. High (highest among physiotherapy materials) heat capacity, heat retention capacity and low (lowest among physiotherapy materials) thermal conductivity of ozokerite determine its high efficiency. According to medical special literature, there are three impact factors that affected the area of treatment: thermal, mechanical and chemical [25-27]. The therapeutic effects that occur, above all, include anti-inflammatory and vasodilating effects, as well as acetylcholine -like, estrogen - like and chemical effects of ozokerite.

Heat treatment technologies provide the preheating of the material (applicator), its application to the surface of the patient's skin and exposure time during the material is cooling to the patient's body temperature. The temperature of the applicator does not exceed 50 °C usually. At the same time, as follows from formulas (1,2), the increase in temperature of the material leads to the occurence of heat-related low-intensity microwave radiation, which, among other factors, has an impact on the human body and needs to be studied.

The authors of [28] conducted a study of EMR of the ozokerite applicator, the process of its formation and changes in the microwave field during the physiotherapy procedure.

From the point of view of physics, the process of heat treatment should be considered as a violation of thermodynamic equilibrium in a system consisting of the surface of human skin and the applied applicator. Energy exchange in any system, parts of which have different temperatures can be carried out through the processes of thermal conductivity, convection and radiation. In our case, convection can be ignored, and the exchange of energy between the surfaces of the applicator and the patient's skin is carried out mainly due to the phenomena of thermal conductivity and electromagnetic radiation.

In Figure 3 (a, b, c) shows two arbitrary objects (O_1 and O_2, with temperatures T_1, T_2), the applicator (A) and the patient's body (H), which are in thermal contact. In a state when the thermodynamic equilibrium is violated ($T_1 \neq T_2$) and the energy flows P_1, P_2 are not balanced, the direction of energy transfer depends on their temperature ratio.

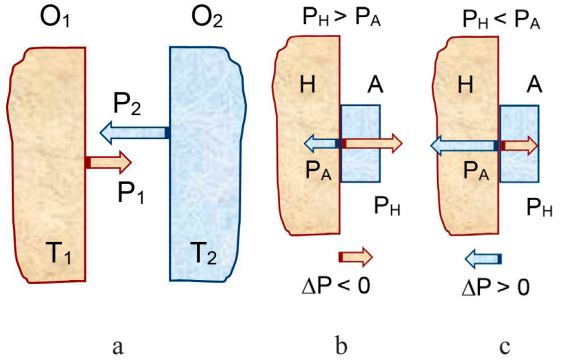

Figure 3. Distribution of energy flows between an arbitrary tangent objects: (a) – applicator and patient's body; b) negative energy flow; c) positive energy flow;

H - patient's body; A - applicator; PH - patient's energy flow; PA - applicator energy flow

For example, if the patient's temperature is higher than the applicator temperature (cooling applicator), the flow of heat energy will be directed from the patient's skin and can be considered negative in relation to the person (Figure 3b).

$$\Delta P = P_A - P_H < 0 \quad (8)$$

If, on the contrary, the applicator is heating, as in the case of heat treatment, the flow will be directed to the patient, and it can be considered positive (Figure 3c)

$$\Delta P = P_A - P_H > 0 \quad (9)$$

EMR power measurements were performed at a frequency of 52±0,1 GHz with an analysis band of 100 MHz. For comparison, the average level of radiation power of the human palm surface (limited antenna aperture plane 2 cm^2) was determined for three respondents, which was $P_H = (4,5 \pm 0,5) \cdot 10^{-13}$ W. Given the area of the aperture of the measuring antenna, this corresponds to the EMR flow

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density $2{,}25 \cdot 10^{-13}$ W/см^2.

The absolute values of the EMR power level were determined using a certified reference noise generator, which is part of the radiometric system. According to the results of measurements at the maximum therapeutic temperature of 50 °C (Figure 4) it is seen that the level of radiation of pure ozokerite is slightly higher than in the human palm. The power level of EMR of pure paraffin at the same temperature does not exceed 20% relatively to the level of radiation of human skin. This can cause the formation of a negative EMR flow, the intensity of which increases with increasing the percentage of paraffin in the mixture with ozokerite.

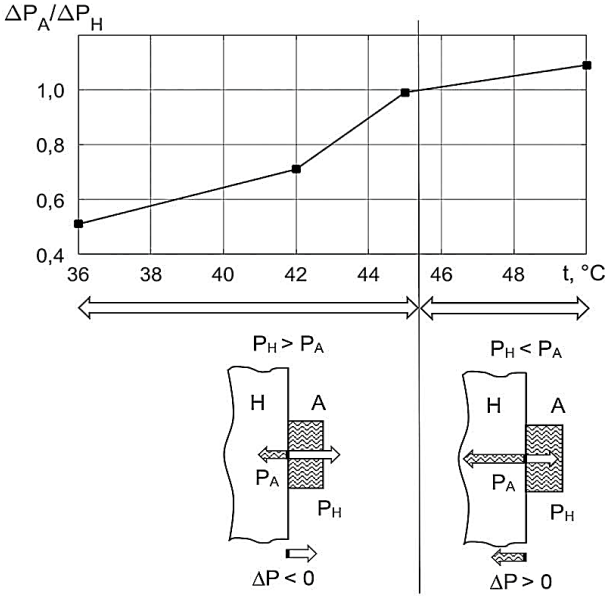

Figure 4. Dependence of relative power on temperature and distribution of electromagnetic energy flow for ozokerite applicator during cooling

From the graph of the temperature dependence of the power of its own radiation of pure ozokerite during its cooling, presented in Figure 4, it is seen that a change in temperature can lead to a change in the redistribution of electromagnetic energy between the applicator and the skin. Thus, on the graph, in the temperature range from 50 to 46 °C, a positive flow of EMR is formed

($\Delta P > 0$), and in the temperature range from 45 °C to 36 °C - negative flow of microwave radiation ($\Delta P < 0$), the intensity of which increases with further cooling.

Experimental studies have shown that ozokerite, paraffin and mixtures thereof form a low-intensity EMR in the millimeter range. This factor, together with the thermal effect, affects the patient's body, creating and enhancing the therapeutic effect.

The addition to ozokerite the paraffin, which has a low emissivity, increases the intensity of the negative flow. The total power of the ozokerite applicator, for example, with the size of 100 cm^2 may be approximately $3*10^{11}$ W, which is for high convergence with low-intensity levels used in millimeter therapy [8,9]. Experimental studies of EMR of materials for ozokerite-paraffin therapy have shown the complexity of electromagnetic microwave processes that affect and interact with the electromagnetic field of the human body, which need to be taken into account during physiotherapy.

Quite often in the treatment the wormwood cigarettes (moxa) for irradiation and cauterization of biologically active points (BAP) are used. Our experimental studies have shown that moxa is a generator of low-intensity natural microwave radiation, the level of which exceeds human EMR by 15…20 dB [11]. In general, it should be noted that the combustion of organic matter, in addition to infrared radiation, is also accompanied by a fairly high microwave energy flow.

2.4 Investigation of Microwave Fields and EMR of the Materials for Clothing

Radiothermal (radiometric) quality control of clothing materials (fabrics, leather, films, composites, etc.) is based on comparing the level of EMR of human skin with the level of EMR of the test material heated to the average human body temperature (310 K) [29]. The closer the level of EMR of material to the level of EMR of human skin, the better the electromagnetic compatibility of the clothing material with the human body, and the feeling of comfort of the dressed person is fuller [30].

Figure 5 presents a model of physical processes that occur at the interface of material and the human body.

To estimate the level of EMR of the material heated to the average temperature of the human body (310 K), the spectral power density of thermal EMR $G_1(f,T)$ at the average frequency of the millimeter wavelength range (52 GHz) was taken. The spectral power density of the EMR was determined by the power measured by the modulating RS divided by the bandwidth of the intermediate frequency amplifier (Δf = 100 MHz).

$$G_M(f,T) = \frac{P_{MRS}}{\Delta f}\left(\frac{W}{Hz \cdot cm^2}\right) \quad (10)$$

In the process of experimental research were used 14 types of textile materials made of natural, chemical and mixed fibers [30]. Designation of research objects: 1 - average value of human EMR (H - human); 2- wool (100%); 3 -linen (100%); 4 - wool (70%) + silk (30%); 5 - wool (45%) + silk (55%); 6 - cotton (100%); 7 - silk (100%); 8 - viscose (100%); 9 - cotton (65%) + polyester (35%);

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10 - cotton (60%) + polyester (40%); 11 - cotton (55%) + polyester (45%); 12 - cotton (47%) + polyester (53%); 13 - viscose (55%) + polyester (45%); 14 - polyester (100%); 15 - polyamide (100%).

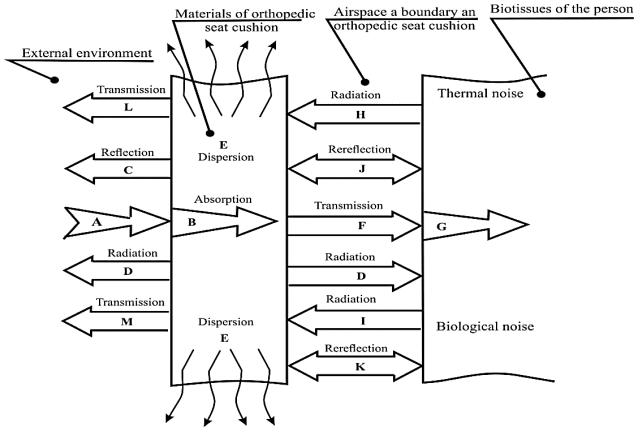

Figure 5. Model of interaction of electromagnetic currents at the material-human boundary

Designation on the Figure 5 A - EMR from external sources; B - input EMR to the material; C - reflected from the material EMR; D - radiothermal EMR of material; E - scattering flows; F - EMR, that passed through the material; G - EMR absorbed by the human body; H, I - radiothermal and biological radiation of the human body; J, K - repeated reflected from the material and skin radio thermal and biological EMR; L, M - radiothermal and biological EMR of a person passing through the material.

The spectral density of noise microwave radiation power of the studied materials is given in Table 3. Analysis of the obtained values allows us to conclude that fabrics made of natural fibers (wool, linen, cotton and silk) have a level of EMR close to the level of EMR of human skin.

Table 3. Spectral power density of radiation of textile materials.

№	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
G_M $10^{-21}\frac{W}{Hz \cdot cm^2}$	5.2	4.3	4,1	4,0	3,9	3,8	3,6	2.8	2.4	2.2	2,1	1.9	1,7	1,5	1,3

Therefore, these materials are most compatible with the human body. In addition, they do not interfere with the electromagnetic exchange of man with the environment, because they absorb and emit electromagnetic energy as well as human skin. At the same time, the increase in the percentage of chemical fibers in the material significantly reduces the level of EMR at the same temperature and negatively affects the electromagnetic exchange, which reduces the feeling of comfort of clothes made of these materials.

Study of materials dyed with natural dyes, also was carried out. Dyes were obtained from the medicinal herbs. An increase in the level of EMR was recorded, it approached the level of the human skin's own radiation. Materials comfort increased too, by 8-10%. It was determined by the formula:

$$\Theta = \left(1 - \frac{G_H(f) - G_M(f)}{G_{cbb}(f)}\right) \cdot 100\% \quad (11)$$

where $G_H(f)$ - EMR level of the human skin; $G_M(f)$ - EMR level of materials, рівень ЕМВ матеріалів, impregnated with natural dyes from medicinal herbs; $G_{cbb}(f)$ - EMR level of the absolutely black body for temperature T=310 K.

Thus, the measurement of low-intensity EMR of textile materials not only contributes to a more objective analysis of the processes of interaction that occur at the boundary between the material and human skin, but also opens the possibility of instrumental choice of ways to improve the quality and comfort of these materials.

2.5 Features of Radiative Ability of Minerals and Semiprecious Stones

Minerals are used in such a highly specialized technology of heat treatment as lithotherapy. In addition, precious minerals are used as jewelry, which are placed on the surface of the body. Heating of minerals leads to the formation of low-intensity microwave EMR. The authors [11] conducted a study of the emissivity of a number of minerals. Experimental conditions: EMR levels were measured at a frequency of 60 GHz at a temperature of objects 310 K, which corresponds to the upper limit of normal human body temperature. Figure 6 shows the distribution of radiation intensity of different minerals in comparison with the level of radiation of the human body and water.

According to their emissivity, the minerals can be divided into two groups, as shown by the dotted line in Figure 6: minerals that at a temperature of 310 K have a higher level of radiation than the human body, and lower. Minerals with higher radiation include jade, onyx, agate, amethyst, amber and jasper. These minerals in thermal contact with the human body generate a microwave signal that is excessive for human skin and this creates a positive flow of EMR. Thus, these minerals provide energy to the body in the case of lithotherapy or constant wearing on the human body. The second group of minerals includes sulfur, fluorite, flint, amazonite, rock crystal, calcite, topaz, morion. When these minerals are heated to body temperature, their radiation levels are lower than the own human radiation and they form a negative flow of energy. Water has the same quality. Some minerals, such as chalk and quartz single crystal, have almost the same level of

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radiation as humans and are electromagnetically balanced relatively to the human body.

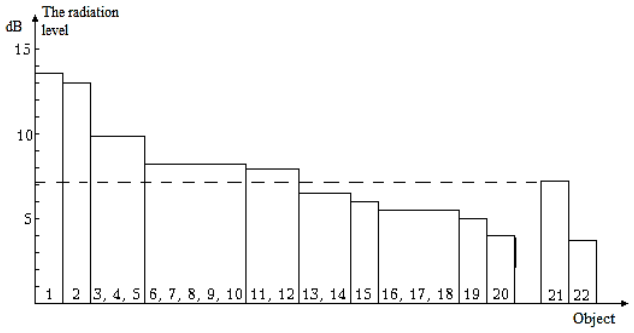

Figure 6. Distribution of emissivity of minerals and other objects

Minerals and objects of research are assigned the corresponding digital indexing: jade stone - 1, onyx - 2, agate - 3, shell rock - 4, tubula bone of animal origin - 5, amethyst - 6, amber - 7, jasper - 8, pyrite - 9, fibula bone of animal origin - 10, quartz (single crystal) - 11, chalk - 12, sulfur - 13, fluorite - 14, Moscow flint - 15, amazonite - 16, rock crystal - 17, calcite (feldspar)- 18, topaz - 19, morion (quartz)- 20; number 21 - EMR level of the human palm, number 22 - EMR of the water.

As can be seen from Figure 6, jade has a significantly higher level of radiation (13.5 dB) than human skin (7 dB). EMR of the quartz (morion) is at the level of the EMR of water. Human bones, shell rock and jade stone include Calcium salts (for example, calcium phosphate in the human bones). Perhaps, this is the cause of the increased level of the EMR of these objects. At the same time, it is known that Ca atoms actively respond to thermal effects. Thus, the root mean square displacement of Ca atoms during thermal oscillations is equal to 0.114 angstroms [32]. In response to thermal stimulation, Ca ranks among such active elements as Li, Na, K, Rb and Cs, some of which (K, Na, Ca) are actively used by biological objects in the process of their life support. Obviously, the increase in the level of radiation of the considered objects (bone, shell rock and jade) is connected with the increase of their "grayness" coefficient. Human bones play a peculiar role of generators and waveguides of microwave oscillations and provide the formation and transmission of electromagnetic oscillations within a biological object, in contrast to human skin, which actively absorbs low-intensity signals in the mm range.

2.6 Microwave Radiation of Building Materials

The authors [11] also studied some building materials - brick, sand, plaster, granite, shell rock, wood - which are most common in living and working spaces, on the street, in places of human recreation, etc. Studies have been conducted to assess possible levels of secondary radiation, which occurs under the influence of heating by sources of heat of physical bodies and the environment in contrast to the background radiation generated by objects at ambient temperature.

Research technology: materials were heated to a temperature corresponding to the maximum allowable temperature gradient, 50…60 °C which can be obtained, for example, as a result of direct exposure to solar radiation on the material in summer, or heating from steam heating pipes in winter. Evaluation of the emissivity was performed by RS at a frequency of 60 GHz. The results of experimental studies are shown in Figure 7.

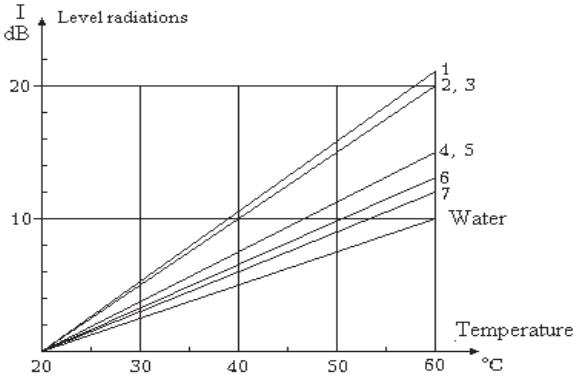

Figure 7. Dependence of radiation level of building materials on temperature

Designation on Figure 7: shell rock- 1, pine board - 2, granite - 3, gypsum - 4, red brick - 5, white marble - 6, sand - 7, water - 8.

Figure 7 shows that building materials have different emissivity. The maximum intensity of radiation is provided by shell rock (>$1 \cdot 10^{-20}$ W/Hz), which is much higher than human own radiation (~$0{,}5 \times 10^{-21}$ W/Hz). The dependence of the change in the radiation intensity of materials during heating is linear and is: shell rock ~0,52 dB/°C, granite and pine board ~0, 5 dB/°C, brick and gypsum ~0,4 dB/°C, marble ~0,35 dB/°C, sand ~0,3 dB/°C, water ~ 0,23 dB/°C.

In comparison with the ambient temperature, the emissivity of materials, when heated to indicated temperatures, increases, in the range from 10 dB (water) to 20 dB (shell rock), which must be taken into account when using them. Thus, the considered building materials have different radiation capacity in the mm range of waves, the level of which may be higher than the actual human radiation. It must be taken into account when using them and when human is in their environment with active temperature

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gradients.

3. Conclusions

1) The environment is filled with low-intensity microwave fields and natural radiation (primary and secondary), to which the human body has adapted well.

2) Recently, the filling of the air space with microwave signals of man-made nature, the intensity of which significantly exceeds the natural background and has the prospect of further growth. Studies by many authors reveal the negative impact of increasing microwave field intensity on sensitive biological objects (butterflies, bees and other insects). It fully applies to the human body, too.

3) The interaction of microwave fields and radiation with biological objects can manifest itself in the form of positive or negative energy flows. Such a manifestation is especially important for the cells of the human body when they come into contact with sources of EMR external or internal location.

4) Studies of the interaction of low-intensity microwave signals from objects in contact with the human body have confirmed the presence of positive and negative EMR flows in many medical technologies associated with the use of reconstructive biomaterials, which can have both positive and negative effects on surrounding biotissues. It is proposed to evaluate the electromagnetic compatibility of biomaterials with the human body by the level of their EMR, the criteria for the evaluation of new types of bio and nanomaterials is identified.

5) The method is offered and experimental researches of EMR of objects in contact with a human body (materials for clothes, precious and semiprecious minerals) are carried out. EMR evaluation reveals the correlations between indicated studied materials and allows to identify objects for their more comfortable contact use.

6) The study of materials and objects of the environment, which are sources of increased levels of EMR, allows us to realize the importance of microwave fields for the natural impact on the surrounding biological objects and the human body.

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ARTICLE

The Gulf Stream and the Californian Current as Factors Affecting the Behavior and Health of Americans

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ABSTRACT

Due to the existence of the Earth's geomagnetic field, Lorentz's forces constantly act on all sea currents. These forces distribute the charges of sea currents in both vertical and horizontal directions. In particular, this distribution manifests itself in the electric polarization of sea currents in directions perpendicular to them. So, earlier it was shown that the same Lorentz forces cause negative electrization of the Sargasso Sea. It is also shown here that the positive electrization of the western edge of the Gulf Stream and, consequently, the eastern coast of the United States is also caused by the Lorentz force arising from the interaction of this sea current with the vertical component of the geomagnetic field. It is also shown here that the positive electrization of east edge of California Current together with west coast of USA is also caused due to the similar reasons. All this allows us to conclude that an increased concentration of positive air ions is constantly retained in the air both in the east and in the west of the United States. This situation has caused the need for an analysis of how the predominantly positive electrization of the air affects both human health and their physical and mental activity. The results of this analysis are presented here. It is also shown that these results can be useful for residents of some other countries.

1. Introduction

It is well known that the Lorentz force F_L acts on charges moving in a magnetic field:

$$F_L = q[v, B] \quad (1)$$

where: q – an electric charge moving in a magnetic field;

v – the speed of movement of such a charge q;

B – magnetic field induction [1,2].

This allows us to conclude that the earth's surface, including water, which continuously crosses the lines of force of the geomagnetic field during its own diurnal rotation (Figure 1), is constantly exposed to the Lorentz forces, which continuously separate positive and negative earthly charges, both in vertical and horizontal directions [3-5]. This separation occurs even more effectively in air and sea currents, which are subjected to the action of additional Lorentz forces arising from the movement of these currents relative to the vertical component of the geomagnetic field [4,5].

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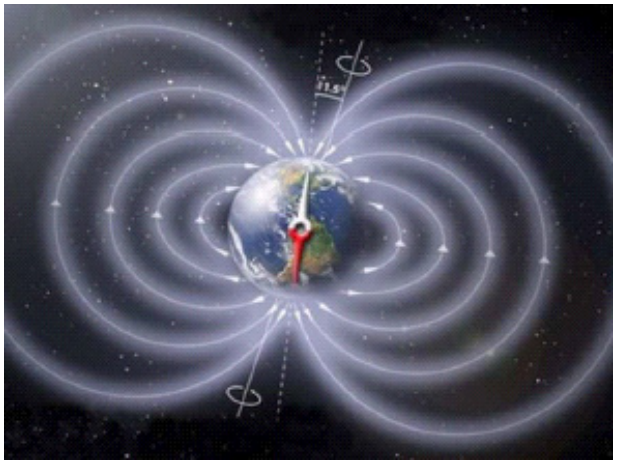

Figure 1. Since the Earth rotates around its own axis, all objects located on the earth's surface constantly intersect the lines of force of the geomagnetic field [3-5].

Thus, as a result of the interaction of the clockwise waters of the Sargasso Sea (Figure 2) with the vertical component of the geomagnetic field, directed downward in the northern hemisphere of the Earth, negative charges are concentrated inside this sea and positive charges – at its periphery [5] (in fact, as a result Hall's effect [1]).

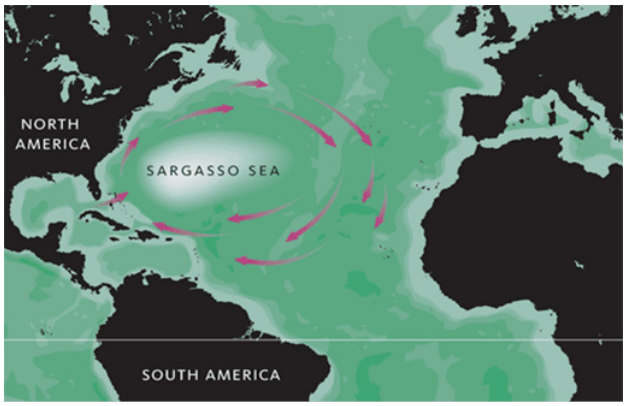

Figure 2. The Sargasso Sea is located in the Northern hemisphere of the Earth and is limited by currents moving clockwise. Equator is marked with a white horizontal line [5].

Thus, as a quite expected result of the interaction of the Gulf Stream (Figure 3, red arrows to the right of North America) with the vertical component of the geomagnetic field, which is directed downward in the northern hemisphere of the Earth, is that positive charges are concentrated on the western side of this sea current (resulting in the same Hall's effect [1]).

For this reason, the land, water and air of the US East Coast is constantly saturated with positive ions, mainly hydrated protons, which most actively evaporate from the surface of positively charged water [3-5].

Moreover, as a result of the interaction of the California Current (Figure 3, downward blue arrow to the left of North America) with the same vertical component of the geomagnetic field, positive charges are concentrated on its eastern side. For this reason, the land, water and air of the US west coast are saturated with positive ions at least constantly.

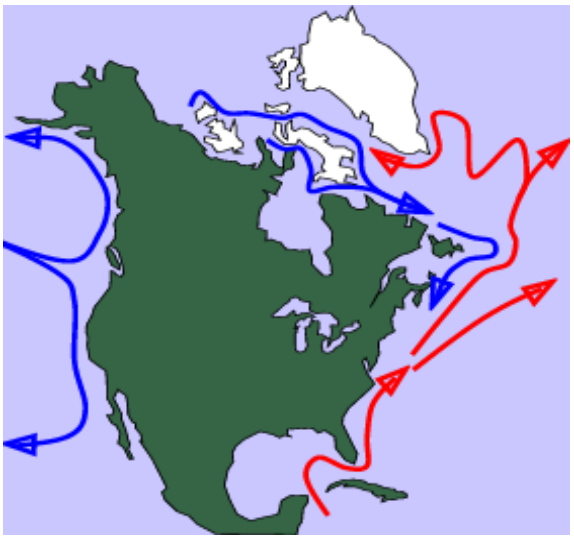

Figure 3. Near North America, there is the Gulf Stream (red arrows) and the California Current (blue arrow pointing down, to the left of the continent).

While important for completeness, it should also be noted that the same positive electrization occurs on the northern coast of the Gulf of Mexico and the east and west coasts of Florida (Figure 3); of course, this electrization is the result of the interaction of the nascent Gulf Stream with the same vertical component of the geomagnetic field.

Thus, people who live on all coasts of the mainland United States, with the exception of Alaska, are constantly under the influence of an all-encompassing positive electrization. Let us discuss how this electrization determines the characteristics of the nervous and physical activity of such people, as well as how it affects their health.

To attract the attention of a larger audience, it should be added that the same reasons for the discussed positive electrization, which were mentioned, exist in other regions of the Earth. So, the sea currents are exist of the east coasts of Japan and Brazil, as well as off the southeast coast of Australia, also charge them positively. (It should be noted that the last two currents are directed from north to south and that the vertical component of the geomagnetic field is directed upwards in the southern hemisphere of the Earth, where both these countries are located.) Thus, the phenomena discussed here have a planetary distribution.

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2. Discussion

First of all, the fact that glucose is transported through the cytoplasmic membranes by means of a symport (Figure 4), the intensity of which is determined by the concentration of extracellular protons, which are directly involved in the creation of the "proton drawing force" (pdf) [6-8], musts be considered. Since glucose is the main "fuel" of nerve and muscle cells, at least the rate of its transport through their outer membranes determines their functional activity and, consequently, the nervous and muscular activity of people in general. Already this transport function of protons suggests that humans are very active in environments that are saturated with them.

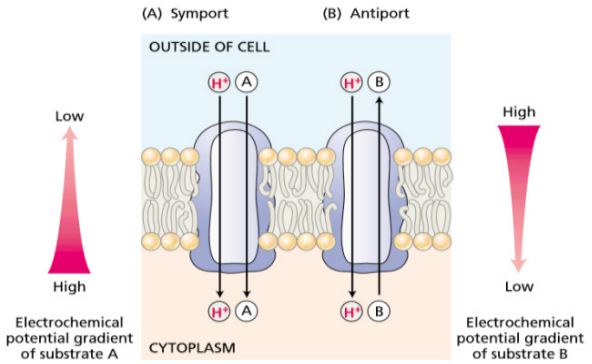

Figure 4. The energy of proton gradients on cytoplasmic membranes allows cells to realize two types of secondary active transport: symport and antiport. At the symptom (A), a proton, penetrating into a cell from the outside, captures one glucose molecule. With antiport (B), the energy "scattered" by a proton entering the cell from the outside can be used to remove cations (for example, sodium ions) from the cell [8].

Moreover, the positive electrization of the environment can cause an increase in the tone of the human body as a whole and, in particular, of its skin and blood vessels. This possibility is due to the fact that positive electrization of water (which is the main component of the human body) increases its surface tension and, as a result, causes its compression, in contrast to negative electrization of water (Figure 5) [9].

It is also appropriate to recall that the head of a standing or sitting person is the most positively charged part of his body [11]. This means that the human brain is evolutionary turned to positive electrization, which increases its metabolism and, therefore, both its activity and development.

Due to the small surface tension, water with negative electric potential can spread throughout the bottom of the Petri dish; due to the large surface tension, water with a positive electric potential cannot spread throughout the bottom of the Petri dish.

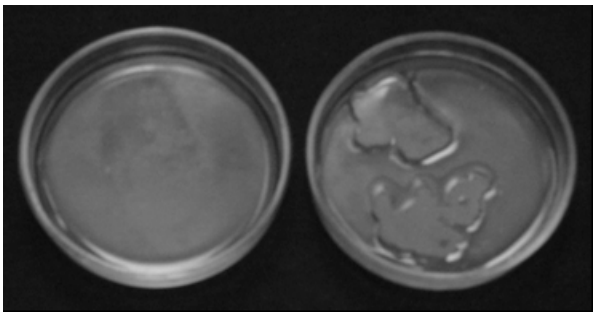

Figure 5. Left: 5 ml of water with a potential of –200 mV completely cover the bottom of the Petri dish. Right: 5 ml of water with a potential of +200 mV do not completely cover the bottom of a Petri dish. Both water used had 20 – 22 °C [5,9].

Given, in addition, the positive electrization of the air stimulates the transfer of essential nutrients from the intestine to the blood [12], one can conclude that the constant saturation of the ambient air with positive air ions and, therefore, hydrated protons determines the permanent physical and intellectual activity of most Americans.

Unfortunately, this activity also has negative manifestations, which include the permanent aggressiveness of the Americans, which manifests itself in both high crime and high accident rates on the roads. Moreover, the constantly high tone of permanently positively charged blood vessels can initiate their destruction and hence bleeding. Starch powder applied to the surface of positively charged water makes it possible to convincingly demonstrate its "destructive" ability: as you can see, positively charged water literally "breaks" a lump of starch powder applied to its surface, unlike negatively charged water (Figure 6).

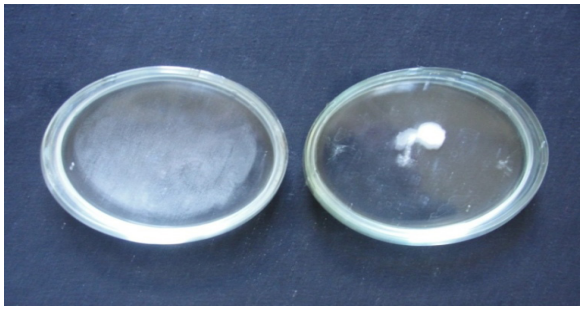

Figure 6. Left: the starch powder covers the surface of the water with potential +250 mV practically wholly. Right: powder starch remains in the same place where it was put in water potential –200 mV. Both water used had 20 – 22 °C [5,9].

Moreover, the "bursting" ability of positively charged water is confirmed by the fact that it destroys the films formed during the drying of collagen solutions prepared in

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such water (Figure 7); besides, it should be born in mind that negatively charged water does not demonstrate such destructive power, at least in relation to collagen.

Figure 7. This is a "cracked" film, into which the drying collagen solution, prepared in water with a potential of +250 mV, has turned. Water used had 20 – 22 °C.

Thus, bearing in mind that elastin, which is a structural analogue of collagen, is the main structural protein of blood vessels [13], the obtained result (Figure 7) suggests that positive electrization can be the main cause of non-traumatic destruction of blood vessel walls, in fact, the main cause of stroke. The fact that only positively charged water is capable of causing swelling of various biopolymers [9] must be also be taken into consideration, because it suggests that the same positive electrization stimulates the formation of blood clots, i.e., thrombus formation. (Probably, this thrombus formation is a defense reaction of the body to the destruction of the walls of the blood vessels. In any case, such coordination looks quite natural, since it allows you to stop bleeding through the ruptured walls of the blood vessel.)

Unfortunately, these are far from all the discussed harmful effects of the discussed positive electrization. So, it is likely that it contributes to the spread of viral infections. To better understand how this might happen, one must first understand the general importance of positive electrization of DNA molecules (together with their immediate environment) for their successful introduction into cells undergoing artificial genetic modification. The need for this electrization is becoming almost obvious if to take into account the efficiency of using cationic (exclusively!) polymers for introducing DNA molecules into target cells, as well as the need for positive electrization in such methods of genetic modification of cells as DE-AE-dextrin method and lipofection method. Since this is relevant right now, it should be added right away that all these methods are also effective for the introduction of RNA to target cells [14].

To better understand this very need for positive electrization of introduced DNAs more fully, it is necessary to analyze the phenomena underlying the cryogenic method of genetic transformation of bacterial cells, which consists in preliminary deep cooling of a mixture containing recipient cells and injected DNA, followed by heating this mixture to 37 – 42 °C [15]. Since this is necessary, let's remember a Kyon's rule right now: when two phases are in contact, the phase with a higher dielectric permittivity receives a positive charge and the phase with a lower – negative [10,16]. Since the dielectric constant of water is ~ 73.1 at 40 °C and 88.3 at 0 °C [10], a cold water mixture accumulates protons and, therefore, acquires a positive charge, and warm water in contact with it loses protons and, accordingly, acquires a negative charge, naturally – in accordance with the aforementioned Kyon's rule. As you can see, the cryogenic method of genetic transformation of cells is also based on the formation of an electrical gradient, most likely a stepwise proton gradient on the outer membranes of target cells. This suggests that the transfer of DNA molecules into modified cells occurs together with a flux of protons directed from a warmer aqueous phase to a colder one, thus striving to create a charge distribution provided for by the Kyon's rule [10,16].

All these examples should convince that the transport function of protons extends not only to the relatively small molecules and ions (Figure 4), but also to large. Accordingly, this suggests that such a function of protons is universal. Besides, all this suggests that positive electrization of the human body via to the correspondingly electrized environment can increase a human susceptibility to viral infections, naturally assuming that the extrapolation of these phenomena to human cells is correct.

3. Conclusions

To make these conclusions easier to accept, initially compare how you feel in bright and cloudy weather, given at the same time that clear weather usually coincides with positive electrization of the lower atmosphere, and cloudy weather – their negative electrization [17]. Moreover, you can compare how you feel during the day and at night, given the increased positive electrization of the daytime side of the Earth [18]. It is likely that all these comparisons can definitively convince you that the variations in air electrization are natural, as well as that they affect people.

Besides, these comparisons will allow us to agree that the targeted electrization of ambient air allows you to control the well-being and behavior of people. Thus, it can be assumed that the targeted negative electrization of the air will reduce the levels of crime and road accidents, as well as the incidence of stroke and unwanted thrombosis. It can also be hoped that the same negative electrization can prevent the ingress of foreign nucleic acids, including

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viral ones, into human cells, preventing the spread of viral infections in general. If we add that negative electrization of public buildings and vehicles can prevent many bacterial infections [19], then its purposeful use would seem more than reasonable. (The fact that such negative electrization can also prevent cancer [20] also speaks in its favor.)

Moreover, any electrization must be sufficiently justified. So, the fact that the brain is abnormally compressed in Alzheimer's patients [21] suggests that this contraction is due to positive electrization, just like the compression of positively charged water (Figure 6, right). Accordingly, it can be assumed that negative electrization of the air surrounding patients with Alzheimer's disease can be transmitted to their brains, causing the same decompression as in the case of negative electrization of water (Figure 6, left). At the same time, one should not ignore the idea that impairment of glucose transport into neuronal cells is the true cause of Alzheimer's disease [21]. Therefore, this idea suggests that positive electrization of the brain of patients will stimulate glucose symport through the outer membranes of brain cells, in accordance with the scheme shown in Figure 4, A. Thus, according to this idea, it is precisely positive electrization of air that may not only be beneficial, but also vital for Alzheimer's patients. (At the same time, one should not forget that the human brain consists mainly of water, where its content is estimated at ~ 80%, and also that the human brain is located next to the respiratory tract.)

At all events, it is necessary to consider all the possible consequences of any electrization of the air. It should be noted that this consideration can be very useful for both climatologists and balneologists using the effect of natural factors on patients. In addition, the same consideration can be no less useful for Feng Shui adherents who seek to use the effect of air and water currents on people, both natural and artificial. In any case, all of them can now consciously use the fact that the direction of rotation of air or water determines the sign of their electrization, which can be negative, as in the Sargasso Sea (Figure 2), or positive, as on the ocean coasts of the United States (Figure 3). In particular, it should be taken into account that it is convenient to obtain the desired electrization of the air with the help of appropriately oriented fans, especially since the effectiveness of this type of electrization is confirmed by visual experiments [20,22].

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ARTICLE

Several Theoretical and Applied Problems of Human Extreme Physiology: Mathematical Modeling

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ABSTRACT

Human cardiovascular system (CVS) and hemodynamics are critically sensitive to essential alterations of mechanical inertial forces in directions of head-legs (+Gz) or legs-head (-Gz). Typically, such alterations appear during pilotage maneuvers of modern high maneuverable airspace vehicles (HMAV).The vulnerability of pilots or passengers of HMAV to these altering forces depends on their three main characteristics: amplitude, dynamics, and duration. Special protections, proposed to minimize this vulnerability, should be improved in parallel with the increasing of these hazardous characteristics of HMAVs. Empiric testing of novel protection methods and tools is both expensive and hazardous. Therefore computer simulations are encouraged. Autonomic software (AS) for simulating and theoretical investigating of the main dynamic responses of human CVS to altering Gz is developed. AS is based on a system of quantitative mathematical models (QMM) consisting of about 1300 differential and algebraic equations. QMM describes the dynamics of both CVS (the cardiac pump function, baroreceptor control of parameters of cardiovascular net presented by means of lumped parameter vascular compartments) and non-biological variables (inertial forces, and used protections). The main function of AS is to provide physiologist-researcher by visualizations of calculated additional data concerning characteristics of both external and internal environments under high sustained accelerations and short-time microgravity. Additionally, AS can be useful as an educational tool able to show both researchers and young pilots the main hemodynamic effects caused by accelerations and acute weightlessness with and without use of different protection tools and technics. In this case, AS does help users to optimize training process aimed to ensure optimal-like human tolerance to the altered physical environment. Main physiological events appearing under different scenarios of accelerations and microgravity have been tested.

1. Introduction

Already in the middle of XX-h century, under piloting of speed air flights it was revealed the fact that the human organism, during the long evolution adapted to earth gravity conditions, is vulnerable to altered dynamic forces accompanying flight maneuvers [1]. Very soon experts realized that special protective technologies, capable of providing pilots' performances in the altered environment,

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have to be created and tested. Airspace flights, later provided by means of high maneuverable vehicles, deepened and widened the problem and identified a number of its additional and actual yet medical and technical aspects [2-10].

For a long time, the empiric way was the only one for searching, developing, and especially testing the every new protective algorithm or suit. This way has two immanent limitations - expensive and potentially hazardous for the human health and life. Therefore the alternative way based on computer simulations is encouraged [11-14]. Our consequential efforts in this direction resulted a special modified autonomic software (AS) for simulating and theoretical investigating of main dynamic responses of cardiovascular system (CVS) of a healthy person, armed by proper protections, to G_z-accelerations. AS is based on a system of quantitative mathematical models (QMM) consisting of about 1300 differential and algebraic equals.

The goal of this article is to introduce QMM, main characteristics of AS, and several simulations.

2. Basic Mathematical Models

Structurally and functionally, QMM is composed of two main blocks. The first - physiological block (PB) describes the physiology of CVS. The second - environmental block (EB) consists of models that describe both the dynamics of external physical forces and their investments in modulations of regional or global hemodynamics. Special part of EB imitates changes of extravascular pressures in cranial, pleural, and abdominal cavities, as well as in legs under voluntarily induced muscle stress and / or use of pneumatic protective suits. Here are also models for imitating the pilot's armchair and its position relative to the vector of accelerations.

PB includes three sub-models. The first sub-model describes the heart pump function (HPF) in quasi-static regimes of systemic and lungs blood flow. In fact, this model imitates continuous blood flows through both system and lung blood circles. The value of each flow is determined by the characteristics of appropriate (right or left) ventricles of the heart and by the venous pressures filling these ventricles. The second sub-model, based on the lumped parameter modeling technology [16-19], describes hemodynamics in a net of lumped parameter vascular compartments. At last, the third sub-model describes mechanisms based on both arterial mechanoreceptor reflexes and additional mechanisms of CNS controlling both the heart pump function and actual values of parameters of vascular compartments.

The model of HPF discloses main relationships between the mean for each cardiac cycle values of cardiac output ($Q_i(t)$) and central venous pressure ($P^V_{a1}(t)$ - for the right heart) or lung venous pressure ($P^V_{a2}(t)$ - for the left heart). Additional factors that have been taken into consideration are the heart rate ($F(t)$) and the inotropic coefficients ($k_i(t)$) of the right or left ventricle, the hydraulic resistance ($R^K_{aVi}(t)$) of atria-ventricular valves, the duration of diastole ($T_L(t)$), the diastolic elasticity ($C_i(t)$), and the unstressed volume ($U_i(t)$) of ventricles:

$$Q_i(t)=\frac{F(t)\cdot k_i(t)\cdot\left[\left(\Delta P^V_{ai}(t)\cdot C_i(t)+U_i(t)\right)-U_{oi}\right]M_i(t)}{\left[1-\left(1-k_i(t)\right)\right]M_i(t)},$$

$$M(t)=1-\exp\left(-\frac{T_L(t)}{R^K_{aVi}\cdot C_i}\right),$$

$$P^V_{ai}(t)=P^{INP}_i(t)+0.735\cdot\rho\cdot H^V_a(t)\cdot N^G\cdot\sin\phi(t)-P^{FD}_i(t),$$

$$T_L(t)=\frac{1}{F(t)}\cdot A+B\cdot\left(1-k_i(t)\right),$$

$$P_i(t)=\begin{cases}0, & V_i(t)<U_i(t)\\ \left(U1_i(t)-U_i(t)\right)/C_i(t), & U_i(t)\le V_i(t)\le U1_i(t)\\ \left(U1_i(t)-U_i(t)\right)/C_i(t)+\left(V_i(t)-U1_i(t)\right)/C1_i(t), & V(t)_i>U1_i(t)\end{cases},$$

$$V_i(t)=V_i(0)+\int_0^t\left(Q^I(t)-Q^O(t)\right)\mathrm{dt},$$

$$R^K_{aV}(t)=\begin{cases}r_1, & \Delta P_K(t)>P_{KP}(t)\\ r_2, & \Delta P_K(t)\le P_{KO}(t)\end{cases},$$

$$V^s(t)=\begin{cases}k_0V^{ED}(t)-V_0(t), & P_v(t)\le P_0\\ k_1V^{ED}(t)-V_1(t), & P_v(t)>P_0\end{cases}.$$

The low index $_i=1,2$ relates the value to the right heart or left heart chambers respectively.

The last formula is another reflection of the well-known regularity of HPF. This regularity is also known as the Frank-Starling's mechanism of HPF's self-control. It shows that relationships between stroke volume ($V^s(t)$) of the ventricle and its end-diastolic volume may be presented as a linear approximation. $C_i(t)$ and $C1_i(t)$ indicate the fact that dependences between pressures ($P_i(t)$) and volumes ($V_i(t)$), also known as $P_i(V_i(t)$ -functions of heart chambers, are nonlinear. The nonlinearity plays an essential role during use of protections.

Our software consists of two version of the vascular net hemodynamics. In the frame of the first version (Figure 1), the vascular net is presented as 1-dimensional structure, consisting of $j=33$ vascular arterial and venous compartments, each with its own fixed $P_j(V_j(t)$ characteristics. These vascular compartments are located on the different levels relatively to the foot level. At the same time, they are completed into the several groups taking into account

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common extravascular conditions in each of cavities or tissues. The atmospheric pressure is the extravascular pressure for the skin arterial and venous compartments.

In the second version of the CVS model, most regional vascular compartments are represented in form of a three-dimensional net. Compared with the scheme depicted in fig 1, in the three-dimensional net version, each compartment of legs vasculature, abdominal and thoracic vasculature have been tripled: each compartment has sub-compartments located below and above the median longitudinal Z-axis that conventionally represents the 0-level for two other additional perpendicular axes, namely, Y- axis (supine-chest) and X- axis (left hand-right hand). The three-dimensional net is necessary for the modeling and evaluating possible investments of blood re-distributions along of every perpendicular direction in the space-condition hemodynamics. The model helped us to better understand intimate mechanisms of specific hemodynamic shifts from the legs' area toward central and cranial basins, observed just after the engine of the space-vehicle stopped working and within the first several hours of the microgravity conditions. Such a model and simulations several results are described in [15,20].

In different arterial or venous vessels, biophysical pressure-volume characteristics (shortly presented as $P_j(V_j(t))$) are essentially nonlinear and specific for each arterial or venous compartment. In the model, these nonlinear curves in j-th compartment of vessels are approximated by means of piecewise-linear characteristics, consisting of three parts. According to this approximation, a typical description of $P_j(V_j(t))$ looks like:

$$P_j^T(t)=\begin{cases}\left(V_j(t)-U_j(t)\right)\cdot D_{0j}(t), & V_j(t)\le U_j(t)\\ \left(V_j(t)-U_j(t)\right)\cdot D_{1j}(t), & U_j(t)\le V(t)_j\le U_{1j}(t)\\ \left(U_{1j}(t)-U_j(t)\right)\cdot D_{2j}(t)+\left(V_j(t)-U_j(t)\right)\cdot D_{1j}(t), & V_j(t)>U_{1j}(t)\end{cases}$$

Here $V_j(t)$ - is volume, $U_j(t)$, $U_{1j}(t)$ - are unstressed volumes, and $D_{0j}(t)$, $D_{1j}(t)$, $D_{2j}(t)$ - represent the vascular total rigidity for different sections of the approximation, $P_j^T(t)$ - is the local transmural pressure.

Blood flows between j-th and l-th vessel compartments, which are connected by means of hydraulic resistance $R_{jl}(t)$, are defined as a result of division of pressure gradients $G_{jl}^P(t)$ by $R_{jl}(t)$. Transmural pressures $P_j^T(t)$, external pressures $P_j^E(t)$, and hydrostatic pressures $P_{jl}^G(t)$ are considered as factors in determining $G_{jl}^P(t)$. Coefficients $K_j^e(t)$, $K_l^e(t)$ for $P_j^E(t)$ or $P_l^E(t)$ reflect differences in the levels of vessels' location and transmission characteristics of different tissues (muscles, cavities, skin) in which the vessel compartment is located:

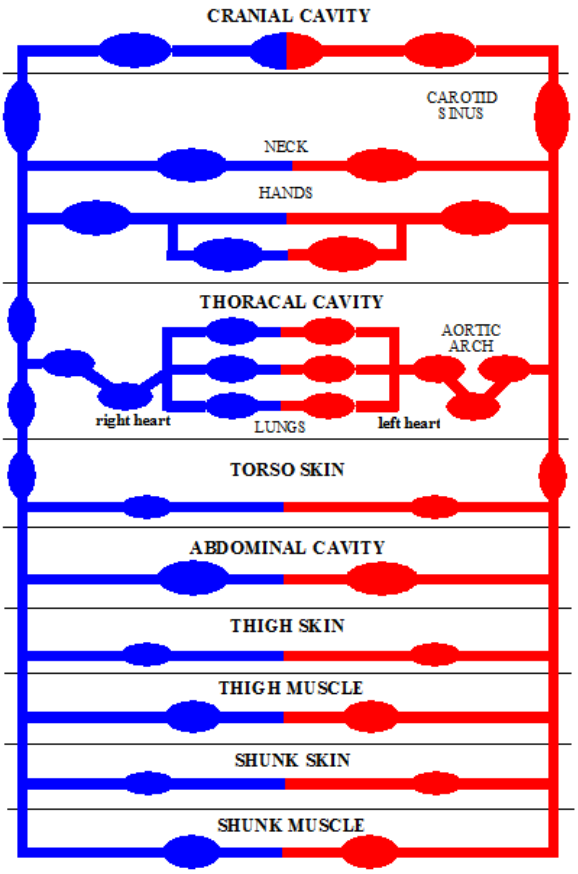

Figure 1. The first version of the lumped-parametric CVS model used for simulating of hemodynamic effects of so-called Gz-accelerations. Each compartment is located on its own distance from the foot-level.

$$q_{jl}(t)=\frac{G_{jl}^P(t)}{R_{jl}(t)}$$

$$G_{jl}^P(t)=\left(P_j^T(t)+K_j^e(t)\cdot P_j^E(t)\right)-\left(P_l^{T(t)}+K_l^e(t)\cdot P_l^E(t)\right)+P_{jl}^G(t)$$

$$P_{jl}^G(t)=N^G(t)\cdot\rho\cdot(L_j(t)-L_l(t))$$

The modeling of hemodynamic effects of acceleration is based on the calculation of every hydrostatic pressure as a function of both human posture and of the value of acceleration. We have two compartment level classes. The first one characterizes the value of distance between the human feet and the place of compartment's localization for human horizontal (clinostatic) or erect positions. The second class of levels (we call them real levels) reflects the value of hydrostatic pressures of human vessel compartments for person's all other positions. Using angle values between the horizontal and the directions of different body parts (α - for calf, β - for thigh, and γ - for all other compartments of body and head vessels), these parameters can be calculated in the model according to the following formulae:

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$$L^S = 0.5A \cdot l^S \cdot \sin\alpha,$$

$$L_1^t = \left(L_C - 0.5l_1^t \cdot \sin\beta\right) \cdot A,$$

$$L_2^t = L_1^t - 0.5A \cdot l_2^t \cdot \sin\beta,$$

$$L_p = L_C \cdot A,$$

$$L_{2i}^b = \left(l_{1i}^b - L_0\right) \cdot A \cdot \sin\gamma + L_0,$$

where l^S - length of calf, l_1^t, l_2^t - lengths of two parts of thigh, L_C - total length of legs, L^S - level of shank vessel compartment, L_1^t and L_2^t - real levels of thigh vessels compartments, L_p - level of aviation armchair seat place, L_0, l_{2j}^b, l_{1i}^b - real levels and initial lengths of localization for each j-th body or head vessel compartment.

Resistances of collapsible vessels have been calculated by means of special formulas:

$$R_1(t) = \begin{cases} R_0 \cdot \left(\dfrac{V_0}{V(t)}\right)^2, P^T(t) > P_0 \\ R_0 \cdot r_0^4 \cdot \dfrac{a^2 + b^2}{2a^3 \cdot b^3}, P_1 \le P^T(t) \le P_0 \\ R_1, R_1 > R_0, P_1 < P_0 \end{cases}$$

$$a(t) = \frac{V(t) \cdot r_0^2}{V_0 \cdot b(t)}$$

$$b(t) = \frac{1}{3} r_0 \cdot \left[d(t) + 2 \cdot \left(1 + \sqrt{1 - 2d^2(t) + d(t)}\right)\right]$$

$$d(t) = \frac{V(t)}{V_0}$$

$$R(t) = R_u \cdot \left(\frac{U(t)}{V(t)}\right)^2$$

$$V_0 = V(t)\big|_{p=0}$$

The total brain flow depends on changes (nervous origin) of the brain vascular resistance $R^{AM}(t)$ that is modeled as:

$$R^{AM}(t) = \begin{cases} R_{min}^{AM}, P^{AM}(t) \ge P_{max}^{AM}; \quad P_{min}^{AM} < P^{AM}{}_{(t)} < P_{min}^{C} \\ R_{max}^{AM} \cdot C, \quad P_{max}^{C} < P^{AM}(t) < P_{max}^{AM} \\ \dfrac{E_1}{P^{AM}(t)}, \quad 0 \le P^{AM}(t) \le P_{min}^{AM} \end{cases},$$

where:

$$C = \left[1 - \exp\left(X_i \cdot \left(P^{AM}(t) - P_{max}^{AM}\right)\right)\right],$$

$$\frac{dR^{AM}(t)}{dt} = \frac{\delta_M \cdot P^{AM}(t) - R^{AM}(t)}{T_m}, \quad P_{min}^{C} < P^{AM}(t) < P_{max}^{C}.$$

δ_M is the time constant, and $P^{AM}(t)$ is the pressure in cerebral arterioles.

In systemic veins, valves' resistance $R_{jv}(t)$ is described as:

$$R_{jv}(t) = \begin{cases} R_{1j}, & q_j(t) > 0 \\ R_{2j}, & qj(t) \le 0 \end{cases}, R_{1j} >> R_{2j}$$

It is assumed that in the short observation intervals the total blood volume is stable:

$$\sum_i V_i(t) + \sum_j V_j(t) = conat.$$

Dynamics of blood volumes in compartments are described by the following equation:

$$V_j(t) = V_j(0) + \int_0^t \left(q_j(t) - q_l(t)\right) dt$$

Three cavities (cranial, thoracic, and abdominal) are specially presented as extravascular environments that have their specific extravascular pressure dynamics. So, by such a presentation of vascular net, we are able to simulate important influences of extravascular pressures changes in these cavities on local hemodynamics. Having aortic arch and carotid sinus compartments, we are able to describe relationships between afferent nervous activity of mechanoreceptors (more exactly, in a multi-fiber afferent nerves) depending on local transmural pressures in these zones of baroreflex. However, before to describe formulas, useful is to explain our concept of the reflector control of hemodynamics under sustained and extreme amplitude Gz accelerations.

Baroreceptor reflexes caused from mechanoreceptors localized in aortic arch and carotid sinuses are well-known acute controllers of hemodynamics. This physiological view is mainly based on experiments, provided on anesthetized animals in their horizontal position. Indeed, in this position, mean pressures in aorta and carotid sinuses do not be essentially different. However, as it was demonstrated by means of mathematical modeling [18-21], already in head-up positions, carotid sinus receptors feel transmural pressure's lowering while receptors in the aortic arch may even be under slightly increased pressure. This compels these two reflexes, in clinostatics functioning in synergy manner, in altered positions to perform antagonism. Under +Gz accelerations [12-14,22], the antagonism becomes much severe and the depressor aortic baroreflex, trying

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to lower the aortic pressure, does limit both the increase of heart rate and the increase of total vascular resistance. This suggests that high levels of the heart rate, observed during centrifuge tests or in real flight conditions, must have alternative providers. We think, mechanoreceptors of right atricus and those located in Willis circle can be these providers. In addition, the general pressor effects can be enhanced by nervous mechanisms associated with the activation of proprioreceptors, humoral stressor factors, as well as with the critical lowering of total brain flow (this will cause general pressor response - GPR). According to this vision, the general structure of hemodynamics control under acceleration is presented in Figure 2.

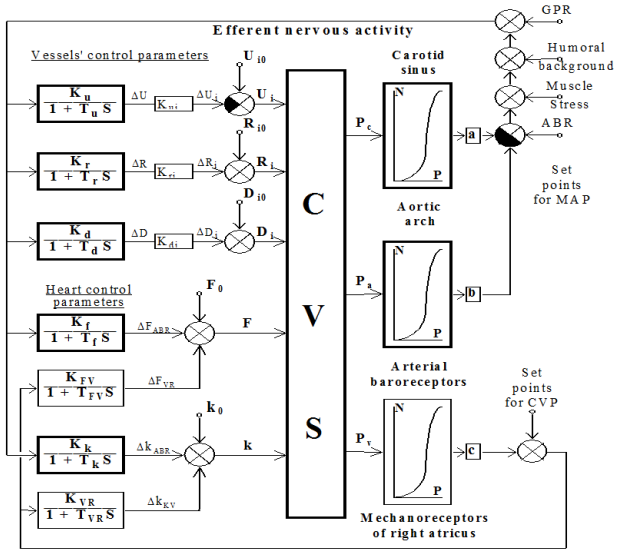

Figure 2. The general structure of hemodynamics' central nervous control model.

As it is shown in Figure 2, there are two heart control parameters (*F,k*) and three integral control parameters of vessels (*D,U,R*). The last three parameters are dispersed on different regional areas of vessels, according to the existing physiological notions about their efferent sympathetic nervous density.

Figure 2 consists of two different feedback channels. The first one in its turn forms two negative feedback channels for arterial baroreceptor reflexes (ABR) from baroreceptors of the aortic arch and the carotid sinus zones. The second feedback channel is a positive feedback channel for the mechanoreceptor reflex from the right atria area (this reflex is known as the Bainbridge reflex). The last one can only change F and k. The ABR is often included in different models of the hemodynamics' control but the Bainbridge reflex is rarely presented in models. In our model, the Bainbridge reflex is included by following reasons. The first reason is the essential increasing of central venous pressure during special breathing procedures. The second reason is that the central venous pressure also increases during the muscle stress or use of extended coverage anti-G-trousers.

The nervous activity in both feedback channels is formed by the difference between the set-points in the central neuronal structures and the summary activity of receptors. ABR is presented in the model as independently functioning proportional regulators. They are based on local nonlinear S-form characteristics between arterial transmural pressures in aortic arch (q=1), carotid sinus (q=2) and brain arterioles (q=3), from the one side, and their summary baroreceptor activity- from the other side. These characteristics take into consideration all known peculiarities of distinctions between threshold pressures and activity of baroreceptors:

$$N_q^R = \frac{1-\exp\left(\beta_q^R \cdot \left(P_q^R - P_q^t\right)\right)}{1+B_q \cdot \exp\left(P_q^R \cdot \left(P_q^R - P_q^t\right)\right)},$$

$$\frac{\mathrm{d}\,\Delta X_i(t)}{\mathrm{d}\,t} = \frac{K_i(t)\cdot E(t) - \Delta X_i(t)}{T_i},$$

$$K_i(t) = \begin{cases} K_i^P \cdot \left[X_i^{max} - X_i(t)\right] & E(t) > 0 \\ K_i^d \cdot \left[X_i(t) - X_i^{min}\right] & E(t) \le 0 \end{cases},$$

$$X_i(t) = X_{\text{ò}} + M_j^1 \cdot \Delta X_i(t),$$

$$E_q = P_q - p_q,$$

$$N_q^S = a.N_a^R + c.N_c^R,$$

$$X_i(t) = XB_i^{min} + \sum_{i=1}^{n} \Delta X_i(t),$$

$$T_q \frac{dN_q}{dt} = K_q \cdot N_q^S - N_q, \quad q = \overline{1,\ 3}.$$

Every central reflector control mechanism was simulated as a proportional regulator that has its stable gain (K_i) and time constant (T_i). Coefficients K_i characterize the power, whereas T_i characterize the values of inertia of reflector processes. We can simulate various conceivable hemodynamic situations by different combinations of changes in these parameters. It is necessary to note that there are some functional relations between K_i and control parameters (X_i), namely, K_i decreases simultaneously with the increasing of X_i. Consequently, the functional reserves of CVS's control parameters have to decrease in parallel with the severity of loads.

In addition to the described model of CVS's own reflector mechanisms, and taking into account the well-

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known physiologic concepts, our complex model includes also some assistant reflexes that might have outside origin (relative to the CVS structures). At the same time, we believe that by having some common tracks in brain structures, these assistant reflexes might influence the normal function of CVS's those own reflexes that are included in the model and essentially modify their hemodynamic effects.

According to this concept, we assume that there are three factors able to modify the arterial pressure's set-point level. They are:

1) Blood concentrations of cardio- and vasomotor active substances (especially cathecholamines) - Y_{cat};

2) The general level of the body muscle activity - Y_m;

3) The mentioned above general pressor reaction - Y_{GPR}.

Appropriate calculations have been provided with following formulas:

$$Y_{cat} = Y_{cat}^{\max} \cdot \exp\left[-\omega \times \left(T - T_{\exp}\right)\right] / \left\{1 + \phi \cdot \exp\left[-\omega \cdot \left(T - T_{\exp}\right)\right]\right\}$$

$$\mathrm{Y_{gpr}} = \mathrm{K_{gpr}} \times \mathrm{Y} \times \left\{1 - exp\left[\eta \times \left(\mathrm{W_{gpr}} - \mathrm{A}\right)\right]\right\} / \left\{1 + 9 \times \left[1 - exp\left(\left[\eta \times \left(\mathrm{W_{gpr}} - \mathrm{A}\right)\right]\right)\right]\right\}$$

$$Y_m = \theta \cdot P_m(t)$$

Formula for describing nonlinear dynamic effects of muscle pressure $P_m(t)$ increasing under muscle stress is:

$$P_m(t) = \left[1 - \xi_p^h \cdot (h-1)\right] \cdot \left[1 - \xi_j^p \cdot (j-1)\right] \cdot \frac{1 - e^{-\theta^P \left[\theta_h^P - G(t)\right]}}{1 + \eta^P \cdot e^{-\theta^P \left[\theta_h^P - G(t)\right]}}.$$

This formula takes into account possible changes in the dynamics of $P_m(t)$ for male persons (j = 1) or female persons (j = 2), and also for the healthy (h = 1) or weak (h = 0) persons.

The next formula approximately presents the dependence between the value of the emotional stress *S* and acceleration. It includes sex-associated specifics and catecholamines' production / utilization differences depending on direction of acceleration's changes (Δg):

$$S = \begin{cases} \gamma_m^s \left(1 - e^{-\rho t}\right) / \left(1 + \omega \cdot e^{-\rho t}\right), \Delta g > 0 \\ 3 \cdot \gamma_m^s (1+\eta) \cdot (j-1) \cdot e^{-\rho_1 \left(t^r - t\right)} / \left(1 + \omega_1 \cdot e^{-\rho_1 \left(t^r - t\right)}\right), \Delta g \le 0 \end{cases} \quad \gamma_m^s = \overline{1,3}, (*)$$

This factor is modifying the coefficients of heart rate's baroreflector control.

$$\Delta F^S = K_\gamma^F \cdot \left[1 + k_\gamma^F \cdot (j-1)\right]$$

$$F_N = F_c \cdot \left[1 + k_j^F \cdot (j-1) + \Delta F_S \cdot \left(1 + k_j^a \cdot a / a_0\right) + K_B^F \left(F^{\max} - F\right) \cdot C1 / \left(F^{\max} - F_{\min}\right) + \Delta F_B^B\right]$$

It also will modify the general output of these control mechanisms as:

$$E_B = \left(1 + a_S \cdot S\right) \cdot Y_G^R - K_a^B \cdot N_a - K_c^B \cdot N_c - K_B^B \cdot N_B + K^m \cdot Y^m$$

Special notes on these modifications are described later in discussion section.

Three next formulas were chosen to additionally approximate changes in central nervous regulators causing by age (a), sex (j) and health (h) factors.

$$E^I = N^R \cdot E_B \cdot \left(1 + \alpha^E \cdot a / a_0\right) \cdot \left[1 + f^E (j-1)\right] \cdot \left[1 / \left(1 + K^h \cdot (h-1)\right)\right]$$

$$T^H = T_B^H \cdot \left(1 + K_h^H \cdot (h-1)\right) \cdot \left[1 - f^H \cdot (j-1)\right]$$

$$T^V = T_B^V \cdot \left(1 + K_h^V \cdot (h-1)\right) \cdot \left[1 - f^V \cdot (j-1)\right]$$

The actual formulas for calculating of vascular tonus characteristics (resistance r, rigidity d and unstressed volume U) are followings:

$$r_n = r_n^B + K_n^r \cdot C^r \cdot C_0^V$$

$$d_n = d_n^B \cdot \left(1 + K_n^d \cdot C^d \cdot C_0^V\right)$$

$$U_n = U_n^B \cdot \left(1 - K_n^U \cdot C^U \cdot C_0^V\right),$$

where

$$C_0^V = \frac{V_B \cdot \left[1 - \xi \cdot (j-1)\right] \cdot (1+S)}{1 + \xi^h \cdot (h-1)},$$

where

$$T \frac{dV_{ES}}{dt} = K_{ES} \cdot E^I - V_{ES}.$$

In the last two mathematical expressions, S reflects emotional stress level, V_{ES} is the activity of efferent sympathetic nerves, E^I - is the output error in central contour of baroreflex.

So, the system of equations described above is the basic quantitative mathematical model capable to imitate responses of the human CVS and its physiological acute regulators to violations of the initial quasi-static values of both systemic and lung circulation. Although accelerations are the main cause of such violations, other factors like alterations of human pose, of local extravascular pressures, as well as changes of the background level of CNS' activity and / or concentrations of certain blood chemicals also can be initiators of hemodynamic violations. Regulator mechanisms presented in the model are activating against these initial violations.

The approximate numerical solution of the system of model equations is carried out by the Euler method. Previously, the model constants were tuned in a way that ensured a good accordance of simulation data with empirical data known for three postures (horizontal, head-up, and head-down) of the healthy human, as well as under several well-studied additional tests. The final version of software provides special algorithms for calculations of the model in accordance with the actual acceleration profile. Calculations also can be interrupted under appearance of two special cases. The first one is if the systolic pressure in ar-

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terioles of eyes is less that the level sufficient for providing pilot's vision. The second one is when the total brain flow is critically low to provide pilot's consciousness. In both cases, calculations interruption is accompanied with proper information about cause of the break. After the calculations have been made, their results appear in graph forms.

3. Several Results of Simulated Accelerations

There were created model versions approximately adapted to the person's age, sex, body mas, and height. All adaptation procedures use the basic model to automatically calculate characteristics of vascular compartments in order to provide initial steady-state hemodynamics. Adaptation algorithms and software use initial quantitative data given for cardiovascular characteristics of the mean healthy man of mass 70 kg and height 170 cm. So, the total blood volume is 5200 cm^3.

Special physiologist oriented user interface (UI), providing both preparations and execution of the computer experiment (in other words - simulation), was created. The screen-forms in Figure 3 illustrates the main opportunities provided by the UI for a scenario constructing for the current computer experiment (simulation). The user can choose one of four options to actualize model parameters, acceleration profile, protections, as well as certain additional options, necessary for the analysis of simulation results, provided as graphs. Namely, the picture below concerns means of protections and their actual parameters. It is shown that the experiment will be provided for the case when all four protections (stressing of muscles, breathing under positive pressures, three-sectional pneumatic suit, and the seat-angles of the pilot armchair) are activated at the time moment, when Gz accelerations overcame the threshold level of 2 g/sec.

Figures 4 and 5 represent both the used acceleration profile (bottom part) and certain hemodynamic variables under trapezoidal acceleration profile.

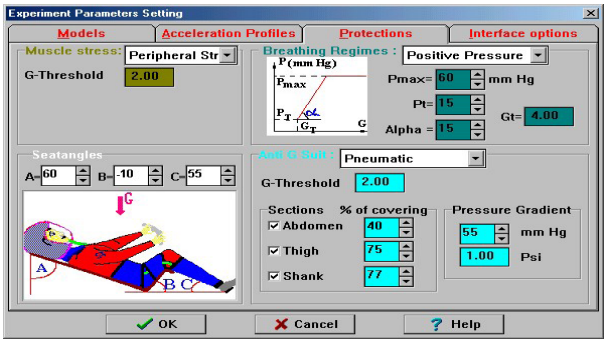

Figure 3. The screen-form of the user interface (UI) for setting actual characteristics of protections.

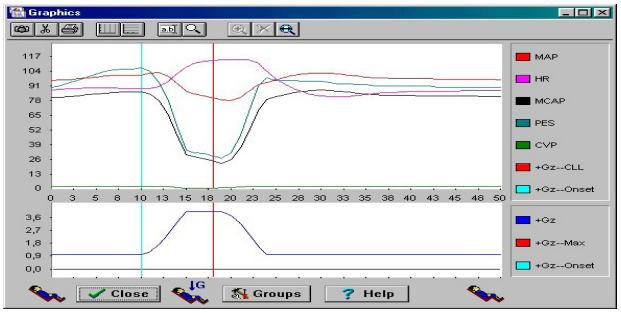

Figure 4. The dynamics of mean arterial pressure (MAP), mean pressure in carotid sinus (MCAP), systolic arterial pressure on the eye level (PES), central venous pressure (CVP) and heart rate (HR) under trapezoid profile accelerations with the acceleration and deceleration gradients 1g/s (the bottom part of the figure). The mean relaxed man. The emotional stress regime is set on moderate position. Seat back angle = 12° .

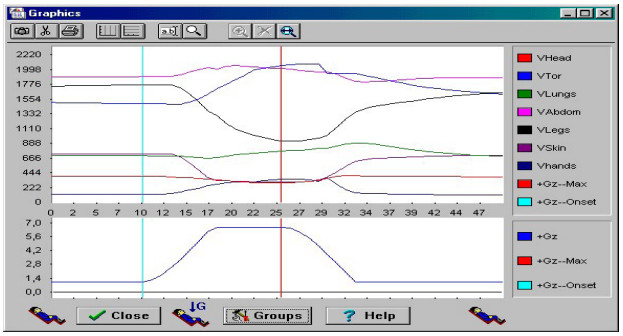

Figure 5. The dynamics of blood volumes in different body sections (Vtor - thorax; Vabdom - abdominal; Vlungs - lungs; Vlegs- legs; Vhead - head; Vhand -Hands; Vskin - Skin) under trapezoid profile accelerations with the acceleration and deceleration gradients 1g/s (the bottom part of the figure). The mean relaxed man with use of pneumatic anti-G suit. The suit is pressured with gradient 1.5 Psi after the acceleration exsids 2 g. Sections' covering percents are the following: abdominal -35%; thigh -75%; shank - 90%. The emotional stress regime is set on moderate position. Seat back angle = 30° .

In contrast, Figure 6 illustrates the case of a steeper acceleration increase and decrease profile under pilot's natural breathing.

The dynamics of mean arterial pressure (MAP), mean pressure in carotid sinus (MCAP), systolic arterial pressure on the eye level (PES), central venous pressure (CVP) and heart rate (HR) under trapezoid profile accelerations with the acceleration and deceleration gradients 1g/s (the bottom part of the figure). The mean relaxed man. The emotional stress regime is set on moderate position. Seat back angle = 30°.

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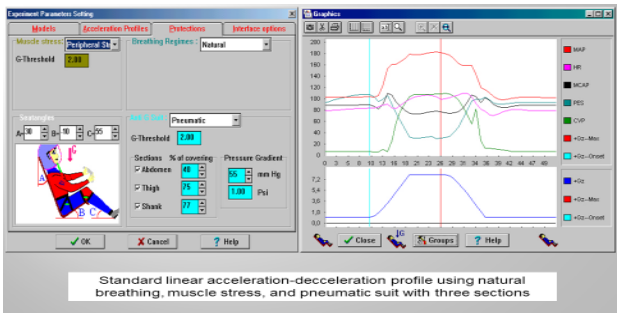

Figure 6. Parameters of used protections (left-side) and simulation results (right-side).

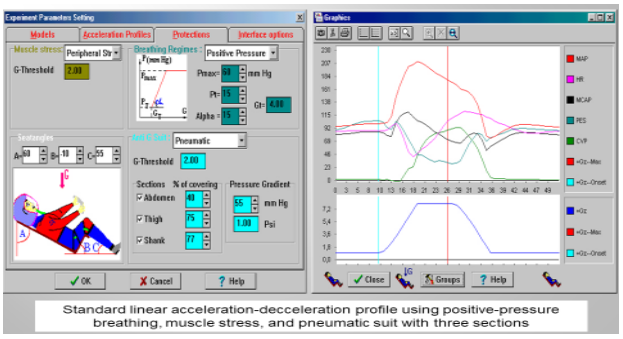

Figure 7. Parameters of used protections (left-side) and simulation results (right-side).

The dynamics of mean arterial pressure (MAP), mean pressure in carotid sinus (MCAP), systolic arterial pressure on the eye level (PES), central venous pressure (CVP) and heart rate (HR) under trapezoid profile accelerations with the acceleration and deceleration gradients 1g/s (the bottom part of the figure). The mean relaxed man. The emotional stress regime is set on moderate position. Seat back angle = 60°.

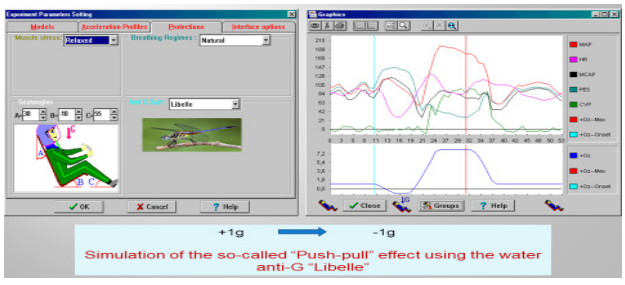

Figure 8. Parameters of used protections (left-side) and simulation results (right-side).

The dynamics of mean arterial pressure (MAP), mean pressure in carotid sinus (MCAP), systolic arterial pressure on the eye level (PES), central venous pressure (CVP) and heart rate (HR) under trapezoid profile accelerations with the acceleration and deceleration gradients 1g/s (the bottom part of the figure). The mean relaxed man. The emotional stress regime is set on moderate position. Seat back angle = 30°.

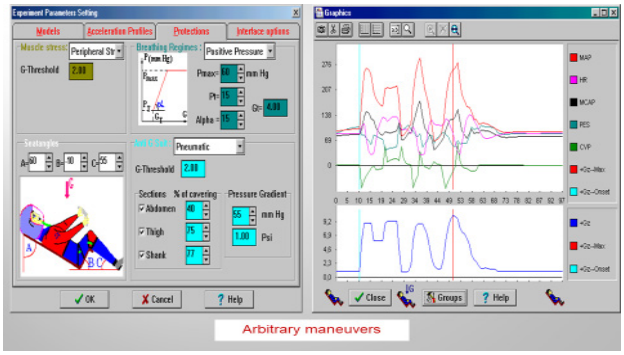

Figure 9. Parameters of used protections (left-side) and simulation results (right-side).

The dynamics of mean arterial pressure (MAP), mean pressure in carotid sinus (MCAP), systolic arterial pressure on the eye level (PES), central venous pressure (CVP) and heart rate (HR) under arbitrary profile accelerations with the acceleration and deceleration gradients 2 g/s (the bottom part of the figure). The stressed man. The emotional stress regime is set on the top position. Seat back angle = 60°.

4. Acute Alterations of Hemodynamics under Weightlessness: Special Role of Diaphragm Biomechanics in Pleural Pressure

Accelerations at the stage of placing a manned spacecraft into orbit, as well as the transition from the active phase to orbital flight, are accompanied by a number of biomechanical and physiological processes that have not been yet clearly understood and estimated. The proper organization of both pre-flight training and the prevention of the adverse effect of microgravity on the organism are important for providing of astronauts performance and health after returning to Earth. However, namely initial processes during the transition to weightlessness condition are still largely unclear. Among the controversial issues, the direction and magnitude of changes in central venous pressure play a key role for hemodynamics. Until the late 1980s, the dominant view was that CVP grows due to blood redistribution from the legs and abdominal cavity to the thoracic and cranial basins. Moreover, direct measurements of CVP in zero gravity were not carried out. The reasoning was based on the puffiness of the neck and faces, as well as on the phenomena known as "bird legs", the appearance of the waist, as well as the expansion of the girth of the chest segment of the astronaut's body. Almost all of these phenomena were well reproduced in terrestrial conditions using an antiorthostatic (head-down) posture with an inclination angle of -4 deg. up to -12 deg. It was

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in accordance with this concept that prevention procedures and algorithms were developed. However, nausea and deterioration in the well-being of astronauts in the acute period of adaptation to microgravity urgently required the development of more effective countermeasures. Therefore, the search for more adequate methods for modeling the primary phase of human adaptation in weightlessness was an important task of space medicine.

Mathematical modeling has become one of the alternative methods. Below are the results of such a simulation. However, before considering them in detail, I would like to dwell on one biomechanical aspect of this problem, namely, the possible role of pressure in the pleural cavity in the changes observed in real space flight.

The long-term adaptation of animal and human life to the conditions on Earth has led to close associations between respiration and blood circulation. Inhalation is carried out due to the combined changes in the activities of the intercostal muscles and the diaphragm. Moreover, exhalation is a largely passive process that occurs due to the return of the chest to its original state (under the influence of weight). It is important that the outer pleura sheet is mechanically attached to the muscles of the chest cavity and to the diaphragm. Thus, the moving of the diaphragm into the abdominal cavity and the expansion of the chest cavity are two independent factors that deepen the level of initially sub-atmospheric pressure in the closed pleural cavity. A drop in pleural pressure expands the lungs and inhalation occurs, while an increase in pleural pressure leads to exhalation. This normal biomechanics of respiration also affects the CVP: during the phase of inhalation, the CVP decreases, and during the phase of exhalation, on the contrary, the CVP increases. These changes in the CVP modulate venous return both in the superior and in the inferior vena cava. So, total blood volumes in cranial basin and in body lower part are negatively correlating with the dynamic of CVP.

Now let us turn attention to Figure 10.

Numbers in the right-side picture indicate: 1- lungs; 2- the heart; 3- the diaphragm; 4- abdominal organs. Three color rectangles symbolize the fact that the descending aorta, the inferior vena cava; and the esophagus, piercing through the diaphragm, mechanically connect the latter with organs of thoracic and abdominal cavities. The left-side picture schematically illustrates relative effects of different inertial forces on the diaphragm position.

The right-side picture schematically illustrates certain anatomical details of thoracic and abdominal organs. Important is that the descending aorta (red rectangle), the inferior vena cava (blue rectangle), and the esophagus (yellow rectangle), that is piercing through the diaphragm thus mechanically connect the latter with organs of thoracic and abdominal cavities. In Earth conditions, because of abdominal organs weight, the diaphragm position does depend on human postures. Moreover, the diaphragm position is associated with the direction and magnitude of mechanical forces, altering under accelerations or weightlessness (left-side picture). Namely, these facts were used for creating and consistent improvement of adequate mathematical model of human hemodynamics under altering gravitational forces [15,20,21].

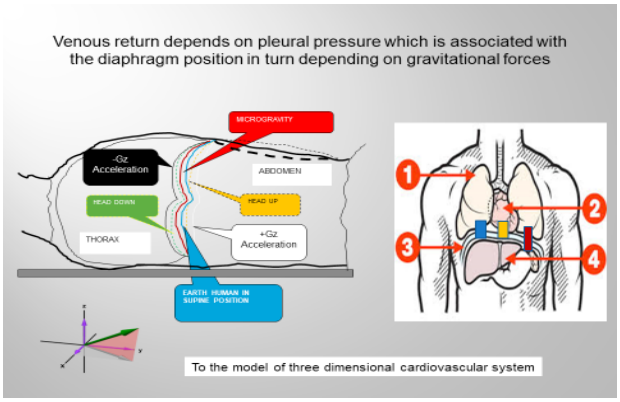

Figure 10. Schematic illustration of relationships between gravity induced mechanical forces and diaphragm position that were taken into account under modeling of hemodynamics in a three-dimensional vascular net.

Partial simulation results concerning blood distributions both in human body segments and in the frame of every segmental levels (back, axis, and chest) are collected in the table.

Data in the table are collected in two groups of columns. The first group, located in the left side, represents four columns of data generally concerned with simulations of four body positions; the rest condition on a back; the head up position of 90 deg.; the head down condition of 90 deg.; and the special head down posture of 6 deg. We can state that the simulated total sectional blood volumes shown in the table are very close to analogous empirical data. This was a reason to start simulate processes appearing in CVS just after the spaceship's engine stops to work. Appropriate simulation data are collected in four right-side columns. Special should be noted that the column, concerned with the engine stopping, presents data simulated under supposing the person has certain emotional stress.

Next four columns collect simulated data for two hypotheses. The first hypothesis is that the microgravity affects only the CVS function. Appropriate volumes present the simulations only for two time moments of weightlessness: in its 30-h seconds and 3-d min. For each time mo-

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Table 1. Simulated blood volumes in body sections and their three layers (chest, axis, and back) under Earth gravity and microgravity conditions.

			Body positions (Earth gravity)				Engine stop	Microgravity (hypotheses)			
			Horizontal on back	Head up 90 deg.	Head down 90 deg.	Head down 6 deg.	Logement position + 3Gz	HO 30 s	HO 3 min	HI 30 s	HI 3 min
BLOOD VOLUMES (ml) IN BODY SECTIONS	Head	Total	415	333	597	431	350	433	423	438	429
		Chest	135	111	166	141	113	144	141	146	143
		Axis	139	111	166	144	117	144	141	146	143
		Back	141	111	166	146	120	144	141	146	143
	Neck	Total	143	90	289	152	95	152	147	157	143
		Chest	35	21	51	39	21	40	39	42	41
		Axis	68	47	85	71	50	72	69	74	71
		Back	40	21	2`	42	24	40	39	42	41
	Thoracic	Total	1870	1575	2490	1990	1620	1915	1890	1620	1540
		Chest	435	388	650	478	340	490	485	390	368
		Axis	820	795	1180	970	810	940	915	845	805
		Back	510	388	650	538	468	490	485	390	368
	Abdominal	Total	1080	1230	1050	1147	1325	1005	1054	1245	1347
		Chest	323	406	357	348	430	332	355	414	446
		Axis	347	415	225	365	445	340	355	419	446
		Back	410	406	357	438	449	332	355	414	446
	Hips	Total	816	983	333	498	895	810	810	835	842
		Chest	245	328	111	183	289	270	270	278	280
		Axis	276	328	111	222	296	270	270	278	280
		Back	295	328	111	394	310	270	270	278	280
	Shins + Fools	Total	520	602	310	415	546	509	508	519	521
		Chest	165	201	103	136	181	170	169	173	174
		Axis	174	201	103	138	182	170	169	173	174
		Back	177	201	103	141	184	170	169	173	174
	Hands	Total	326	351	384	327	337	338	330	345	339

ment, two hypotheses have been simulated. In the frame of the hypothese0 (in the table denoted "H0"), the only hemodynamic influence is caused by the loss of the blood hydrostatic pressure. The hypothese1 (in the table denoted "H1") supposes additional changes, namely, increase of pleural pressure on 12 mm Hg and decrease of extravascular pressure in abdominal cavity on 6 mm Hg.

As one can see, the simulated cranial hypervolemia accompanied by decreases of blood volumes in legs and abdomen area is fixed. Namely, such a general picture of hemodynamic shifts have had been observed during the real cosmic flights [4,5,8-10].

5. Discussion

Two fundamental problems covering multiple aspects of human physiology in extreme environmental conditions have been analyzed using non-traditional approach based on quantitative mathematical models and computer simulations. Earth gravity is the consistent environmental factor evolutionarily determined structural-functional aspects of human body anatomy and physiology. Adaptation boundaries were mainly concerned with loads associated with postural changes. As modern airspace flights revealed, these boundaries are not sufficient for providing human health and performance under sustained acceleration and / or microgravity [1-9,23-26]. Mathematical modeling and computer simulations have been recognized by physiologists-empiricists as prospective assistant research tool, making the process of research and development of protective technologies both less dangerous and cost-effective [27-31]. However, it is important to take into account a huge number of physiological mechanisms, facts, and observations capable help to disclose real acting forces accompanying modern airspace flights. A particular but not less important problem is models verification. As a rule, empiricists have not the complete measurements necessary for models verification. The only way to get out of the existing impasse, use heuristics based both on

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the experience of creating simpler models and on testing models in those situations that are most studied. But even the indicated paths do not guarantee the correctness of the simulation results. Therefore, the conclusions that follow from the simulations are subject to empirical verification. Our experience in modeling of various physiological systems and mechanisms allows us to hope that the results presented in the article will meet the due interest of traditional physiologists.

Computer simulations on the model of a three-dimensional cardiovascular system has shown that the slight elevation of the pleular pressure is the most likely mechanism impeding venous return from the cranial basin [6]. Simulations gave arguments for proposing the following conceptual scheme of alterations in hemodynamics under short-time microgravity.

As to modeling of hemodynamic effects of positive (+Gz) or negative (-Gz) accelerations, it is useful to provide some additional arguments for the adequacy of the models. First of all, our models have a long prehistory. The basic models were developed and properly verified for simulating human cardiovascular responses to postural tests [18]. The next phase of models modernization was their augmentation for simulating slow (about 0.1 g/sec) increasing moderate (up to 3 g) +Gz accelerations without use of protection suits [12]. Step-by- step, new physiological mechanisms and protective technologies were added, tuned, and tested. As a result, a simulator "PILACCEL" was successfully created and tested using data presented by experts of the Laboratory of Biodynamics (chief at that time - Dr. William Albery) in Wright Patterson Air Force Base USA [13,14]. After that time, both models and software were modified [19,14]. These modifications of models were based on data presented in [33-36]. Results, presented in this article, have been obtained by means of the advanced software.

Experts know that the top value of human tolerance to standardized profile of +Gz acceleration loading may have essential variability. The variability is characteristic both during results comparison observed on different subjects and even in frame of different observations for one subject. Factors determining this variability were analyzed to include them in our models. Such approach will help one both to understand why the published results of different

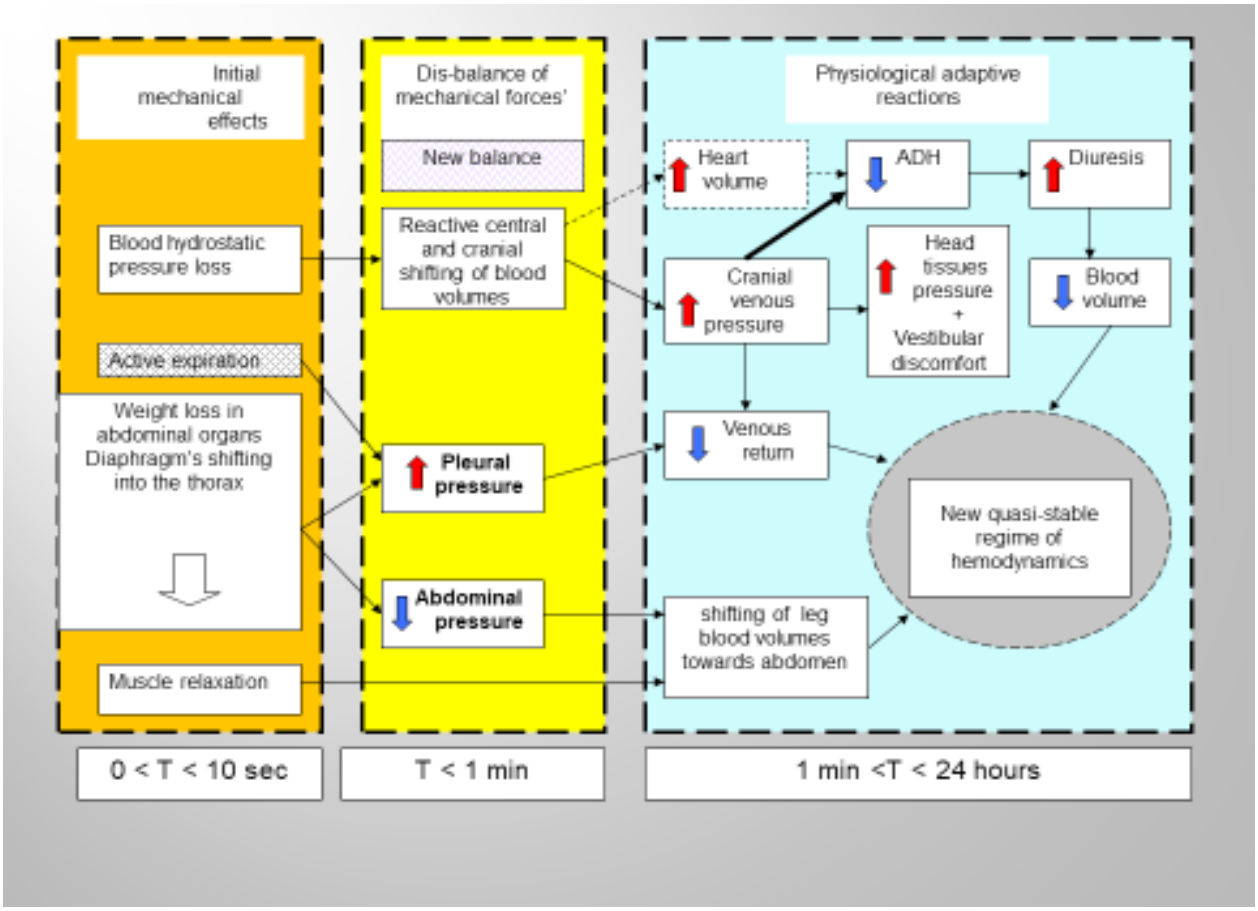

Figure 11. Conceptual scheme of alterations in hemodynamics under short-time microgravity.

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investigators have a wide disperse, and how to effectively use our models. This analysis is also aimed to determine an acceptable approach to the problem, how to optimize protections use.

Generally speaking, all anthropologic, psychological, physiological and environmental factors that theoretically may influence on the top limit of human tolerance to +Gz acceleration may be divided into two different groups, containing observable and non- observable factors. Let's the factors that potentially might be controlled by investigator, consider here as the first factors group. Into the factors' second group we include the factors that may be considered as causal within every observation. So, this vision platform lets us to imagine that the variability between every two observations is sooner a regular event than an exclusive one. An additional useful condition for our analysis is the assumption that among the factors of the first group we also can mark two subgroups according to the factor's relative role in providing of human tolerance to Gz acceleration. The list of the major factors determining top value of the tolerance consists of several anthropometric, psychological, physiological and environmental characteristics. Perhaps, in the most advanced model, these characteristics should have been considered input parameters too.

Special notes concerning emotional stress under extreme accelerations (see formula (*)) could help the reader to better imagine both the necessity and the technology of simulation. In our initial model of moderate accelerations [12], values of regulators' gains had been the same that was argued for the model created to simulate human hemodynamics under postural tests [18]. However, trying to simulate extreme accelerations, we meet a problem - responses of the heart rate were essentially lower than empirical results. In addition, the simulated loss of vision appeared earlier than it was known for centrifuge tests. I have had consulted on this subject with well-known experts (professors Russell Burton and Ulf Balldin). They recommended to pay attention on the fact that blood tests just after sustained centrifuge accelerations have shown essential elevations of blood catecholamines compared with the rest conditions before centrifuge onset. Namely, approximation formula (*) was chosen in assumption that accelerations a priori increase the concentration of blood catecholamines. Approximation parameters in (*) were chosen in order to have acceptable adequacy of simulated and empirical observations for heart rate and the time of loss of peripheral vision.

Concerning microgravity conditions, some thoughts can be added. In ground conditions, the weight of the organs of the chest cavity, in particular - of the abdominal cavity - is an independent modulator of the shape and tension of the diaphragmatic muscle. Therefore, this weight plays a significant role in forming of the pleural pressure. Just before the transition to orbital flight, the diaphragm of the astronaut, experiencing about 3 units of + Gz accelerations, is both tensed and maximally displaced into the abdominal cavity. So, the pleural cavity is increased thus the pleural pressure is minimal. As soon as the ship's engines cease to create thrust, the weight of the internal organs disappears, and the muscular tension of the diaphragm removes it into the chest cavity until a balance of mechanical forces acting on the diaphragm from its both sides is achieved.

The key to this transformation is that the pressure in the pleural cavity rises. But this rise in real conditions has one more reason - exhalation in weightlessness can only be active, i.e. the intercostal respiratory muscles contract and press on the pleura. Thus, venous return in zero gravity will be difficult, which will lead to accumulation of blood in the cranial basin and in the vessels of the lower body. It remains to explain why the blood in the lower part of the astronauts decreases in flight.

In my opinion, the explanation is related to two nuances. First, due to the fact that the adaptation of a bipedal person to Earth's gravity was aimed at preventing the collapse of cerebral circulation, a natural asymmetry of the innervation of the arterioles of the lower and upper parts of the body has developed. The density of the innervation of the arterioles of the abdominal cavity and legs is much greater than the density of the innervation of the vessels of the upper body. Secondly, arterial mechanoreceptors respond to the value of transmural pressure, which will be the lower, the higher the extravascular (specifically, pleural) pressure is. Consequently, reflex reactions developing in conditions of short-term weightlessness will contribute to a greater narrowing of the arterioles of the lower part of the body and a decrease in the volume of blood in them. In this case, the outflow of blood from the vessels of the cranial basin is still difficult. A gradual decrease in these symptoms is the result of increased urine output, which is most likely caused by stretch receptors in the cerebral sinuses.

6. Conclusions

Human hemodynamics is critically sensitive both to essential alterations of mechanical inertial forces in directions of head-legs (+Gz) or legs-head (-Gz) and to microgravity condition. Typically, such alterations appear during pilotage maneuvers of modern high maneuverable airspace vehicles (HMAV). Pilots' or passengers' vulnerability to these altering forces depends on force's

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three main characteristics: amplitude, dynamics and duration. Special protections, proposed for minimizing of the vulnerability, should be improved in parallel with the increasing of these hazardous characteristics of HMAVs. As the empiric testing of novel protection methods and tools is both expensive and hazardous, computer simulations are encouraged. Autonomic software (AS) for simulating and theoretical investigating the main dynamic responses of human cardiovascular system (CVS) to altering gravitational forces is developed. AS is based on a system of quantitative mathematical models (QMM) consisting of about 1300 differential and algebraic equals. QMM describes the dynamics of both CVS (the cardiac pump function, baroreceptor control of parameters of cardiovascular net presented by means of lumped parameter vascular compartments) and non-biological variables (inertial forces and used protections). The main function of AS is to provide physiologist-researcher by visualizations of calculated additional data concerning external and internal environments under high sustained accelerations and short-time microgravity. Additionally, AS can be useful as an educational tool able to show both researchers and young pilots the main hemodynamic effects caused by accelerations and acute weightlessness with and without use of different protection tools and technics. In this case, AS does help users to optimize training process aimed to ensure optimal-like human tolerance to the altered environment. Main physiological events appearing under different scenarios of accelerations and microgravity have been tested.

It is worth to underlie that simulations have shown principally new phenomenon. Namely, extreme Gz accelerations are special environmental factor capable of transforming the normally synergic functions of aortic arch and carotid sinuses baroreflexes to their antagonistically functioning. This publication reveals some intimate aspects of the modeling that were not reflected in models analyzed in [37]. The modeling is also approachable for the deeper understanding of other physiological mechanisms responsible both for the normal and for the several pathological functioning of CVS. In the next publication, I would like to present models and simulations, concerned with the much more complex physiology of mechanisms that are responsible for acute, middle-time and long-time neural-humoral control of human circulation.

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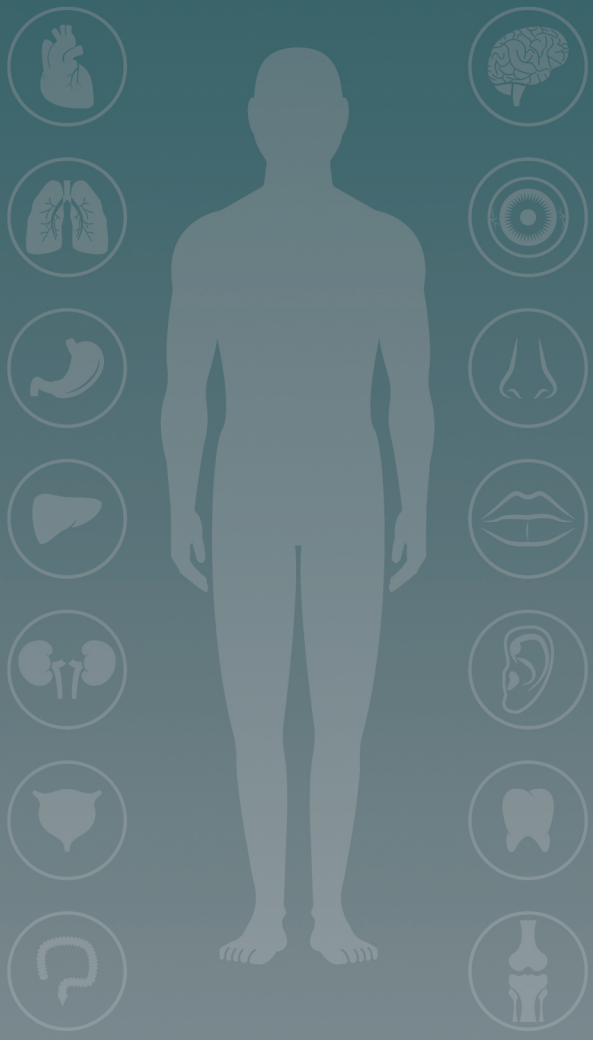

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