International Journal of Physiotherapy and Research,
Int J Physiother Res 2022, Vol 10(3):4258-68. ISSN 2321-1822
DOI: *https://dx.doi.org/10.16965/ijpr.2022.124*

Review Article

Exercise Performance and Immune Competence [EPIC]: Background of Natural Immunity, Immune Diversity and Immuno-iatrogenesis

R. Vinodh Rajkumar.

Physiotherapist, Medical Anthropologist & Gerontologist, Prabhanjeet Vitalityarium, Tamilnadu, India. **ORCiD:** https://orcid.org/0000-0002-6656-3178

ABSTRACT

Impeccable Metabolic Maneuvers Upbring Natural Immunity To You [IMMUNITY]. Homeostatic competence of human body is an output of meticulous and interdependent/integrated/impeccable metabolic functions to resist or overcome diseases and facilitate a lengthy lifespan along the healthy ageing trajectory. Principles of homeostasis are seldom employed in the clinical applications. Perhaps this has led to almost an irreparable derailment of ethics and core competence of medical profession. Ivan Dominic Illich emphasized his criticisms on iatrogenesis and argued that modern medicine had hubristically taken on a mission to eradicate pain, sickness, even death but expropriated the autonomous power of humans to cope with their ailments. It is also quite obvious that the medical profession has failed to learn about 'healthy individuals' elaborately. Healthy individuals possess quintessential epigenetic efficiency and homeostatic competence built through several years of disciplined lifestyle, and especially their fitness characteristics are incomparably superior to individuals who never or rarely display propensity to improve their health standards. The disastrous perception of Immunology that 'Best Homeostasis' and 'Worst Allostasis' are same, hence all the individuals regardless of their health status are equally a potential source of disease transmission during an infectious disease outbreak, has caused severe disruption in various aspects of human life across the globe. Even the healthiest/fittest athletes and outstanding exercisers could asymptomatically transmit an infection to unhealthy people [who led an unhealthy lifestyle] whose disease could be anywhere in the allostasis spectrum ranging from early-stage co-morbidities to severe functional deterioration? Under the aegis of homeostasis and non-specific antibodies [Secretory IgA], a long-lasting Natural Immunity [NI] should be possible excluding the need of 'specific antibodies'. Expanded Trained Immunity [ETI] proposed by Cassone has been found not only in innate immune system but also in nonimmune cells [both cells of hematopoietic and nonhematopoietic origin] associated with immunological memories from previous microbial encounters. Interesting discoveries about NI and ETI could emerge if they are linked with homeostasis and allostasis to develop objective immunologic tests to differentiate the healthy and unhealthy individuals, and enhance the clarity of immunology. Exercises are strongly linked to immunity; thus, measurements of exercise performance standards could accurately reveal the status of NI of the individuals if exercise performance data are systematically interpreted and correlated with immunologic function. Exercise performance data can be gathered using easily accessible non-invasive inexpensive tools. From the perspectives of homeostasis, we may not have distinct departments in the body to curb/defeat immunological or other non-immunological diseases, but any disease could be a threat to recovery to pre-existing conditions or even survival, if the homeostatic functions are impaired by iatrogenesis.

KEYWORDS: Homeostasis, Innate Immunity, Adaptive Immunity, Exercise, Epigenetics, Trained Immunity, Secretory IgA, Allostasis, Immunosenescence, Iatrogenesis.

Address for correspondence: R. Vinodh Rajkumar, Physiotherapist, Medical Anthropologist & Gerontologist, Prabhanjeet Vitalityarium, Tamilnadu, India.
E-Mail: dreamofkalam@rediffmail.com

Access this Article online	Journal Information
Quick Response code	**International Journal of Physiotherapy and Research** ISSN (E) 2321-1822 | ISSN (P) 2321-8975 **https://www.ijmhr.org/ijpr.html** **DOI-Prefix:** https://dx.doi.org/10.16965/ijpr
DOI: 10.16965/ijpr.2022.124	**Article Information** Received: 20 Apr 2022 Peer Review: 22 Apr 2022 Accepted: 12 May 2022 Published (O): 11 Jun 2022 Published (P): 11 Jun 2022

INTRODUCTION

Homeostasis is the basis of health and survival at any stage of life. Homeostatic competence signifies the benchmark harmonious state of the body facilitated by integration of three-dimensional functionality [functions pertinent to acid-base balance, immunity and metabolism] of various physiologic functions or factors [1]. Each physiologic function [like breathing, detoxification] or factor [like blood glucose, hemoglobin, platelets] originates from specialized cells or organs to exhibit both peculiar and common duties, aligning with homeostasis. Allostatic load is the long-term result of failed adaptation or allostasis, resulting in pathology and chronic illness, caused by failure of adaptation process of the complex physiological system to physical, psychosocial and environmental challenges or stress [2]. Principles of homeostasis are seldom employed in the clinical applications and community/global health strategies. Homeostasis is an underappreciated, far too often ignored central organizing principle of physiology and disruption of homeostatic mechanisms is what leads to disease, and effective therapy must be directed toward re-establishing these homeostatic conditions [3]. "Kinanthopometry evaluations show Altered Body Composition with Disability [ABCD] and premature functional deterioration due to severe gravitational torque deficiency syndrome even among apparently healthy individuals, thus we have extremely diverse human populations on the planet ranging from best homeostasis to worst allostasis. Many humans enter into unhealthy ageing trajectory very early in life, and struggle to even maintain minimum essential VO2 max, gait and various key fitness variables, eventually acquiring multiple morbidities and get ruined irreversibly by polypharmacy or iatrogenesis" [4].

Ivan Dominic Illich emphasized his criticisms on iatrogenesis and argued that modern medicine has expropriated the autonomous power of humans to cope with their ailments. It is also quite obvious that the medical profession has failed to learn about 'healthy individuals', and their 'disease-resisting' fitness and natural healing potential without pharmaceutical products, elaborately. Healthy individuals possess quintessential epigenetic efficiency and homeostatic competence built through several years of disciplined lifestyle, and especially their fitness characteristics are incomparably superior to individuals who never or rarely showed propensity to improve their health standards. The disastrous perception of Immunology that the 'Best Homeostasis' and 'Worst Allostasis' are same, hence all the individuals regardless of their health status are a potential source of infectious disease transmission, has caused severe disruption in various aspects of human life across the globe. Immunology revolves around innate immunity and adaptive immunity, but how to assess and quantify them? Quantification of immunologic status on an individual level is particularly important if asymptomatic transmission of infectious diseases and compulsory vaccinations for all age groups, irrespective of the health standards, are widely accepted. 'Unvaccinated healthy individuals will develop an infectious disease and continue to transmit diseases asymptomatically whilst vaccinated unhealthy individuals will not develop or transmit the same infectious disease' has become the recent chaos. By administering pharmaceutical products, allostasis can never be made better than homeostasis without applying the principles of homeostasis. Conspicuously, in reality, no one undergoes any quantifiable immunologic test before and after vaccination because neither the government nor the doctors make such crucial test mandatory. Without any objective testing, how a prophylactic or therapeutic procedure in medical science be considered trustworthy? Immunology, though appears as an impeccable and versatile branch of medical science dealing with infectious diseases, has complicated the public health so deep because [i] it does not trust any healthy individual without any symptoms but take them as a source of asymptomatic disease transmission for granted [ii] it does not trust any healthy and unhealthy individual who took recommended doses of vaccine but continues to recommend booster doses without confirming the immunologic fitness or

the level of antibodies for a specific disease as proclaimed by the approved vaccines [iii] it is over-optimistic that there will be zero iatrogenesis from vaccinations despite its quite obvious weaknesses, but seldom or never engage in follow-up studies at the community level to investigate the adverse reactions. Immunology has almost rejected Natural Immunity [NI] and herd immunity but has tightly embraced the concept of production of 'specific antibodies' through vaccines [and compulsory vaccination for all] to resist the spread and eradication of every infectious disease, thus puts it focus only on strengthening the adaptive immunity. Under the aegis of homeostasis and non-specific antibodies [Secretory IgA], Natural Immunity [NI] should be possible excluding the need of 'specific antibodies. Even among the individuals with dysregulated homeostasis and unhealthy ageing process, NI could render protection [certainly not equivalent to the NI of the healthy individuals], which probably could improve further if appropriate lifestyle changes are incorporated. Expanded Trained Immunity [ETI] proposed by Cassone has been found not only in innate immune system but also in nonimmune cells [cells of hematopoietic and nonhematopoietic origin] associated with immunological memories from previous microbial encounters and it is an exciting perspective for novel thinking and improved approaches to the fight against infectious and inflammatory diseases. [5]. As the line between innate and adaptive immunity continues to blur, it remains imperative to determine the precise mechanisms underlying durable immunological memory [6].

The innate immune response is a rapid and precise activation in response to pathogens or danger signals not only to efficiently eliminate pathogens but also to avoid excessive inflammation and tissue damage [7].

"As an organism, we must respond aggressively to foreign antigens, but an over-exuberant reaction is damaging and potentially fatal, therefore immune termination is too important to fail. The ideal immune response is rapid, proportionate and effective. Crucially, it must also be finite" [8].

'Asymptomatic carriers' of microorganisms was accepted by Koch, but, in recent times, immunology has included 'asymptomatic transmission', which led to stringent and coercive public health strategies without diagnosing and quantifying the immune status of individuals. "Even Koch had to modify or bend the strictest interpretation of the first postulate 'the microorganism must be found in diseased but not healthy individuals'. Koch discovered asymptomatic carriers of *Vibrio cholera* and *Salmonella typhi*, yielding the important distinction between asymptomatic clinical colonization and infection" [9]. In fact, in the absence of valid immunodiagnostics to grade the immunologic status of healthy and unhealthy individuals, the inculcation of 'asymptomatic transmission' in the minds of people or in the medical curriculum is capable of manufacturing perpetuating complications and threats for societal serenity. "Interactions between microbes and human hosts can lead to a wide variety of possible outcomes including benefits to the host, asymptomatic infection, disease [which can be more or less severe], and/or death. Whether or not they themselves eventually develop disease, asymptomatic carriers can often transmit disease-causing pathogens to others" [10]. Medical science has become imbalanced during this COVID-19 pandemic by disregarding other important scientific findings and logical/ethical objections. "SARS-Cov-2 has never been isolated in accordance with standard practice. The diversity of symptoms among patients makes it impossible to associate specific symptoms with the presence of SARS-Cov-2 RNA or to isolate the virus with precision. Significant uncertainty surrounds the isolation of this virus and the characterization of its genome" [11]. "COVID-19 vaccine requirements have generated significant debate. Such policies should have recognised proof of natural immunity as a sufficient basis for exemption to vaccination requirements. We suggest that we lack clear and convincing scientific evidence that vaccine-induced immunity has a significantly higher protective effect than natural immunity. Not only vaccine requirements represent a substantial infringement of individual liberty, but without

compelling evidence for the superiority of vaccine-induced immunity, subjecting people with natural immunity to vaccine mandates is therefore not justified" [12].

Immunology has failed to create at least one reliable mandatory immunodiagnostic procedure to estimate the immunologic status of the people to prove the efficacy of all the strategies to prevent, control and eradicate any infectious disease. Lack of clinical diagnosis and treatments on the basis of homeostasis could lead to public health damage, disingenuous medical curriculum, and eventually iatrogenic pseudoscience [4]. It is impossible to create a homeostatic foundation without exercise, optimal nutrition and hydration, and other lifestyle constituents, favouring healthy longevity naturally. "World's population has become aging, unfit, corpulent, and immunodeficient society increasing the likelihood of pandemics. This is indeed a wake-up call, a tocsin, to the world that primary prevention countermeasures focused on health behaviours and hygiene demand our full attention and support. Secondary and tertiary prevention approaches centered on vaccine and therapeutics development will take time and may not be fully effective, giving even more urgency to staying fixated on primary prevention" [13]. We should put our faith in the innate immune system — after all, organisms have been doing it for over half a billion years [14].

"The effects of exercise related to the function of innate immune cells is a field in which comparisons are made between the innate immune cells of trained athletes and sedentary people. Results generally point to a higher immune function in athletes versus non-physically active people. Second, it is a field related to investigating the changes in immune cell functions in subjects who train for a certain period of time with various intensities and durations under specific conditions. It is known that the number of leukocytes [leukocytes, neutrophils, lymphocytes] and Natural Killer [NK] cells in exercise groups are higher than control groups, after moderate exercise, as well as after incremental maximal exercise. In addition, when the intensity of exercise is gradually increased and the maximum level is reached, leukocytes, neutrophils, lymphocytes, T cells, B cells, and NK cells increase. Greater attention should be given to the role of exercise and how innate immunity system can be strengthened" [15]. Interesting discoveries about NI and ETI could emerge if they are linked with homeostasis and allostasis to enhance the clarity of immunology. Exercises are strongly linked to homeostasis and immunity; thus, measurements of exercise performance standards could accurately reveal the status of NI of the individuals if exercise performance data are systematically interpreted and correlated with immunologic functions/variables. Exercise performance data can be gathered using easily accessible non-invasive inexpensive tools. From the perspectives of homeostasis, we may not have distinct departments in the body to curb/defeat immunological or other non-immunological diseases, but any disease could be a threat to recovery to pre-existing conditions or even survival, if the homeostatic functions are impaired by iatrogenesis.

Background of Natural Immunity, Immune Diversity and Immuno-Iatrogenesis: The innate immune system is the first line of defense against infection and is activated with in minutes, reacting in a nonspecific, pre-programmed, and patterned manner to various infectious or foreign [non-self] stimuli [16]. Various cell types that compose the innate immune system share antigen recognition ability through their invariant receptors which do not undergo rearrangement and have no immunological memory [17].

Microbial infections are recognized by the innate immune system both to elicit immediate defense and to generate long-lasting adaptive immunity [18]. "Innate immunity can be viewed as comprising four types of defensive barriers: anatomic [skin and mucous membrane], physiologic [temperature, low pH], endocytic/phagocytic [neutrophils, monocytes], and inflammatory [leakage of vascular fluid leading to influx of phagocytic cells into the affected area]. There is a great deal of synergy between the adaptive immune system and its innate counterpart, and defects

in either system can provoke illness or disease, such as inappropriate inflammation, autoimmune diseases, immunodeficiency disorders and hypersensitivity reactions" [19].

"Unlike the adaptive immune system, the innate immune system has classically been characterized as being devoid of memory functions. However, recent research shows that innate myeloid and lymphoid cells have the ability to retain memory of prior pathogen exposure and become primed to elicit a robust, broad-spectrum response to subsequent infection. This phenomenon has been termed innate immune memory or trained immunity" [20]. "Trained immunity—a concept recently proposed by Cassone, that challenges the dogma of immunologic memory being attributed solely to the adaptive immune system. Trained immunity proves to be an indispensable element of host defense. This de facto innate immune memory is elicited by distinctive epigenetic and metabolic programs. Trained immunity is not restricted to innate immune cells, and evidence is accumulating that long-term adaptation can develop following brief stimulation of various nonimmune cells including vascular endothelial cells, vascular smooth muscle cells, fibroblasts, epithelial stem cells, and microglia" [21].

"Trained immunity has emerged as a focal point in immunology research and has added a layer of complexity to our previous understanding of immune memory, that is, a trait limited to antigen- specific responses of the adaptive immune system. Trained immunity can mount a faster and greater response against a secondary challenge with homologous or even heterologous pathogens [22].

There are several factors like Red blood cells, White blood cells, Platelets, Plasma proteins, Breathing, Skeletal Muscle, Bone, Temperature, Hormones, Kidneys' electrolyte homeostasis, Hepatocytes' pathogen detection and clearance, Blood glucose concentration are responsible for protecting the body against infections, metabolic dysfunctions, acid-base disturbances and functional deterioration [1]. Quite obviously, all these factors are immeasurably diverse among humans apart from age, gender, somatotype, lifestyle and environmental stressors, to challenge the generalizations of any immunological finding too. In addition, IgA act like non-specific antibodies. "Secretory IgA has several features and functions that make it ideal for mucosal defense. First, SIgA is constitutively localized in mucus, ensuring that this antibody is ready to neutralize almost any pathogen or toxin trying to make contact with epithelial cells. Second, independent of antigenic specificity, the carbohydrate moieties of SIgA molecules can bind to adhesion molecules expressed by many pathogens, trapping the invaders on the luminal surface. Third, at least in the gut, about half of all SIgA antibodies are unusually cross-reactive, meaning that a broader range of threats can be countered with fewer antibodies. Fourth, SIgA is not an efficient activator of complement, so there is less chance of triggering the cascade and initiating damaging inflammation" [23].

If asymptomatic individuals are found lacking specific antibodies [because the pathogen could not overcome the primary resistance from innate immune system], they should be regarded as 'Grade 1 – Immunocompetent' [1]. Various contributors of metabolic maneuvers strengthen the homeostatic foundation for a long-lasting resistance against all the diseases known to man [Table – 1].

"The immune system possesses immense individual-to-individual diversity. The extreme diversity of the human immune system, forged and maintained throughout evolutionary history, provides a potent defense against opportunistic pathogens. Genetic variation is an important driver of immune variation. The evolution of immunity has not halted with modernity. Understanding variation in response to environmental factors in particular, such as diet, microbiome, and environmental exposure, holds the promise of using simple environmental manipulations in a targeted manner to reroute an individual's immune system toward a less pathogenic configuration. Although the advantages of personalized immune modification are manifold, they first require a baseline knowledge of the source of our individual

Table 1: Broad range of contributors to immunity that are also responsible for impeccable/integrated/ interdependent metabolic maneuvers and flawless homeostatic foundation. Many other contributors also exist beyond the scope of this enumeration.

Contributor	Literature background
White Blood Cells	White blood cells play a most important role in phagocytosis and immunity and therefore in defense against infection [24]
Red Blood Cells	The paramount function of the red blood cells [RBCs] is generally reckoned to be oxygen carriage but the RBCs are both mechanical and biochemical barriers against infections, bacteria, and blood parasites [25]
Platelets	In addition to their role in coagulation and healing, platelets also act as the immune system's first responders when a virus, bacterium, or allergen enters the bloodstream [26]
Plasma proteins	Immunoglobulins constitute about 20% of the protein in plasma and being the major antibody in secretions, IgA is found in saliva, tears, colostrum, intestinal, genital tract and respiratory secretions [27]
pH	Because acidic pH predominates at inflammatory loci and other sites of immune activity, most studies to date focus on the effect of acidic rather than alkaline pH. Many of the clinical acidosis are accompanied similarly by immunodeficiency [28]
Skin	Skin functions as more than a physical barrier: it is an active immune organ. Immune responses in the skin involve an armamentarium of immune-competent cells [29]
Skeletal muscle	Skeletal muscle has emerged as a potent regulator of immune system function. Therapeutic approaches targeting skeletal muscle might be able to restore both muscle and immune system function [30]
Bone	Bone marrow is thought to be a primary hematopoietic organ but it is also an immune regulatory organ capable of fine-tuning immunity [31]
Temperature	Immune system works more efficiently when the body gets hotter. Immune cells that act as first responders to infection, such as dendritic cells, macrophages and neutrophils, have been shown to arrive at the scene faster, and have an improved capacity to engulf and destroy infectious agents at 38°C to 40°C. Permitting a fever in the viral condition is likely to allow your immune system to do its job – as it has been designed by millions of years of evolution – better, says Peters [32]
Blood glucose	Both low and high glycemic conditions can modulate immune function [33]
Blood Cholesterol	Unbalanced lipid metabolism contributes to the development of a wide range of immune disorders including autoimmune diseases, allergies, cancers, and infectious diseases [34]
Endocrine	Infections and stress, immune responses, and hormones are interconnected, ensuring immune competence to deal with immediate threat of overwhelming infection and metabolic collapse [35]
Epigenetics	Epigenetic mechanisms play crucial roles in the development and function of immune system, the environment modifies epigenetic marks throughout lifetime, and epigenetic marks are reversible. Under the effect of intrinsic and extrinsic factors, such as metabolic profile, hormones, nutrition, drugs, smoke, and stress, epigenetic marks are actively modulated [36]
Lungs	Innate critical defensive abilities of lungs are usually able to maintain near-sterility of the lungs without the intervention of 'conventional' cells of the immune system [37]
Liver	The human liver is usually perceived as a non-immunological organ engaged primarily in metabolic, nutrient storage and detoxification activities but hepatocytes perform a number of important immunological roles too [38]
Gut	The gastrointestinal tract harbors the largest microbiota load in the human body, hence maintaining a delicate balance between immunity against invading pathogens and tolerance toward commensal. Such immune equilibrium, or intestinal homeostasis, is conducted by a tight regulation and cooperation of the different branches of the immune system, including the innate and the adaptive immune system [39]
Kidneys	Kidney failure increases susceptibility to infection and promotes exaggerated inflammatory responses, both of which increase mortality, due to disruption in its central role in electrolyte homeostasis and the removal of toxins [40]
Heart	Heart possesses an innate immune system that is intended to delimit tissue injury, as well as orchestrate homoeostatic responses, within the heart [41]
Central nervous system	Despite the presence of effective barriers, various pathogens such as viruses, bacteria, fungi, protozoa, and parasites can disrupt the blood brain barrier [BBB] that may often have chronic implications or prove to be fatal. Increasing evidence indicates that astrocytes, as the most abundant CNS glial cell population, regulate innate and adaptive immune responses in the CNS under pathological conditions in addition to their role in the maintenance of CNS homeostasis and neuronal function [42]
Reproductive system	The immune system in the reproductive tract of both men and women has evolved distinct adaptations that meet the physiologically challenging demands of both successful reproduction and the maintenance of full protection against microbial invasion. The compartmentalization of systemic immunity and mucosal immune responses is a distinct feature of the male and female genital tracts [43]
Oral-pharyngeal cavity	The oral cavity is a complex immunological site. Both mucosal immunity and systemic immunity merge and play significant roles in protection against infections and damage [44]
Sino-nasal	The sinonasal mucosa is exposed to large quantities of particulates, antigens, and potential pathogens. To address these possible threats, the human sinonasal epithelium has developed a range of protective functions that effectively clear foreign material with minimal collateral tissue damage. This barrier to the outside world is both physical and immunological in nature [45]
Eyes	The eye is considered as an immune privileged site to preserve vision. The cornea is mainly protected from autoimmunity by the lack of blood and lymphatic vessels, whereas the retina–blood barrier is maintained in an immunosuppressive state by the retinal pigment epithelium. The eyes are a window to the soul of the immune system [46]
Lymphatic system	The lymphatic vasculature is not considered a formal part of the immune system, but it is critical to immunity. One of its major roles is in the coordination of the trafficking of antigen and immune cells [47]
Autonomic Nervous System	Two major components of leukocytes, namely, granulocytes and lymphocytes, have adrenergic receptors [chemotactic function] and cholinergic receptors [phagocytic function], respectively. In this regard, granulocytes are activated in number and function by sympathetic nerve stimulation, whereas for lymphocytes this is done by parasympathetic nerve stimulation [48]
Sleep	Sleep and the circadian system are strong regulators of immunological processes. Prolonged sleep curtailment and the accompanying stress response invoke a persistent unspecific production of pro-inflammatory cytokines, best described as chronic low-grade inflammation, and also produce immunodeficiency [49]
Food	Exploring and analyzing origins of immunity reveals evolutionary and developmental ties to diet and nutrition, ancient connections in function and development. Foods are capable of influencing immune function [50]
Exercise	Several decades of research in the area of exercise immunology have shown that the immune system is highly responsive to acute and chronic exercise training. Exercise-induced improvements in immune function may play a critical role in countering immunosenescence and the development of chronic diseases [51]

differences. The confounding interaction of many of these variables currently makes it difficult to assign definitive contributions to human immune diversity" [52].

Taking the background of innate immunity and highly complex immune diversity into account, infectious disease prevention/eradication protocols should give paramount importance to objective immunodiagnostic procedures to grade the immune status of people and identify the actual number of immunocompetent and immunodeficient individuals in the community [to investigate the immune diversity], and implement strategies to strengthen the innate immunity [that is, strategies to strengthen the homeostatic foundation] predominantly to avoid Immuno-iatrogenesis. Immuno-iatrogenesis can be defined as the health risks caused by prophylaxis or treatments or public health mandates in the context of immunology without examining the NI of the individuals through at least one reliable and quantifiable immunodiagnostic test. If viewed from the point of immune diversity and immuno-iatrogenesis, it would be predictable or comprehensible that not all the healthy and unhealthy humans on the planet need to be subjected to similar stringent public health mandates during any disease outbreak. Immune dysregulations can also be intervened through feasible lifestyle modifications [example, aptly calibrated individualized exercise programs].

Exercise Immunology and Immunocompetence: "Exercise represents a major challenge to whole-body homeostasis provoking widespread perturbations in numerous cells, tissues, and organs that are caused by or are a response to the increased metabolic activity of the contracting skeletal muscles. To meet this challenge, multiple integrated and often redundant responses operate to blunt the homeostatic threats generated by exercise-induced increases in muscle energy and oxygen demand. Molecular techniques led to greater understanding of the multiplicity and complexity of cellular communications done by muscle with other organs [adipose tissue, liver, pancreas, bone, brain] to mediate beneficial effects on health and performance" [53]. "The practice of physical exercises acts as a modulator of the immune system. During and after physical exercise, pro- and anti- inflammatory cytokines are released, lymphocyte circulation increases, as well as cell recruitment. Such practice has an effect on the lower incidence, intensity of symptoms and mortality in viral infections observed in people who practice physical activity regularly, and its correct execution must be considered to avoid damage" [54].

"Multiple studies in humans and animals have demonstrated the profound impact that exercise can have on the immune system. There is a general consensus that regular bouts of short-lasting [up to 45 minutes] moderate intensity exercise is beneficial for host immune defense, particularly in older adults and people with chronic diseases. In contrast, infection burden is reported to be high among high performance athletes. This has shaped the common view that arduous exercise [i.e. those activities practiced by high performance athletes/ military personnel that greatly exceed recommended physical activity guidelines] can suppress immunity and increase infection risk. However, the idea that exercise per se can suppress immunity and increase infection risk independently of the many other factors [e.g. anxiety, sleep disruption, travel, exposure, nutritional deficits, environmental extremes, etc.] experienced by these populations has recently been challenged. A key point of agreement between the groups is that infection susceptibility has a multifactorial underpinning. An issue that remains to be resolved is whether exercise per se is a causative factor of increased infection risk in athletes" [55].

"Acute exercise is an immune system adjuvant that improves defense activity and metabolic health. Habitual exercise improves immune regulation, delaying the onset of age-related dysfunction. Immunosenescence is defined as immune dysregulation with aging. Emergent data support that habitual exercise is capable of improving regulation of the immune system and delaying the onset of immunosenescence. Exercise immunology

views acute exercise [moderate to vigorous intensity, less than 60 minutes] as an important immune system adjuvant but, in contrast, high exercise training workloads, competition events, and the associated physiological, metabolic, and psychological stress are linked with transient immune perturbations, inflammation, oxidative stress, muscle damage, and increased illness risk" [56].

"Many components of the immune system exhibit adverse change after prolonged, heavy exertion lasting longer than 90 minutes. These immune changes occur in several compartments of the immune system and body [eg, the skin, upper respiratory tract mucosal tissue, lung, blood, and muscle]. During this "open window" of impaired immunity, viruses and bacteria may gain a foothold, increasing the risk of subclinical and clinical infection. In general, if symptoms are from the neck up, moderate exercise is probably acceptable [and some researchers would argue even beneficial] when an athlete is sick, whereas bed rest and a gradual progression to normal training are recommended when the illness is systemic" [57]. "A classic paradigm in exercise immunology is that an "open window" of immunode pression can occur during recovery from intense exercise. In particular, this paradigm proposes that after intense exercise, some immune variables [e.g., lymphocyte and natural killer cell numbers and antibody production] transiently decrease below pre-exercise levels. As a result of this immunodepression, microbial agents, especially viruses, may invade the host or reactivate from a latent state, leading to infection and illness. If exercise is repeated again while the immune system is still depressed, this could lead to a greater degree of immunodepression and potentially a longer window of opportunity for infection. In the recovery phase after intense exercise is found suppressed blood concentration of lymphocytes, suppressed natural immunity of blood lymphocytes, decreased concentration of secretory IgA in mucosa, but increased blood concentration of neutrophils and increased levels in the blood of inflammatory cytokines. Thus, after intense long-term exercise, the immune system is characterized by concomitant inflammation and temporary suppression of the cellular immune system, the most pronounced findings being two to four hours after the exercise. The underlying mechanisms are multifactorial and include neuroendocrinological and metabolic factors" [58]. Two best markers of overtraining: [i] decreased performance on standard exercise tests [like VO2 max] [ii] self-analysis of well-being by the athlete such as with Profile of Mood State [59].

"Periods of intensified training [overreaching – OR] can result in a transient decline in performance; however, when appropriate periods of recovery are provided a supercompensation occurs and performance is greatly enhanced compared to baseline. This short term, effective form of OR is called functional OR [FOR]. But if FOR continues too long [ie, weeks] it becomes non-functional OR [NFOR], which becomes overtraining [OT], and the athlete moves toward overtraining syndrome [OTS]. These events and the progression can be compounded by inadequate nutrition, illness, and sleep problems. OTS reflects the unsuccessful attempt of the body to cope with the physiological and psychological stress of exercise training and life—the total allostatic load and resultant wear and tear on the body from chronic stress. Thus, medically it can be understood partly within the context of the general adaptation syndrome of Hans Selye. The difference here between these two training conditions is the amount of time needed for performance restoration, not the type or duration of training stress or degree of physiological impairment if any. Two varieties of OTS have been proposed, a hypoarousal and a hyperarousal form. This categorization is based upon the finding of divergent symptomology in some physiological and psychological parameters of athletes. Hypoarousal is also called parasympathetic or Addison's OTS. It is commonly seen in endurance athletes [long-distance runners, rowers, cross-country skiers, cyclists, and swimmers]. Hyperarousal is also called sympathetic or Basedow's OTS. It is commonly seen in power athletes [sprinters, jumpers, and

weight lifters] and occurs slightly less frequently than the hypoarousal form.

The two forms have some similar characteristics and warning signs, particularly the persistent decline in physical performance. Decreased physical performance, increased incidence of infections, decreased maximal lactate response to exercise, amenorrhea in women, hypogonadism in men, loss of competitive desire, weight loss, disturbed sleep, fatiguability are some common features of hyperarousal OTS and hypoarousal OTS" [60]. Exercise immunology reveals the necessity of well-balanced exercise dosages to maximize health gains and avoid or minimize negative impact on homeostasis. Understanding the beneficial effects of structured exercises needs careful documentation and monitoring of exercise performance. Exercise immunology should also give its attention to some highly stressful occupations characterized by prolonged physical activity challenged by socioeconomic and environmental conditions like scorching heat or extreme cold.

Exercise Performance Data: "Of all the fields that comprise the physiological sciences, exercise is one of the hardest to categorize even though it is a common everyday experience for nearly everyone whether it is a formal exercise program or simply walking from one place to another. In recent years, a sentiment has arisen that since "everything that is important about exercise physiology is known"; attention should be diverted away from the basic science of exercise to increased emphasis on promotion of exercise. The individuals who support this view ignore the basic fact that not all the important questions have been answered, and further that basic research provides the evidence that gives the exercise sciences their legitimacy as serious subjects, as well as allowing for its application to medical practice" [61]. "The capacity for human exercise performance can be enhanced with prolonged exercise training, whether it is endurance- or strength-based. Our continued drive to understand how to prescribe exercise to maximize health and/or performance outcomes means that our knowledge of the adaptations that occur as a result of exercise continues to evolve" [62]. Unfathomable magnitude of favourable adaptations could happen through exercise participation but the exercise dosages should be customized and adjusted regularly based on the individuals' requirements, strengths and weaknesses, which only competent Physiotherapists and Exercise professionals can administer. Positive adaptations to exercise can be measured using various inexpensive non-invasive tools and techniques. "Mitochondrial biogenesis refers to changes in the volume, number of mitochondria per mass unit of muscle that is well known to occur following exercise training resulting in an increased capacity for ATP production" [63]. After a single training impulse, the body first reacts with fatigue, then with a temporary increase of performance. This is called supercompensation [64].

Periodization is a concept of systematic progression—that is, resistance training programs that follow predictable patterns of change in training variables. There is a paucity of data in rehabilitation research using the principles of periodization in the design of rehabilitation programs. Manipulating training variables to facilitate maximum gains—including sets, repetitions, load, and rest periods—can be daunting [65].

"On the basis of Newton's law, it can be expressed that Fitness Excellence Equals Mass x Acceleration [FEEMA] in which mass and acceleration are actually ideal body composition and ability to accelerate effectively against gravitational force, respectively. Well-trained physically efficient individuals are so different from sedentary individuals though there can be some similarities like age, gender, height and weight, so ideally none of the health reference values of sedentary individuals suffering from gravitational torque deficiency syndrome [GTDS] can be considered normal. Obtaining all the health reference values through stratified random sampling of only well-trained individuals on the basis of similar kinanthr opometric characteristics should be considered reliable for drawing statistical conclusions and such advanced research work in the health sector can derive revolutionary health education paradigms" [66].

All the exercise variables are quantifiable. In order to estimate the benefits of exercise participation, exercise programs must be structured neatly accompanied by documentation of the exercise performance of the individuals using appropriate units of measure [Table – 2]. Regular periodic reviews of exercise capacity attain complete meaning only if they are correlated with various vital signs and medical laboratory tests but such holistic assessment model has been non- existent. Exercise participation of the individuals generally go entirely futile due to unstructured exercise programs and lack of documentation of exercise performance, which is very common characteristic in various fitness clubs that employs and fosters incompetent fitness trainers.

Standard exercise prescriptions should be made affordable to general population also. Exercises can be customized [based on the health status, age, objectives] and exercise performances can be documented even if the access to exercise machines/equipment are limited. In the absence of advanced exercise laboratory and equipment, even just a stop clock would suffice to gather accurate information about an individual's exercise performance if few other variables are known [loads in kilograms or pounds, distance in centimeters or meters or kilometers]. An example of fitness progression data of a 21-year-old male can be found in Table – 3 and Table – 4, and the prescribed exercises are shown in Figure- 1. There are myriad ways to design individualized exercise programs, collect exercise performance data using inexpensive tools and investigate/describe the homeostatic or allostatic conditions of the individuals, therefore, only one example has been encompassed in this discourse.

Table 2: All the exercises are measurable and vast majority of the exercises are measurable using inexpensive tools. Some other exercise variables [like Calorie expenditure estimations, Lactate Threshold, VO2 max, other micro details of exercise adaptations] may need sophisticated laboratory.

UNITS OF MEASUREMENT	PHYSICAL ACTIVITY
Loads [kilograms, pounds], Repetitions, Sets, Rest period, Speed of work [power]	Weight lifting exercises
Distance, Time & Speed [DTS], VO2 max	Walking, Running, Cycling, Rowing, Swimming, Stair climbing
Cadence, Step length	Walking, Running
Resistance level, Gradient	Cycling, Rowing, Walking, Running
Stair height, Number of stairs	Stair climbing
Revolutions Per Minute	Cycling
Strokes Per Minute	Rowing
Distance only [Centimeters, Inches, Meters]	Jumping, Lunges, Throwing
Range of Motion in degrees, Centimeters, Inches	Flexibility
Time only [seconds, minutes]	Isometric exercises [Single leg balance, Plank]
Kilogram or Pounds only	Grip strength
Heart rate, Blood pressure, Respiratory rate [Pre- and Post-exercise]	Weight lifting, Endurance tasks

"Depending on the lifestyle of the individuals, the functional status or outcomes of exercise participation can be classified into three categories [Category A = Alpha to Epsilon, Category B = Zeta to Nu, Category C = Xi to Omega] and such diversities are determined by multifactorial background of functional efficiency or functional decline. Athletes know their training intensities and performance standards but various labourers [farmer, load man, mason, shepherd, fisherman, road worker, washer man, house keeper, street sweepers, manual scavenger] may not know that they possess excellent health status, almost equivalent or even better than the successful athletes, despite their exposures to highly challenging climatic conditions, environmental hazards and socioeconomic pressures" [67]. Competency of physiotherapists and exercise professionals should be strong enough to prescribe exercises in the domains of sports, rehabilitation [injuries, surgeries, medical conditions], healthy ageing, public health and exercise pharmacology.

The broad scope for exercise innovations to refine public health paradigms has not been utilized adequately. Exercise innovations are

Table 3: This 21-year-old male was given these three exercises to be performed as many rounds or sets as possible in 30 minutes. He did seven rounds by taking little extra time above 30 minutes during his first attempt [on 19.07.2021] but exhibited progressions in the subsequent months as shown in Table – 4 when seven rounds of same exercises were prescribed/stipulated.

Exercise	Dosage in every round
Barbell Clean [18 Kg]	10 repetitions
Weighted squats [7.5 kg pair Dumbbells]	10 repetitions
Push ups	10 repetitions

Table 4: Time taken was measured for each round/set using a stop clock. Exercise performance can be monitored precisely. On 27.08.2021, he performed seven rounds of the same program 11 minutes faster as compared to 19.07.2021. On 27.10.2021, he performed seven rounds of the same program 13 minutes 10 seconds faster as compared to 19.07.2021. Likewise, there are so many individuals in this world, progressed incrementally to strengthen their homeostatic foundation, innate immunity and attain their personal 'peak fitness excellence'. It is important to study the 'disease-resisting' potential of such exercisers and athletes.

ROUND	19.07.2021	27.08.2021	27.10.2021
Round 1	0 – 3.54	0 – 2.37	0 – 1.37
Round 2	5. 10 – 8.19	3.34 – 5.28	1.54 – 3.48
Round 3	9.39 – 12.38	6.43 – 8.35	5.12 – 7.09
Round 4	14.43 – 17.33	9.58 – 11.48	7.32 – 9.32
Round 5	19.00 – 22.03	12.45 – 14.34	11.15 – 13.03
Round 6	23.40 – 27.00	15.58 – 17.59	13.33 – 15.47
Round 7	28.53 – 32.10	19.14 – 21.10	17.00 – 19.00
TOTAL TIME	32 minutes 10 seconds	21 minutes 10 seconds	19 minutes

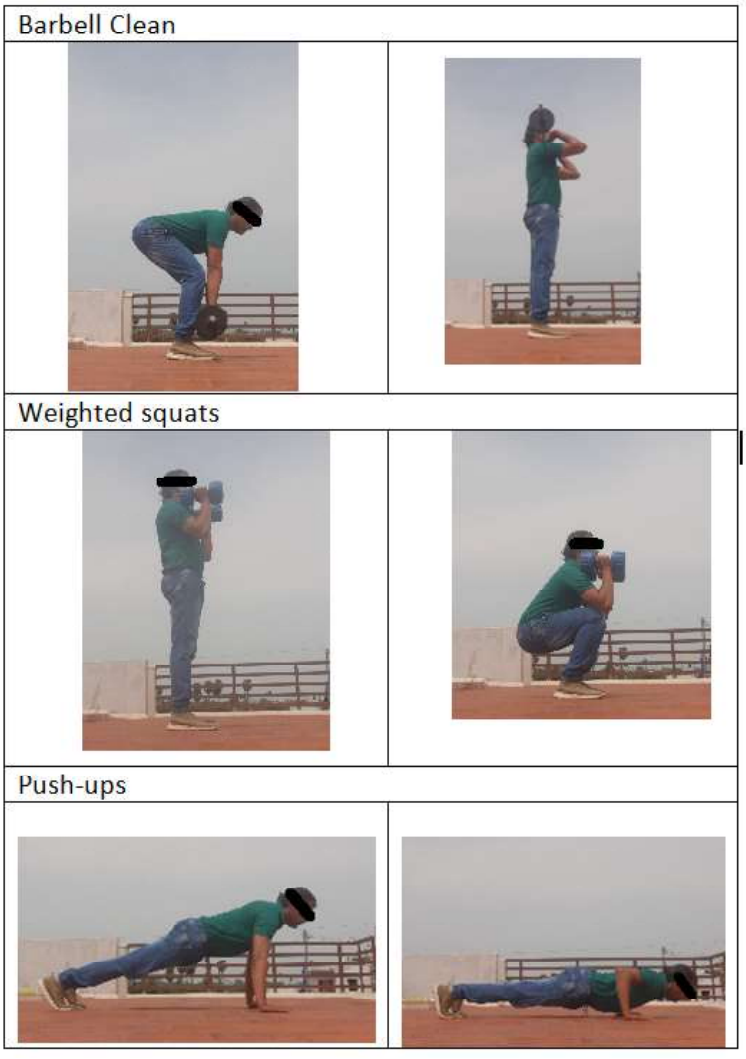

Figure 1: Three exercises that were prescribed to a 21-year-old Indian male. Weight = 62 Kg. Height = 172 cm. Somatotype = Balanced Endomorph [Endomorphy = 6.7, Mesomorphy = 2.7 and Ectomorphy = 3.2]. He began strength training thrice per week when he was 19 years old.

not necessarily about novel exercise equipment but about deriving plentiful benefits from every exercise that can be performed using body weight, free weights, resistance band and few other equipment to reinforce innate biomechanics [like multidirectional push/pull, Lunges, Squats, Bending] and all the exercise dosages/benefits should be quantifiable. Generally, the resistance bands [elastic tubes] are available in different resistance levels but the exercisers may not be aware of their load equivalence but simple experiments had revealed their load equivalence in kilograms [68]. Large number of contemporary exercise equipment and exercise techniques could go invalid if they are verified on the basis of biomechanics and pathomechanics [like posture, kinematics, leverage, mechanical advantage, injury risks, Newton's law].

Another important facet of physical activity is 'Exercise Pharmacology' which many health care professionals ignore, thus, adding strength to iatrogenesis. "Several studies have shown that diet and body composition as well as exercise are lifestyle components that can influence many components of drug metabolism and efficacy. Patients are often not aware of the potential risk factors, which are particularly important if drugs with a narrow therapeutic range/window are used" [69]. "Physiological adaptations to acute and chronic exercise are such that there is good reason to suspect that exercise has the potential to significantly influence drug absorption and bioavailability, drug distribution within the body, and drug elimination from the body. A traditional focus of exercise scientists studying the interaction of drugs and exercise has been on the effects of drugs on exercise performance or functional capacity. In contrast, there is limited information available about the effects of exercise on the efficacy of drugs that have been prescribed and ingested for therapeutic reasons" [70].

There are instances where patients exclusively need exercise-based rehabilitation and they would be also responding very well to exercises but medicines or polypharmacy rendered at par act as an iatrogenic barrier which cannot be easily communicated to the patient or any member of the rehabilitation team [4]. "Blood flow distribution is fundamental to the study of pharmacokinetics and can vary dramatically during rest compared with exercise. The liver and the kidney play significant roles in calculating the pharmacokinetic parameters of medications. Blood flow to these organs is significant at rest but decreases during exercise. These changes in blood flow, as well as other physiological changes during exercise, have shown to alter the pharmacokinetics of some drugs. Medications that require extra therapeutic monitoring may be affected by this drug-exercise interaction" [71].

"In fact, many initially promising antiarrhythmic medications were subsequently found to increase rather than to decrease cardiac mortality. It is now known that cardiac disease alters cardiac autonomic balance and that the patients with the greatest changes in this cardiac neural regulation [i.e., decreased parasympathetic coupled with increased sympathetic activity] are also the patients at the greatest risk for sudden death. A growing body of experimental and epidemiological data demonstrates that aerobic exercise conditioning can dramatically reduce cardiac mortality, even in patients with pre-existing cardiac disease. It is well established that aerobic exercise conditioning can alter autonomic balance [increasing parasympathetic tone and decreasing sympathetic activity], a prudently designed exercise program could prove to be an effective and nonpharm acological way[nonpharmacological antiarrhythmic intervention] to enhance cardiac electrical stability, thereby protecting against sudden cardiac death" [72].

"The importance of mitochondrial dysfunctions in the progression of chronic disease has been well established. Patients with chronic diseases are often prescribed a variety of medications, many of which have been shown to induce mitochondrial dysfunction. Exercise is a known stimulus for mitochondrial biogenesis. Increasing physical activity is a common lifestyle recommendation for hypertension and hypercholesterolemia; however, drugs such as β -blockers and statins that are commonly prescribed for their treatment have

the potential to limit the beneficial effects of exercise on mitochondria. Similarly, NSAIDs used to ameliorate postexercise pain or decrease cardiovascular disease risk may also impact skeletal muscle recovery from exercise. Experiments should be designed to evaluate the impact of pharmaceutical compounds during rest, exercise, and postexercise recovery, with emphasis on the postexercise period, since this is when most exercise-induced adaptations occur. Researchers, especially those investigating exercise and chronic disease, should continue to explore the interaction between drugs, exercise, and mitochondrial adaptation. If it can be determined where detrimental effects occur, it may be possible to eliminate negative interactions to facilitate the transition to a state of health based on exercise rather than medication" [73]. "With the development of new drugs, it is common practice for drug manufacturers to measure their pharmacokinetic parameters. This testing involves the discovery of the absorption, distribution, metabolic, excretory and toxicological properties of drugs. The testing is usually done in non-stressful conditions at rest; however, this does not necessarily tell the entire picture as there is increasing knowledge about the effects that high levels of physical activity can have on the pharmacokinetics of some medications. Patients and healthcare providers should be aware that exercise can adversely affect the way some medications are intended to work. Patients taking certain medications should be closely monitored when performing high amounts of physical activity" [74].

"Certain physiological changes caused by aerobic exercise can alter the pharmacokinetics of some drugs. The risk of hypoglycaemia may increase when patients with diabetes mellitus inject insulin into a muscle just prior to exercising that muscle. Much is still unknown regarding the interactions that exist between exercise and drug therapy. More studies need to be completed in this area before definite conclusions are made and clinical relevance can be established. Clinicians should be aware that the potential for such interactions exists, especially for drugs with a narrow therapeutic range and in patients who participate in extreme sporting activities" [75].

Immunosuppressive drugs increase the risks of infection, malignancy, cardiovascular disease and bone marrow suppression; hence vigilance is needed as adverse effects may have atypical clinical presentations and this surveillance may need to continue long after the drugs have been stopped [76].

Exercise performance monitoring and data collection methods should be given prime importance in the exercise science curriculum, and in different settings where exercises are employed.

DISCUSSION

Over the last decades, there was increasing evidence for the presence of innate immune memory in living organisms. innate immune responses have the capacity to be "primed" or "trained" [77]. "The lack of physical activity in modern life is a main reason for the decline of national physical fitness. Guiding people to take part in exercise properly to enhance physical fitness is more urgent and more important than ever. Exercise therapy is a safe method for improving patients' physical performance and alleviating the symptoms of diseases" [78]. "Contemporary evidence from epidemiological studies shows that leading a physically active lifestyle reduces the incidence of communicable [e.g., bacterial and viral infections] and non-communicable diseases [e.g., cancer], implying that immune competency is enhanced by regular exercise bouts. However, to this day, research practice, academic teaching, and even physical activity promotion and prescription continues to consider a prevailing myth that exercise can temporarily suppress immune function. In addition, we present evidence showing that regular physical activity and frequent exercise might limit or delay immunological aging. We conclude that leading an active lifestyle is likely to be beneficial, rather than detrimental, to immune function. It is a misconception to label any form of acute exercise as immunosuppressive, and, instead, exercise most likely improves immune competency across the lifespan" [79].

Link between obesity, chronic disease, lifestyle factors and the immune system indicates the need of societal interventions to enhance global immunity for which collective effort is needed to ameliorate modifiable risk factors on a global scale [80]. "Every stage of immune response is dependent on the availability of specific micronutrients. A plethora of micronutrients have been studied for their multiple properties in the maintenance of the immune system. Both exercise and a well-balanced diet can enhance immunity and resistance to infection in a large number of people. More short-term and long-term controlled, randomized interventional clinical trials using different exercise regimens with nutritional habits are needed to identify additional moderating factors and understand the mechanisms of immune cell mobilization and resistance to infections to guide clinical practice" [81]. To have a strong and healthy immune system, a healthy diet is needed. Immune system also needs water to work properly and effectively [82]. "DIET must be aimed at improving the functional capacity, thus can be remembered or regarded as Diet Improves Exercise Tolerance. Food is the sole determinant of evolution and extinction. Food should not only be regarded as the base for the survival or life, but as the principal divine energy in health care practices dealing with all the diseases, ageing and lifespan. Foods Obstruct and Overcome Diseases" [83].

Nature poses persistent challenges to adaptation and survival of living beings, and at the same time, continually provides all the resources for adaptation and survival too. "Milk plays more than a simply nutritional role in mammals, interacting with infant saliva to produce a potent combination of stimulatory and inhibitory metabolites that regulate early oral–and hence gut–microbiota. Consequently, milk-saliva mixing appears to represent unique biochemical synergism which boosts early innate immunity" [84]. "Colostrum is the most potent natural immune booster known to science. Breastfeeding protects infants against infections mainly via secretory IgA [SIgA] antibodies, but also via other various bioactive factors" [85]. "The decline of the immune system with age is reflected in the increased susceptibility to infectious diseases, poorer response to vaccination, increased prevalence of cancer, autoimmune and other chronic diseases. Both innate and adaptive immune responses are affected by the aging process; however, the adaptive response seems to be more affected by the age-related changes in the immune system" [86]. Immunosenescence is characterized by the inability to mount effective [protective] humoral and cellular immune responses against a pathogen or vaccine, as well as a systemic low-grade inflammatory state [termed "inflammaging"], which contributes to the dysregulation of several components of" the innate and adaptive immune systems [87]. Much can be achieved, "when the science, engineering and health communities embrace human rights as an area suitable for and deserving of robust inquiry, and become an influential voice in the defense of human rights [88].

"Healthy gut development relies on sensing of dietary nutrients, commensal, and pathogenic microbes via immune receptors. Malnutrition, which encompasses under- and overnutrition, is responsible for an enormous morbidity and mortality burden globally. Malnutrition results from disordered nutrient assimilation but is also characterized by recurrent infections and chronic inflammation, implying an underlying immune defect. Defects emerge before birth via modifications in the immunoepigenome of malnourished parents, and these may contribute to intergenerational cycles of malnutrition" [89]. "Like so many other institutions in contemporary society, medicine has come under heavy fire. Medicine, as practised today, has begun to be questioned and criticised. Some critics have even described modern medicine as a threat to health. High-technology medicine seems to be getting out of hand and leading health systems in wrong direction away from the health promotion towards elite-oriented health services" [90].

"Science proceeds by revolution. This holds for theories, which are always successive. One enlarges science in two ways: by adding new facts and by simplifying what already exists. The microbe is nothing. The terrain is

Table 5: It is important to explore if all these types of human variants are possible associated with positive or negative test report for a pathogen during any disease outbreak. Scientific explanations for the possibility or impossibility of these human variants [in all age groups] and their relationship with innate immunity, adaptive immunity, immunological memory, homeostasis, allostasis, fitness characteristics, lifestyle, etc., are essential. Immunological explorations in this direction could reveal [i] if healthy and unhealthy people should be subjected to similar public health mandates [ii] if healthy people can be freed from stringent public health policies and unhealthy can also be encouraged/enabled to modify their lifestyle to improve immunity.

VARIANT	INFECTION 'specific 'ANTIBODIES	
	PRESENT	ABSENT
Not infected, not vaccinated, asymptomatic		*
Not infected, not vaccinated, asymptomatic	*	
Not infected, not vaccinated, symptomatic		*
Not infected, not vaccinated, symptomatic	*	
Not infected, vaccinated, asymptomatic		*
Not infected, vaccinated, asymptomatic	*	
Not infected, vaccinated, symptomatic		*
Not infected, vaccinated, symptomatic	*	
Infected, not vaccinated, asymptomatic		*
Infected, not vaccinated, asymptomatic	*	
Infected, not vaccinated, symptomatic		*
Infected, not vaccinated, symptomatic	*	
Infected, vaccinated, asymptomatic		*
Infected, vaccinated, asymptomatic	*	
Infected, vaccinated, symptomatic		*
Infected, vaccinated, symptomatic	*	

everything - Claude Bernard" [91]. Asymptomatic transmission cannot be an overgeneralized science to stipulate public health strategies equally for all [as happened in COVID 19 pandemic, possibly a basis for other immunization programs too in the future] but should investigate the immune diversity of both innate and adaptive immunity in all age groups [Table - 5]. "Somatotype diversity was investigated on non-athlete population using Heath-Carter anthropometric method. Endomorphy dominance was found among various non-athlete population in all the ranges of body mass index, accordingly various health risks may be hidden inside non-obese body frames as well" [92]. Immune diversity and its link with somatotype diversity should also be researched. "Asymptomatic infection is a tricky and uncharted territory for infectious disease immunologists and clinicians. Our natural territory is understanding the mechanism underlying severe infection and protection against it. By contrast, relatively few studies have investigated potential differences in innate immune responses in individuals with symptomatic or asymptomatic infection. An initial question was whether some people become infected but are able to rapidly control the virus through innate immune pathways and therefore do not become ill" [93]. Ideally, the medical field should shift its primary focus to learn about plenty of unnoticed asymptomatic biomechanical dysfunctions associated with gravitational torque deficiency syndrome and unhealthy ageing trajectory.

"Today the two arms of antigen-specific acquired and antigen-nonspecific innate immunity are best viewed as a yin–yang concept, with highly intertwined, partly overlapping, and mutually beneficial activities. Perspectives on immunology progressed from a dichotomy between cellular-unspecific innate immunity and humoral-specific acquired immunity, toward the concept of complementary binarity" [94]. "Underlying individuals' unique, invaluable, and enigmatic metaphysical qualities, the human organism is, in a physical sense, essentially a self-regulating biochemical machine. At any moment, our thoughts and feelings, our actions, metabolism and physical well-being all stem from the sum of dynamic, intricate biochemistry working with in a distinctive genetic context; innumerable

biochemical reactions are taking place to prepare the enzymes, hormones, neurotransmitters and all that we need to undertake the tasks required for daily life. We are truly wonderfully crafted" [95].

Intensifying impeccable prophylaxis, clinical applications and public health policies on the basis of homeostasis need in-depth and persistent emphasis on 'Homeostaticology', 'Iatrogenicology' and 'Salutogenicology' [4].

CONCLUSION

"MICROBIOLOGY detects and describes the pathogens, VACCINOLOGY develops vaccines, IMMUNOLOGY necessitates everyone to exclusively strengthen the adaptive immunity, EPIDEMIOLOGY supplies 'frequency, distribution' statistics to justify all the above" is an old school of thought that needs revamping with the support of various contemporary scientific insights, and thorough understanding of human examples ranging from 'Best Homeostasis to Worst Allostasis'. Lack of methods to quantify the innate and adaptive immunity of the people has been a massive weakness in the field of medicine because every medical approach must rely on appropriate diagnosis and quantifiable outcome measures on an individual level. Either immunocompetent or immunodeficient individuals, who would not asymptomatically transmit an infectious disease or who would not need vaccination or who would fight against any pathogens without 'specific antibodies' must be confirmed ideally through a quantifiable immunodiagnostic test on innate immunity.

If such immunodiagnostic test is unavailable at present, immune competence could be understood by assessing the homeostatic conditions [exercise capacity, medical laboratory tests, vital signs]. Researchers have cautioned about confounding interaction of many variables that currently challenges our definitive understanding about human immune diversity. It also becomes necessary to introduce a new dimension; 'Immuno-iatrogenesis', to deal with adverse reactions caused by prophylaxis, therapeutic procedures and public health mandates originated from [or accredited by] immunology. Under the aegis of homeostasis, non-specific antibodies [Secretory IgA] and Expanded Trained Immunity [ETI], a long-lasting Natural Immunity [NI] should be possible excluding the need of 'specific antibodies'. Even among the individuals with dysregulated homeostasis and unhealthy ageing process, NI could render protection [certainly not equivalent to the NI of the healthy individuals], which probably could improve further if appropriate lifestyle changes are incorporated. Natural Immunity cannot be confined to infections but all other minor and major diseases known to man, thus, it is the HOMEOSTATIC FOUNDATION required for stronger adaptations and long-term survival that needs to be researched deeply and comprehended entirely. Exercise prescriptions for athletic and non-athletic populations should take into account of kinanthropometry, periodization, overtraining syndrome, exercise immunology, exercise pharmacology, exercise performance data collection, periodic health reviews, etc., Without exposures in the anaerobic exercise zones, holistic benefits from exercises would be highly unlikely, but still in some occasions or disease circumstances, relaxed breathing exercises alone could do miracles – 'Pulmonary Panacea'. Adaptations to exercise can be accurately measured using various inexpensive non-invasive quantifiable tests to authenticate 'Impeccable Metabolic Maneuvers Upbring Natural Immunity To You – IMMUNITY'.

Conflicts of interest: **None**

REFERENCES

[1]. R. Vinodh Rajkumar. Perfect Homeostasis: pH. Int J Physiother Res 2022;10[1]:4111-4124.

[2]. Logan JG, Barksdale DJ. Allostasis and allostatic load: expanding the discourse on stress and cardiovascular disease. J Clin Nurs. 2008 Apr;17[7B]:201-8.

[3]. Billman GE. Homeostasis: The Underappreciated and Far Too Often Ignored Central Organizing Principle of Physiology. Front Physiol. 2020;11:200.

[4]. R. Vinodh Rajkumar. Homeostaticology, Iatrogenicology and Salutogenicology. Int J Physiother Res 2022;10[2]:4188- 4203.

[5]. Cassone A. The Case for an Expanded Concept of Trained Immunity. mBio. 2018;9[3]:e00570-18.

[6]. Lau CM, Sun JC. The widening spectrum of immunological memory. Curr Opin Immunol. 2018;54:42-49.

[7]. Qian Zhang, Xuetao Cao. Epigenetic Remodeling in Innate Immunity and Inflammation Annual Review of Immunology 2021;39:1:279-311.

[8]. Kane B, A, Bryant K, J, McNeil H, P, Tedla N, T: Termination of Immune Activation: An Essential Component of Healthy Host Immune Responses. J Innate Immun 2014;6:727-738.

[9]. Segre JA. What does it take to satisfy Koch's postulates two centuries later? Microbial genomics and Propionibacteria acnes. J Invest Dermatol. 2013;133[9]:2141-2142.

[10]. Jamrozik E, Selgelid MJ. Invisible epidemics: ethics and asymptomatic infection. Monash Bioeth Rev. 2020 Dec;38[Suppl 1]:1-16.

[11]. Clément Bezier, Géraldine Anthoine and Abdérafi Charki. Reliability of real-time RT-PCR tests to detect SARS-Cov-2: A literature review. Int. J. Metrol. Qual. Eng., 2020;11:13.

[12].Pugh J, Savulescu J, Brown RCH, et al. The unnaturalistic fallacy: COVID-19 vaccine mandates should not discriminate against natural immunity. Journal of Medical Ethics Published Online First: 07 March 2022.

[13]. David C. Nieman, Coronavirus disease-2019: A toxsin to our aging, unfit, corpulent, and immunodeficient society, Journal of Sport and Health Science 2020; 9[4]:293-301.

[14]. Leonard Angka, Marisa Market, Michele Ardolino, Rebecca C. Auer. Is innate immunity our best weapon for flattening the curve? J Clin Invest. 2020;130[8]:3954-3956.

[15]. Jee YS. Physical exercise for strengthening innate immunity during COVID-19 pandemic: 4th series of scientific evidence. J Exerc Rehabil. 2020;16[5]:383-384.

[16]. Medzhitov R, Janeway C Jr. Innate immunity. N Engl J Med 2000; 343[5]:338–44.

[17]. Gandhi R, Laroni A, Weiner HL. Role of the innate immune system in the pathogenesis of multiple sclerosis. J Neuroimmunol. 2010;221[1-2]:7-14.

[18]. Iwasaki A, Medzhitov R. Control of adaptive immunity by the innate immune system. Nat Immunol. 2015;16[4]:343-353.

[19]. Marshall, J.S., Warrington, R., Watson, W. et al. An introduction to immunology and immunopathology. Allergy Asthma Clin Immunol 2018;14:49.

[20]. Edward R. Sherwood, Katherine R. Burelbach, Margaret A. McBride, Cody L. Stothers, Allison M. Owen, Antonio Hernandez, Naeem K. Patil, David L. Williams, Julia K. Bohannon. Innate Immune Memory and the Host Response to Infection. The Journal of Immunology February 15, 2022;208 [4]: 785-792.

[21]. Helin Tercan, Niels P. Riksen, Leo A.B. Joosten, Mihai G. Netea, Siroon Bekkering. Trained Immunity: Long-Term Adaptation in Innate Immune Responses. Arteriosclerosis, Thrombosis, and Vascular Biology. 2021;41:55–61.

[22]. Divangahi, M., Aaby, P., Khader, S.A. et al. Trained immunity, tolerance, priming and differentiation: distinct immunological processes. Nat Immunol 2021;**22:**2–6.

[23].Tak W. Mak, Mary E. Saunders, Bradley D. Jett, Primer to the Immune Response [Second Edition], Academic Cell, 2014;269-292.

[24]. Blumenreich MS. The White Blood Cell and Differential Count. In: Walker HK, Hall WD, Hurst JW, editors. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition. Boston: Butterworths; 1990. Chapter 153. Available from: https://www.ncbi.nlm.nih.gov/books/NBK261/

[25]. Bishlawy IM. Red blood cells, Hemoglobin and the immune system. Med Hypotheses. 1999 Oct;53[4]:345-6.

[26]. Université Laval. [2018, February 1]. Unexpected role of platelets in immune response. ScienceDaily. Retrieved April 14, 2022 from www.sciencedaily.com/releases/2018/02/180201115733.htm

[27]. https://www.statpearls.com/ArticleLibrary/viewarticle/23392#ref_2186517, dated 14.04.2022.

[28]. Lardner A. The effects of extracellular pH on immune function. J Leukoc Biol. 2001 Apr;69[4]:522-30.

[29]. Salmon JK, Armstrong CA, Ansel JC. The skin as an immune organ. West J Med. 1994;160[2]:146-152.

[30]. Nelke C, Dziewas R, Minnerup J, Meuth SG, Ruck T. Skeletal muscle as potential central link between sarcopenia and immune senescence. EBioMedicine. 2019 Nov;49:381-388.

[31]. Zhao E, Xu H, Wang L, et al. Bone marrow and the control of immunity. Cell Mol Immunol. 2012;9[1]:11-19.

[32].Geddes L. The fever paradox. New Sci. 2020;246[3277]:39-41.

[33]. Von Ah Morano, AE, Dorneles, GP, Peres, A, Lira, FS. The role of glucose homeostasis on immune function in response to exercise: The impact of low or higher energetic conditions. J Cell Physiol. 2020; 235: 3169– 3188.

[34]. Kim D, Chung H, Lee JE, Kim J, Hwang J, Chung Y. Immunologic Aspects of Dyslipidemia: a Critical Regulator of Adaptive Immunity and Immune Disorders. J Lipid Atheroscler. 2021;10[2]:184-201.

[35]. Romesh Khardori, Alys Adamski, Nancy Khardori. Infection, Immunity, and Hormones/Endocrine Interactions, Infectious Disease Clinics of North America, 2007;21[3]:601-615.

[36]. Jasiulionis Miriam G. Abnormal Epigenetic Regulation of Immune System during Aging. Frontiers in Immunology. 2018;9.

[37].The lungs at the frontlines of immunity. Nat Immunol 2015;16:17.

[38]. Robinson, M., Harmon, C. & O'Farrelly, C. Liver immunology and its role in inflammation and homeostasis. Cell Mol Immunol 2016;13:267–276.

[39]. A Montalban-Arques, PhD, M Chaparro, MD, PhD, Javier P Gisbert, MD PhD, D Bernardo, PhD, The Innate Immune System in the Gastrointestinal Tract: Role of Intraepithelial Lymphocytes and Lamina Propria Innate Lymphoid Cells in Intestinal Inflammation, Inflammatory Bowel Diseases, 2018;24[8]:1649–1659.

[40]. Kurts, C., Panzer, U., Anders, HJ. et al. The immune system and kidney disease: basic concepts and clinical implications. Nat Rev Immunol 2013;13:738–753.
[41]. Mann DL. The emerging role of innate immunity in the heart and vascular system: for whom the cell tolls. Circ Res. 2011 Apr 29;108[9]:1133-45.
[42]. Geyer Sohair, Jacobs Muazzam, Hsu Nai-Jen. Immunity Against Bacterial Infection of the Central Nervous System: An Astrocyte Perspective. Frontiers in Molecular Neuroscience. 2019;12.
[43]. Nguyen, P., Kafka, J., Ferreira, V. et al. Innate and adaptive immune responses in male and female reproductive tracts in homeostasis and following HIV infection. Cell Mol Immunol 2014;11:410–427.
[44]. Stephen J. Challacombe, Penelope J. Shirlaw, Martin H. Thornhill, Chapter 102 - Immunology of Diseases of the Oral Cavity. Mucosal Immunology [Fourth Edition], Academic Press, 2015;1943-1983.
[45]. Kern, Robert & Decker, Jennifer. Functional Defense Mechanisms of the Nasal Respiratory Epithelium. 2013.
[46]. V.L. Perez, A.M. Saeed, Y. Tan, M. Urbieta, F. Cruz-Guilloty. The eye: A window to the soul of the immune system, Journal of Autoimmunity, 2013;45:7-14.
[47]. Randolph GJ, Ivanov S, Zinselmeyer BH, Scallan JP. The Lymphatic System: Integral Roles in Immunity. Annu Rev Immunol. 2017;35:31-52.
[48]. Abo, T., Yamamura, S. [1999]. The Immune System Under the Regulation of the Autonomic Nervous System. In: Takahashi, H.E. [eds] Mechanical Loading of Bones and Joints. Springer, Tokyo.
[49]. Besedovsky L, Lange T, Born J. Sleep and immune function. Pflugers Arch. 2012;463[1]:121-137.
[50]. Edwin L. Cooper, Melissa J. Ma. Understanding nutrition and immunity in disease management. Journal of Traditional and Complementary Medicine, 2017;7[4]:386-391.
[51]. Nieman DC, Pence BD. Exercise immunology: Future directions. J Sport Health Sci. 2020 Sep;9[5]:432-445.
[52]. Liston, A., Humblet-Baron, S., Duffy, D. et al. Human immune diversity: from evolution to modernity. Nat Immunol 2021;22:1479–1489.
[53]. John A. Hawley, Mark Hargreaves, Michael J. Joyner, Juleen R. Zierath. Integrative Biology of Exercise, Cell, 2014;159[4]:738–749.
[54]. da Silveira, M. P., da Silva Fagundes, K. K., Bizuti, M. R., Starck, É., Rossi, R. C., & de Resende E Silva, D. T. Physical exercise as a tool to help the immune system against COVID-19: an integrative review of the current literature. Clinical and experimental medicine, 2021;21[1]:15–28.
[55]. Simpson RJ, Campbell JP, Gleeson M, Krüger K, Nieman DC, Pyne DB, Turner JE, Walsh NP. Can exercise affect immune function to increase susceptibility to infection? Exerc Immunol Rev. 2020;26:8-22.
[56]. David C. Nieman, Laurel M. Wentz, The compelling link between physical activity and the body's defense system, Journal of Sport and Health Science 2019;8[3]:201-217.
[57]. Nieman DC. Current perspective on exercise immunology. Curr Sports Med Rep. 2003 Oct;2[5]:239-42.
[58]. Pedersen BK, Rohde T, Ostrowski K. Recovery of the immune system after exercise. Acta Physiol Scand 1998;162:325–332.
[59]. Marc R. Silberman. Netter's Sports Medicine, Chapter-94, 713-723.e1.
[60]. Anthony C. Hackney, Chapter 9 - Bottom Line: Why Should I Exercise?. Exercise, Sport, and Bioanalytical Chemistry, Elsevier, 2016, Pages 97-106.
[61]. Iwamoto GA. The role of the study of exercise in defining the Frontier of Integrative Biology. Front. Physio. 2010;1:142.
[62]. Hughes DC, Ellefsen S, Baar K. Adaptations to Endurance and Strength Training. Cold Spring Harb Perspect Med. 2018;8[6]:a029769.
[63]. Holloszy JO. Biochemical adaptations in muscle. Effects of exercise on mitochondrial oxygen uptake and respiratory enzyme activity in skeletal muscle. J Biol Chem 1967;242:2278–2282.
[64]. Schaefer, David & Asteroth, Alexander & Ludwig, Melanie. Training Plan Evolution based on Training Models. 2015.
[65]. Lorenz DS, Reiman MP, Walker JC. Periodization: current review and suggested implementation for athletic rehabilitation. Sports Health. 2010;2[6]:509-518.
[66]. R. Vinodh Rajkumar. Gravitational Torque Deficiency Syndrome [GTDS]: A Prospective Clinical Terminology - Part 1. Int J Physiother Res 2016;4[5]:1668-1678.
[67]. R.Vinodh Rajkumar. Necessity of an exclusive health care model for individuals with quintessential epigenetic efficiency. Int J Physiother Res 2021; 9 [5]: 3992-4000.
[68]. R.Vinodh Rajkumar. Load equivalence of transient deformation characteristics of exercise elastic tubes used in physiotherapy rehabilitation and fitness training programs. Int J Physiother Res 2015;3[4]:1156-1162.
[69]. Niederberger, Ellen; Parnham, Michael J. The Impact of Diet and Exercise on Drug Responses. International Journal of Molecular Sciences; Basel 2021;22[14]:7692.
[70]. Jacobs, I., Ruderman, E., & McLaughlin, M. A Primer on Exercise Pharmacology, Kinesiology Review, 2015;4[1]:113-117.
[71]. Lenz, T.. Pharmacokinetic Drug Interactions With Physical Activity. American Journal of Lifestyle Medicine, 2010;4[3]:226-229.
[72]. George E. Billman. Aerobic exercise conditioning: a nonpharmacological antiarrhythmic intervention. Journal of Applied Physiology 2002;92[2]:446-454.
[73]. Matthew M. Robinson, Karyn L. Hamilton, and Benjamin F. Miller. The interactions of some commonly consumed drugs with mitochondrial adaptations to exercise. Journal of Applied Physiology 2009;107:1:8-16.
[74]. Lenz TL. The effects of high physical activity on pharmacokinetic drug interactions. Expert Opin Drug Metab Toxicol. 2011 Mar;7[3]:257-66.

[75]. Lenz TL, Lenz NJ, Faulkner MA. Potential interactions between exercise and drug therapy. Sports Med. 2004;34[5]:293-306.

[76]. Hsu DC, Katelaris CH. Long-term management of patients taking immunosuppressive drugs. Aust Prescr 2009;32:68-71.

[77]. Gourbal, B, Pinaud, S, Beckers, GJM, Van Der Meer, JWM, Conrath, U, Netea, MG. Innate immune memory: An evolutionary perspective. Immunol Rev. 2018; 283: 21– 40.

[78]. Luan X, Tian X, Zhang H, Huang R, Li N, Chen P, Wang R. Exercise as a prescription for patients with various diseases. J Sport Health Sci. 2019 Sep;8[5]:422-441.

[79]. Campbell JP, Turner JE. Debunking the Myth of Exercise-Induced Immune Suppression: Redefining the Impact of Exercise on Immunological Health Across the Lifespan. Front Immunol. 2018 Apr 16;9:648.

[80]. de Frel DL, Atsma DE, Pijl H, Seidell JC, Leenen PJM, Dik WA, van Rossum EFC. The Impact of Obesity and Lifestyle on the Immune System and Susceptibility to Infections Such as COVID-19. Front Nutr. 2020 Nov 19;7:597600.

[81]. Shao Tianyi, Verma Henu Kumar, Pande Babita, Costanzo Vincenzo, Ye Weibing, Cai Yuyan, Bhaskar L. V. K. S. Physical Activity and Nutritional Influence on Immune Function: An Important Strategy to Improve Immunity and Health Status. Frontiers in Physiology. 2021;12.

[82]. Özkaya, Ýsmail & Yýldýz, Melike. Effect of water consumption over the immune system response given during Covid-19. Magna Scientia Advanced Research and Reviews. 2021;2:040-044.

[83]. R.Vinodh Rajkumar. Foods Obstruct and Overcome Diseases [FOOD]: The Missing Interdisciplinary and Transdisciplinary Public Health Art till COVID-19 Pandemic. Int J Physiother Res 2020;8[5]:3586-3594.

[84]. Al-Shehri SS, Knox CL, Liley HG, Cowley DM, Wright JR, Henman MG, et al. Breastmilk-Saliva Interactions Boost Innate Immunity by Regulating the Oral Microbiome in Early Infancy. PLoS ONE 2015;10[9]: e0135047.

[85]. Palmeira, Patricia and Carneiro-Sampaio, Magda. Immunology of breast milk. Revista da Associação Médica Brasileira [online]. 2016;62[6]:584-593.

[86]. Castelo-Branco, Camil & Soveral, Iris. [2013]. The immune system and aging: A review. Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology. 2013;30.

[87]. Crooke SN, Ovsyannikova IG, Poland GA, Kennedy RB. Immunosenescence: A systems-level overview of immune cell biology and strategies for improving vaccine responses. Exp Gerontol. 2019;124:110632.

[88]. Rebecca D. Frank, Risk in trustworthy digital repository audit and certification, Archival Science, 2021;22[1]:43-73.

[89]. Bourke CD, Berkley JA, Prendergast AJ. Immune Dysfunction as a Cause and Consequence of Malnutrition. Trends Immunol. 2016;37[6]:386-398.

[90]. K.Park, Park's textbook of Preventive and Social Medicine. Chapter: Man and Medicine: Towards health for all. Page 8, 14th Edition, 1994.

[91]. Mister Seun Ayoade. The Differences Between the Germ Theory, the Terrain Theory and the Germ Terrain Duality Theory; JOJ Nurse Health Care. 2017; 4[2]: 555631.

[92]. R.Vinodh Rajkumar. Endomorphy dominance among non-athlete population in all the ranges of body mass index. International Journal of Physiotherapy and Research 2015;3 [3]:1068-1074.

[93]. Boyton, R.J., Altmann, D.M. The immunology of asymptomatic SARS-CoV-2 infection: what are the key questions?. Nat Rev Immunol 2021l;21:762–768.

[94]. Kaufmann Stefan H. E. Immunology's Coming of Age. Frontiers in Immunology. 2019;10.

[95].Genuis SJ, Sears ME, Schwalfenberg G, Hope J, Bernhoft R. Clinical detoxification: elimination of persistent toxicants from the human body. ScientificWorldJournal. 2013;2013:238347.

How to cite this article: R. Vinodh Rajkumar. Exercise Performance and Immune Competence [EPIC]: Background of Natural Immunity, Immune Diversity and Immuno-iatrogenesis. Int J Physiother Res 2022;10(3):4250-4268. **DOI:** 10.16965/ijpr.2022.124