e-ISSN: 2595-5527
Doi: 10.32435/envsmoke.2022521-9
Volume 5, Issue 2, p. 01-09
2022

Full Article

ENVIRONMENTAL SMOKE

IMMUNOSUPPRESSION CAUSED BY EMOTIONAL STRESS: FROM ETIOLOGY TO PATHOGENESIS

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Abstract

The lifestyle unleashes biological processes that lead the body to a mixed exhaustion, leading to a state called "stress", getting sick or aggravating pathologies. The aim of this study is to analyze the emotional stress on the immune system and to develop a comprehensive concept that allows for fewer erroneous ramifications in its approach. This is a literature review based on articles in Immunology taken from the PubMed database. Articles that related the stressor problem with the immunopathogenic etiology, published between 2021 and 2022 (until March 16, 2022) and searched with the truncated terms "stress immunology", "stress physiology" and "stress psychology" were selected. We evidenced that emotional stress is multifaceted, changes according to the nature of the stimulus, can be benign or deleterious and can affect populations of TCDs, which start to carry "scars" that make them hyper-responsive to inflammatory activities in stem cells, B and NK cells. Molecules such as mTOR and PI3K, which expose APCs viral agents, lead to the paucity of the process. In a situation contrary to stress, the pro-inflammatory cytokines TNF-α tend to balance, improving coping with *noxa*. Stress can aggravate numerous conditions in biological systems. However, "positive" stress is responsible for learning, making the allostatic process less expensive. The cognitive condition and the stressful nature can influence better responsiveness and learning. We found that negative stress that raises glucocorticoid levels is cognitive-dependent, predicting the worsening of chronic pathologies or producing sequelae. Finally, we conclude that stress is all exogenous cause and effect that physiologically are neuroimmunoendocrine triggers of cognitive-dependent response, which allostatically lead the system to homeostasis by nature regardless of the cause of its damage, be it benign and/or deleterious, in the acute form of bioinformational character and in the immunopathogenic chronic form.

Keywords: Psychoneuroimmunology. Immunopathology. Psychopathology.

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Submitted on: 09 Jun. 2022
Accepted on: 18 Aug. 2022
Published on: 31 Aug. 2022

1 Introduction

The economic, technological and institutional developments that have taken place in recent decades have had an impact on the way in which various social demands are managed, due to the increase in competitiveness, a phenomenon that has been reproduced in a geometric way (REIS; FERNANDES; GOMES, 2010) and which, combined with the increase in adversities, results in growing population volume, economic inconstancy, among other variants, which we can uniquely call and conceptualize as “excess of the whole, everything and everyone”.

The superabundance of information received by the individual, moves the center of balance and this vector, which adjacently removes the organism from this delicate threshold, has repercussions not only on a single result, but on several ones, which obey the responses of Newtonian mechanics; therefore, every action contrary to this tenuous balance (ecological, biochemical and social) will have a reaction, although not elementary (of equal proportion and/or intensity), but singularly geometric - since the reception of stimuli/information is multiple and, when thus, it can obey a geometric sequence by triggering results/reactions/symptoms in a closed system, with several other subsystems that establish this very delicate threshold called homeostasis - as Walter Cannon, in 1929, called this fine and singular threshold and physiological balance of homeostatic state, a term that suggests the set of physiological mechanisms for maintaining balance in the internal environment (CANNON, 1929).

This leads us to also characterize the mechanisms of change and adaptation, called allostasis and is proposed by Sterling in 1988, when the author points to the nervous system as the regulatory center of this phenomenon. Which is defined as the set of mechano-cognitive responses that compels the improvement and efficiency of the organism when responding to a certain stimulus that displaces the organism from this fine balance, obviously this set of physiological movements tends to energy expenditure, heat production and an increase in entropic levels. Depending on this demand, which we call allostatic load, this set can lead to an exacerbation of cellular processes, followed by greater damage and the result of an allostatic failure, which, in turn, becomes an event of clinical importance (SOUSA; SILVA; GALVÃO-COELHO, 2015).

This exacerbated demand for occupations in an individual, together with the progressive increase in the speed with which they appear, responds as a stressor stimulus (by effort), such as the physiological phenomena that occur in a prey in front of the predator. Its primary phase is called the "general alarm reaction", followed by the resistance phase, and ending with the exhaustion phase, as Hans Selye reported in 1946 in his manuscript for publication in the Nature journal, when he called this process the "syndrome of general adaptation”, sentence later replaced by the term "stress" (SEGERSTROM; MILLER, 2004).

The body generates, as a result of the stressor stimulus - in which fear occupies a protagonist space - a hormonal, immunological and energetic discharge, of short duration, which outlines immediate responses to fight or flee in threatening situations (TAFET, 2022), where the nervous system responds with a strong gradient of catecholamines, increasing, for example, heart rate , blood pressure and wakefulness, and generating an analgesic effect that accelerates the synthesis and expenditure of energy coordinated by the nervous system allostasis from negative feedback. Then, when moving to the next phase – of “resistance” – the body seeks to adapt to the new physiological condition and there is hypertrophy of certain glandular tissues and hypoplasia of lymphoid tissues (BEAR, 2017).

This phenomenon generates a series of deleterious effects that in a long time can become chronic stress (CS) and generate unique symptoms, leading to the genesis of pathologies of psychosomatic origin of great relevance. This leads to several damages, such as affective, cognitive and work, since in the acute phase the symptoms resulting from exposure to a stressful stimulus last only a few hours (ZUARDI, 2010). And the longer the duration of the damage caused, more complex it becomes to repair after the exhaustion phase.

This makes us suggest stress as a key point in the emergence and/or worsening of systemic pathologies, with high emotional, physical and cognitive costs that reduce the ability to perform activities such as work and social interactions, since mental and physical health are at risk closely linked (GONÇALVES et al., 2021), this makes stress an object of pandemic level, with immeasurable economic, clinical and social importance. This study aims to: reflect the influence of negative emotions and chronic stress on the vulnerability of the immune system; describe the decrease in defense competence in pathological response; reflect on the different concepts of stress and develop a concept that avoids the numerous ramifications.

2 Methodology

The study is a descriptive literature review with reflective analysis, drawn from scientific articles and books on basic and advanced immunology. This review had as its guiding question: "What is the interference of emotional events (stressors) that cause incompetence in the immune defense?" Scientific documents were collected from the PubMed database. Only articles that best related the

problem of the stressor stimulus with the immunopathogenic etiology and published between 2021 and 2022 (until March 16, 2022) were selected, so that the publications found were the most scientifically updated within the desired parameters. We used the search keywords “stress immunology, “stress physiology” and “stress psychology” in a truncated way and in English, that is: “immunological stress”, “physiological stress” and “psychological stress”, using the linking article “and”. The study is divided into 3 processes: 1) collection of articles, 2) reading and analysis, 3) textual elaboration according to the reflections raised. As the search in the database resulted in n=12, we decided to analyze all the articles. As certain works found were being used in this work, their referred data were placed in italics and bold so that it is possible to differentiate such works from supplementary materials and abstract materials, the last ones have been differentiated in a footnote.

3 Collected data

We did a new search and found 303 results (between 1969 and 2022), and from 2009 to date there was the highest number of publications in this database with the crossing of the truncated terms above: 18 articles. On March 16, 2022, we performed a new search and found 12 items with the temporal filter of 2021-2022.

However, of the 12 results found, only 9 were open access (we used the “free full text” filter for this purpose) and 3 were made available only with abstracts. We contacted the authors of the abstracts, but we did not receive feedback from two authors. Despite not being methodologically usual or scientifically correct, we carried out a brief analysis of the findings in the abstracts, and in the full-text articles we will carry out a deeper and more thorough analysis. So we have: total n=12; open access n=9; restricted n=3; author provided n=1; therefore, full articles n=10 and abstracts n=2. From these data, we prepared the Table 1:

Table 1. Results configured from the advanced search in the PubMed database on March 16, 2022, with the terms truncated in English: ((IMMUNOLOGICAL STRESS) AND (PHYSIOLOGICAL STRESS)) AND (PSYCHOLOGICAL STRESS).

N	Title	Authors	Year
1*	Psychological Stress on Wound Healing: A Silent Player in a Complex Background	BASU, S.; GOSWAMI, A.G.; DAVID, L.E.; MUDGE, E.	2022
2	Loneliness: An Immunometabolic Syndrome	POURRIYAHI, H.; YAZDANPANAH, N.; SAGHAZADEH, A.; REZAEI, N.	2021
3**	The costs of coping: Different strategies to deal with social defeat stress might come with distinct immunologic, neuroplastic, and oxidative stress consequences in male Wistar rats	VASCONCELOS, M.; CHATAIN, C.P.; GEHRES, S.W.; STEIN, D.J.; GUAHYBA, B.L.; GÉA, L.P.; DA ROSA, E.D.; PFAFFENSELLER, B.; ROSA, A.R., DE ALMEIDA, R.M.M.	
4	Chronic stress primes innate immune responses in mice and humans	BARRETT, T.J.; CORR, E.M.; VAN SOLINGEN, C.; SCHLAMP, F., BROWN, E.J.; KOELWYN, G.J.; LEE, A.H.; SHANLEY, L.C.; SPRUILL, T.M.; BOZAL, F.; DE JONG, A.; NEWMAN, A.A.C.; DRENKOVA, K.; SILVESTRO, M.; RAMKHELAWON, B.; REYNOLDS, H.R.; HOCHMAN, J.S.; NAHRENDORF, M.; SWIRSKI, F.K.; FISHER, E.A.; BERGER, J.S.; MOORE, K.J.	2021
5	Stress responses in high-fidelity simulation among anesthesiology students	STECZ, P.; MAKARA-STUDZIŃSKA, M.; BIAŁKA, S.; MISIOŁEK, H.	2021
6“”	Impact of Air Pollution on Allergic Rhinitis and Asthma: Consensus Statement by Indian Academy of Pediatrics	REDDY, K.R.B.K.; GUPTA, N.; BHATTACHARYA, B.G.; DEKA, N.M.; CHANDANE, P.; KAPOOR, R.; GUPTA, S.; NAGARAJAN, S.A.; BASAVARAJA, G.V.; PAREKH, B.J.	2021
7**	Adaptation to Asthma in Children: A Matter of Coping and Stress Control	SEGURA MORENO, C.C.; DIAZ HEREDIA, L.P.	2021
8	Immunological Aspects of Isolation and Confinement	PONOMAREV, S.; KALININ, S.; SADOVA, A.; RYKOVA, M.; ORLOVA, K.; CRUCIAN, B.	2021
9	Mindfulness-Based Interventions for Physical and Psychological Wellbeing in	MARINO, F.; FAILLA, C.; CARROZZA, C.; CIMINATA, M.; CHILÀ, P.; MINUTOLI, R.; GENOVESE, S.; PUGLISI, A.; ARNAO,	2021

	Cardiovascular Diseases: A Systematic Review and Meta-Analysis	A.A.; TARTARISCO, G.; CORPINA, F.; GANGEMI, S.; RUTA, L.; CERASA, A.; VAGNI, D.; PIOGGIA G.	
10	A Review of Inflammatory Bowel Disease: A Model of Microbial, Immune and Neuropsychological Integration	TAVAKOLI, P.; VOLLMER-CONNA, U.; HADZI-PAVLOVIC, D.; GRIMM, M.C.	2021
11	Waterfall Forest Environment Regulates Chronic Stress via the NOX4/ROS/NF-κB Signaling Pathway	ZHU, Z.; ZHAO, X.; OUYANG, Q.; WANG, Y.; XIONG, Y.; CONG, S.; ZHOU, M.; ZHANG, M.; LUO, X.; CHENG, M.	2021
12	Short-Term Relocation Stress-Induced Hematological and Immunological Changes in Saimiri boliviensis boliviensis	NEHETE, P.N.; NEHETE, B.P.; PATEL, A.G.; CHITTA, S.; SCHOLTZOVA, H.; WILLIAMS, L.E.	2021

Legend: * Restricted access item, whose author sent the complete article; ** Items that only present abstracts; “”Article excluded from analysis as it did not connect emotional interaction with immune activity.
Source: Prepared by the author.

4 The evolution of the concept of stress over time, in an evolutionary, philosophical and neurobiological historical concept

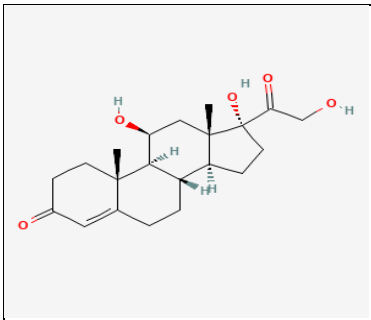
During evolutionary, cognitive and biological development - Darwinian - from prehistory that comprises the Paleolithic, Mesolithic and Neolithic periods to the present day, individuals (animals) are bombarded by an excess of informational and/or bioinformational stimuli, interactive experiences of type subject>object; subject>subject; subject>object>subject (ADÃO, 2013).

These data were collected by the sensory nerves, which participated in a neuronal circuit, produced a chemical or electrical synapse, were cycled by a cognitive process and resulted in the primitive-primordial state of stress, that is, the minimum stimulus necessary that displaces the homeostasis of the brain. Its harmonic threshold, inducing obligatory enthalpic movements of this system and does not establish an intrinsically deleterious character to stress in all its faces, but rather rhetorical, informational, mediatic, transitory and necessary, even if it produces an oxidative equivalent.

Reinforcing the informational physicochemical epistemology, Bruce Alberts and collaborators, in the book *Molecular Biology of the Cell* (ALBERTS et al., 2002), describe the oxidation phenomenon as the addition of oxygen to a molecule generically, or the loss of electrons (e^-) and, more singularly, any reaction in which there is a covalent sharing of e- of the protagonist atom (O^2), or of its reactive species: radical or non-radical, which in the organism are derived from the Fenton reaction in cellular respiration and other events of nature peroxidative (ALBERTS et al., 2002). We can deduce a mechanical nature in this process if there is a continuity that can be measured by velocity and, if during such a process it presents a certain variance measured by acceleration, it consequently has a predictive vector, since these bonds obey an order of binding affinity.

Cortisol (see Figure 1) is the molecular genitor protagonist of this whole process, it modulates unique and particular responses to other steroid molecules, and cognitive and environmental inflections further differentiate the specificity of each response.

Figure 1. Image and description of the chemical structure of the cortisol molecule.



Data deposited or computed by PubChem:
- Structural formula: c21h30o5.
- Molecular formula: c 21 h 30 or 5.
- IUPAC: (8s, 9s, 10r, 11s, 13s, 14s, 17r)-11,17-dihydroxy-17-(2-hydroxyacetyl)-10,13-dimethyl-2,6,7,8,9,11,12,14,15,16-decahydro-1h-cyclopenta[a]phenanthren-3-one.
- PubChem CID: 5754.

Source: Adapted from National Center for Biotechnology Information (2022).

Stressful events, from successful experiences, added to the individual in the construction of self-confidence, courage and personality, adjectives that participate in the construction of individuality, in perceptive improvement, in cognitive flexibility and emotional intelligence. These will give rise to 'interpretation' for the person to recognize the first nuances of this new abstract sense - 'doubt, certainty, restlessness' - making it possible to recognize the first primitive adding-symptoms of stress. The shocks

suffered by the body are the result of prostration, exposure to situations of calorimetric exacerbation (cold or heat), fear, bodily injuries, illnesses, biological, psychological and social outcomes of a negative nature, which demanded some kind of effort, and made the to understand the deleterious genesis of this phenomenon (SILVA; GOULART; GUIDO, 2018); culminate in the displacement of the homeostatic axis that causes a load of biological energy - whether chemical or protein - for the generation of dynamic movement towards physiological (tissue) repair, causing a vector energy expenditure adjacent to the dynamic balance of the organism. In the course of the evolution process, these adversities - which we can also call according to Physiology, Physics and Psychology as stressful stimuli/events - lead the body to physiological responses of survival, adaptation and learning. We thus realize that when the individual understands that he is capable of overcoming the stressor agent, the harmful load produced - or, better saying, the volume of this "biochemical mix" of substances - is minimized, this generates a feedback response by a gradient of decreased or unrecognized concentration, failing to cause harm. Perception, which generates physiological responses, thus presents a subjective character, directly linked to psychoneuroimmunological traits that cognitively come to modulate this response (ROCHA et al., 2018).
However, the type of stressor agent results in different responses and, commonly, there is a tendency to suppress cellular immunity and preserve humoral immunity. However, when stress becomes chronic, it leads to the suppression of both complementary systems of immune responses. The response to stressful stimuli varies according to the type and sequence of events (trauma and loss), and the maintenance of the stressful stimulus (increase or decrease in time (t)) depends on subjective variables, such as age, illness, physical state - emotional and/or physiological, they then become protagonists of the form of response and duration of the event, determining the type and severity of damage (SEGERSTROM; MILLER, 2004).

In a eutrophic state, stress is not only related to deleterious events, it plays an important role in cognitive development, in coping with stressful variables, overcoming challenges, mediating the sense of caution and acting as a motivating agent (SILVA; GOULART; GUIDO, 2018; SILVA, 2005 apud ROCHA et al., 2018).

We agree with Segerstrom and Miller (2004), when they point out in their research that, in a century of studies and more than 300 documents, great difficulty was still found to define a unique taxonomy for the term 'stress', and with Castiel (2005), who affirms the difficulty in defining a concept and about an exhaustive discussion, which leads to further conceptual developments in relation to the theory of stress. However, the author points out two important factors in the taxonomic modeling of the term: "1) manifestations whose predictability is not delimitable; 2) phenomena that are found at different hierarchical levels" (CASTIEL, 2005, p. 103). As previously stated, the large proportion of variables and the lack of a precise measurement parameter make it difficult to limit these parameters - the expression of symptomatological levels arising from stress is directly proportional to the experiences (whether good or bad), to the intellectual and to the cognitive sequelae of the individual. These variances not only depend on how the personality characteristics of habits were constructed, but also on the state in which the individual was in the initial stage of measurement and data collection. In addition, Pourriyahi et al. (2021) report in their research a series of neuroimmunoendocrine changes in the different ways in which we socialize and - mainly - we do not socialize, which are managed in a way by the psychosocial environment around the individual and activate triggers that behave as stressors. Ponomarev et al. (2021), in turn, in their research, observe the immune system in controlled environments and report the difficulty of accuracy in the data due to the colossal variance of the results, as these are a consequence of the relationship between the neurological, endocrine and immune systems. In this sense, Basu et al. (2022) report that both the physiological system in general and the psychoneuroimmunoendocrine axis are also the result of the medium cognitive experiences and their interpersonal relationships.

However, these events, epistemologically common sense, are considered as deleterious effects to the body, or life, but they truly fulfill informational (benign) functions, simple examples we find in learning and adaptation from a behavioral (psychological) and biological point of view (Darwinian concept). On the other hand, from a clinical point of view, we should not overestimate these events of emotional construction of the individual, since their exacerbation can generate phenomena or symptoms of clinical importance, signaling the worsening of a preexisting pathology.

Thus, we can conclude that stress is: all exogenous cause and effect that physiologically are neuroimmunoendocrine triggers of cognitive-dependent response and allostatically make the body enter homeostasis by the nature of the cause of its damage, be it benign and/or deleterious, in the acute form of bioinformational character and in the immunopathogenic chronic form.

5 The dawn of pathological chaos - when information stops being information

To understand the starting point of a stressful event, we need to internalize this sentence: Cortisol is the hormone that, when released, triggers all physiological events related to some physical or psychological alarm/response phenomenon. In addition, we need to recognize that neither stress nor inflammatory processes resulting from this phenomenon have a single face - the "negative, deleterious, harmful one", as they are important informational stimuli.

We know that the stressor stimulus is not notoriously a stressor when we observe it from a psychological perspective, it becomes a stressor when it is sufficient to activate behavioral mechanisms that, through the individual's perception, are able to trigger the physiological processes responsible for the shock phase.

More about the original text Taking into account that these emotional stimuli add up to a learning process (experiences), cognition and personality that determine individual uniqueness, they do not necessarily make stress a negative event, it depends on their nature. Below we present what we found in eight publications, in alphabetical order of the first author of each one.

Barrett et al. (2021), about the innate immune response in humans under chronic stress , observing the monocytic and myelocytic activity suggest that individuals exposed to stress have cellular and genomic traits that elevate the monocyte, this fundamental protagonist of systemic inflammation, and carry scarring traits that lead them to hyperinflammatory biochemical behaviors. As for TCRs (Toll like receptors), they exhibit a hyper-responsive signature under antigenic stimulators due to the transcriptogenic insult.

Marino et al. (2021), in their meta-analysis research and systematic review on physical and psychological well-being in cardiovascular diseases under practical mindfulness-based interventions, showed that the technique has a significant result in reducing levels of anxiety, depression, stress and BP, and improvement in physiological performance. Despite the heterogeneity of the analyzed studies, they were able to conclude that the technique translates first-line effectiveness in the search for psychological and physiological well-being for patients with cardiovascular diseases.

Nehete et al. (2021) analyzed squirrel monkeys in situations of environmental change and colony relocation, which are stressors, and showed a series of immunological changes, in the detailed analysis of the blood, they showed changes in lymphocytes and other biochemical markers. Under flow cytometry analysis, the indices indicated a reduction in the cell population of CD3+, CD4+, CD8+ T cells. Monocytes, B cells and natural killer had functional changes.

Segura Moreno and Diaz Heredia (2021), in a quantitative correlational study with a sample of n=280 in an age group of individuals between 6 and 16 years old, with asthma, admitted to an outpatient and inpatient consultation at a level IV institution in Colombia, showed that individuals with reduced stress levels have greater control over their condition.

Stecz et al. (2021) in their study they analyzed anesthesiology students in emergency situations. Handling a hospital emergency is an activity that demands, is exhausting, of high cognitive demand; therefore, a stressor stimulus. The research by these authors had a sample of 56 medical students and 3 measurements: 1st before the emergency activity; 2nd after this activity; 3rd two hours after this activity. Stress-related biochemical agents were taken: cortisol, testosterone, secretory immunoglobulin A (IgAsec), α-amylase, oxygen saturation (SpO2) and HR and BP. The authors found that, before the emergency situation, the concern caused the SpO2 to increase. After the emergency, BP and HR increased, which is a curious finding. From an immunological point of view, the lymphocytic activity was manifested by the increased secretion of IgA, however, it was quickly suppressed by the significant increase in glucocorticoids. Thus, the signature obtained in the study relates the IgAsec manifestation to negative psychological events in proportion to immunological incompetence.

Tavakoli et al. (2021), in their review study on inflammatory bowel diseases, also showed a certain link - although not very well understood - between the genetic response, the environment, the psychological state and the immunological efficiency, and emphasize that there is a need new studies correlating these factors with severity indices;

Vasconcelos et al. (2021), showed the impact of stress on the ability to deal with the event, it was performed with rats and suggests that there may be an alteration in the antioxidant defenses, revealing greater oxidative damage in individuals who had difficulties in coping.

Zhu et al. (2021), in their study with a human and animal model, exposed patients to nature spaces and waterfalls, and showed a significant change in the levels of inflammatory factors such as IL-1β, TNF-α, IL-6 and IL -10, which decreased during the intervention and reduced the damage caused by chronic stress in rats, inhibiting the NOX4/ROS/NF-κβ pathways.

Based on these studies, we clearly show that the entire stress mechanism is characterized by an immediate response, responses that also adaptively confer responsiveness to decision-making and cognition. We also clearly evidenced the inflammatory participation of caspase 1 (casp1) in the processes of population decrease of the Ts cell lineage due to the action of casp1 in the

phenomena of immunological hyperresponsiveness and due to injuries by negative stress.

6 Conclusions

We conclude that negative stress may be the etiology and aggravation of numerous systemic pathological conditions in mammalian biological systems, especially humans, since it triggers events that potentially accelerate the metabolic reaction rate, which cause oxidative damage to biomolecules by increase the volume of reactive oxygen species (radical and non-radical), producing redox signaling and inflammatory pathways, for example, those of caspases 1 precursors of Il-1b maturation.

However, 'positive' stress is responsible for learning, commitment, personality formation and resilience. On the other hand, the cognitive condition and the stressful nature can both influence the best immune responsiveness and its depletion, and it does not stop causing damage since every molecule/substance has its unique and singular useful life, which is rapidly reduced according to its use.

As much as the heterogeneity of the documents analyzed was high, we can conclude that, yes, stress of a negative nature, which raises glucocorticoid levels, is cognitive-dependent and a predictor of the worsening of the pathology when its nature is chronic. Thus, stress is all exogenous cause and effect that physiologically are neuroimmunoendocrine triggers of cognitive-dependent response, which take the system out of its harmonic form and allostatically cause the body to enter homeostasis by the nature of the cause of its damage, whether benign or deleterious, in the acute form of bioinformational character and in the immunopathogenic chronic form.

Acknowledgments

To my supervisors, Professors Elizabeth and Roberto, who led me along untraced paths. Especially to Professor Ana L. P. Reis, who, without having any kind of bond and without knowing each other, answered my doubts and supplied me with very rich literature. To Dr. Somprakas Basu, for their collaboration. And, above all, to Professor Maria Helena Soethe, Specialist in Heritage Art and 'the best mother in the world'.
To all of you I extend my thanks!

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

The study was prepared and interpreted by the academic student Thiago Soethe Ramos with medical guidance from Professor Doctor Elizabeth Ohjama. Methodological guidance by the Professor Doctor Roberto Recart dos Santos.

DECLARATION OF INTEREST

The authors disclose that they have no known competing financial interests or personal relationships that could have appeared to influence the study reported in this manuscript.

FUNDING SOURCE

The authors declare that no funding is applicable for this research.

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