HORMONE-MEMBRANE-MITOCONDRIUM-APOPTOPIC THEORY OF TUMOROGENESIS
ACHIEVEMENTS, CHALLENGES AND PROSPECTS FOR THE NEXT DECADE

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SUMMARY:

Objective: To develop a rational theory of cancer pathophysiology.
Material and Methods: The bibliographic review of international and personal publications, in interaction with the experiences of clinical practice and its inevitable subjective component, influenced by therapeutic successes and failures, have for the author a scenario that is described below.
The disease "cancer" is a set of multifaceted and multifactorial morbid entities. Furthermore, such a nosological entity shows an evolution through sequential steps whose order has not been fully clarified. Its presence among human beings dates back to ancient times, perhaps to the very beginnings of human presence in the world, and is also shared by other living beings. Its research under the rules of scientific reasoning has already exceeded a century. A production mechanism still with unknown segments and an enormous, deep and costly research effort without a final success, have promoted concerns that cover the wide spectrum that goes from a strict and exclusive scientific conception to other modalities that, at their extreme, constitute distortions opposed to science and ethics, the latter particular approaches that have been discarded in this work.
However, healthy inspirations, eventually epiphanies such as that of one of the bibliographical references, followed by rational verification, emerge as another proposal of the present work. Therefore, the complementarity between Faith and Reason would constitute a viable conception in scientific production.
Results: The establishment of new multi-objective investigations, inspired by the variety of factors hypothetically involved in the disease such as: hormonal alterations, membrane disruption, mitochondrial dysfunction and non-homeostatic apoptosis, may have an important place in basic and clinical cancer research.
Conclusions: In the context of the above data, the proposed objective has been achieved. An achievement that, with a view to the future, appears preliminary and fragile. Going forward, some actions remain uncertain: their dissemination, their acceptance as a hypothesis, their adoption as a rational basis for laboratory work and their integration into clinical research protocols. At least; new facts that constitute as many challenges.

KEYWORDS: *central hormonal axis, membrane alterations, mitochondrial dysfunction, non-homeostatic apoptosis.*

IINTRODUCTION:

Since the prehistory of medicine, we have received information regarding how human beings interpreted diseases for their understanding and management through the assembly of traditional philosophical-religious arguments; closer to the present, science and art burst onto the scene.
Such concepts built on the foundations of praxis, beliefs, traditions, studies and dogmas of faith (Fides) were accepted and remain valid as solid realities in some contemporary cultures; in the same way for us, until now, the application of scientific reasoning (Ratio) is obligatory.
The preceding paragraph refers to the beginning of emerging transcendental conceptions in environments that are not strictly university-based.

Thus, in an extensive tour, it is possible to recall Plato's conversations in the forests of Academos (*) and the author's own reflections when recalling his brainstorming on the meaning of the membrane abnormality in malignant cells[2]. Additionally, [1]simultaneously with the present writing, it seems appropriate to point out what was published in the New York Times on July 14, 2023, about the epiphany (**) of Gerald R. Crabtree, a biologist member of Stanford University, while walking through a contemporary forest [3].

(*) Groves of Academos: in Athens, beyond the walls, sacred place near the tomb of the mythical Greek hero Akademos, around 387 BC Plato founded his famous Philosophical School. Hence the concept of "Academy".

(**) Epiphany (noun): moment when, suddenly, something of great importance to a person comes to his or her awareness. Powerful religious experience (Cambridge Dictionary).

From a historical perspective, a century and a fraction of that, like the time spent on scientific research into cancer, does not represent, as a time span, a great impact on human history; however, it has a significant value for contemporary generations who suffer or have suffered the onslaught of a disease whose solution, despite the constant advances of science, is still not in our hands.[3]

The work must continue steadily, through the analysis of higher levels of abstraction towards so many enigmatic intracellular structures, among which is the mitochondria.

MATERIAL AND METHODS:

As noted in the abstract, the main support of this work is the bibliographic review.

Personal perceptions arise from care experiences and through the validation of sources of inspiration, always supported by ethics, professional reasoning and scientific verification.

Scientifically regulated research into the disease of "cancer" has lasted for over one hundred and thirty years; theories of tumor genesis have been grouped into viral, hormonal and physical-chemical theories[4].

All of them are fundamental as determinants of one or more alterations of the genetic material, this as an initial step towards the establishment of a tumor clone.

Although hormonal causes have been mentioned, such as the identification of autocrine production of growth factors and alterations in control mediated by intercellular communication[5] , [6]; it was the mutagenic theory that gained the most followers.

This line of work led to categorical statements such as the following: "Cancer is a genetic disease"[7].

The preceding development evolved simultaneously with therapeutic evolution.

Historically, cancer treatment has been based on empirical principles founded on accidental findings and conditioned by ignorance - in the beginning - of all the pathophysiological steps throughout the malignant transformation.

DISCUSSION:

The advent of molecular biology has provided tools that facilitate an ever-increasing process of abstraction, but a definitive solution has not yet been achieved.

Despite the extraordinary advances made to date, cancer remains a challenge to public health around the world.

Typical in its beginnings, current therapeutic management maintains certain characteristic concepts of non-specificity.

In summary, tumor genesis includes multiple steps, diverse pathways and possible multiple causalities that have not been fully revealed until now.

Thus, its rational treatment is also not defined.

At this point and in the direction of a new hypothesis, a reflection, a complete review and further research on the role of mitochondria in the genesis of neoplasia and their negative influence on the normal pathway of apoptosis (***) in the cells of the transformed clone seems necessary.

For the above, a publication is especially cited that, with a significant level of abstraction, convergently analyzes mitochondrial physiology and the development of apoptosis[8].

First of all, it is important to remember that this organelle is the energy center, its transfer of electrons through the internal transport chain (respiratory chain) produces and stores energy; this source will be used for various actions; it is legitimate to think that cell division is one of them.

Other internal energy-related processes in membranes and matrix are the highly complex oxidative cycles of fatty and citric acids.

All examples of the exquisite mitochondrial "machinery."

Among the various electron transporters of the respiratory chain, Ubiquinone and Cytochrome C stand

out.

An important discovery is the discovery of DNA (mitochondrial genome) and the ability of mitochondria to reproduce through division and thus increase their number in humans.

Apoptosis is a unique homeostatic mechanism by which the number of cells in a population is kept functionally constant.

The stimulation or overexpression of genes that regulate the synthesis of proteins that promote or inhibit apoptosis (bcl 2 among the latter) could be involved in the immortality of the tumor clone; in addition, it is important to highlight that programmed cell death is a rapid process that leaves no traces, this is consistent with a normal physiological process, unlike cell death due to injury (necrosis), apoptosis does not dump debris or toxic waste into its vicinity or general circulation, in short, it does not induce inflammatory phenomena[9].

(***) The term “apoptosis” takes us back to the cradle of our culture. It comes from the Greek: “autumn fall of leaves and petals” (Homer)[8].

The search for a deeper understanding of the inextricable interactions between cells and the extracellular matrix is the reason for locating relevant publications.

Such an attitude allows us to recall a refined model called "dynamic reciprocity" developed by Bissell and Carcellos-Horf[10,11], which postulates the influence of the matrix on genetic expression through transmembrane proteins and components of the cytoskeleton.

Contemporary research efforts can then be synthesized into a new line of thinking: the repositioning of genetic alterations within a context of sequential phenomena. Such a conception developed synchronously within global research communities.

European oncologists engaged in basic and clinical research, while maintaining a focus on somatic mutation and clonal origin of cancer, have published extensively on signaling transduction and its perturbations in the pathway of malignant transformation[12].

Returning to tangible considerations, the unresolved nature of the problem motivated an exploration of additional biological and molecular levels to analyze carcinogenesis, thus promoting the rational design of innovative therapies.

This informed the design of investigative treatment protocols focused on membrane alterations, a modified microenvironment, and signaling abnormalities, locally known as "restorative treatment"[2].

This local approach was remarkably modest compared to the powerful international work concentrated on "molecular targeting"[13].

Consequently, and beyond their specific nomenclature, they were constituted as simultaneous initiatives to neutralize the intimate mechanisms of cellular transformation. Unquestionably, the level of abstraction from the recent past to the future corresponds precisely to the domain of molecular biology.

Subsequently, a logical, albeit simplified, review of tumor onset allows us to hypothesize the convergence of two or more of the following factors involved:

1. A local harmful effect: chronic injury and irritation, prolonged inflammatory phenomena, radiological, chemical, viral and other potential aggressions.
2. A non-homeostatic reactive cell growth potentially promoted or mediated by a central hormonal axis, which merges with an apoptotic deficit.
3. Stimulation/inhibition of auto and paracrine signaling, with implications for mesenchymal and vascular neogenesis.
4. Mitochondrial dysfunction is currently postulated to be very likely present in neoplastic, neurodegenerative and autoimmune diseases. One of the quotes contained here indicates this.

Furthermore, the central focus of this report is to identify a mitochondrial participation in the progression of apoptosis during which an irreversible point of no return would be established in the second specific apoptotic phase.

In conclusion, regarding the role of mitochondria, it is possible to indicate that this remarkable organelle is situated in the path of intracellular signaling.

Under normal conditions, cell growth is mediated by one of the four hypothalamic-pituitary axes, functionally through the homeostatic feedback mechanism.

This particular case is that of the insulin-like growth hormone-releasing hormone (GHRH) axis.

Once growth hormone (GH) release is induced, general and local conditions determine the target tissue.

An important part of this determination is made up of circulating proteins to which GH binds.

One of these proteins, called "high affinity protein", is identical to the corresponding membrane receptor and therefore has the ability to reduce plasma clearance, becoming a true modulator of hormonal action.

Returning to GHRH, certain actions have been identified and effects on neoplastic cells have also been demonstrated, specifically the increase in intracellular calcium independent of the external gradient and the activation of Phospholipase C.

Growth hormone (GH) acts through a transmembrane receptor related to Tyrosine Kinase C; it involves not only a single enzyme but [8] a family with distinctive characteristics: dependence on calcium and its participation in signal transduction initiated by growth factors, steps in which phosphorylation-dephosphorylation processes also coexist.

Other actions of GHRH are well documented: among them, it is important to remember the induction of cyclic AMP synthesis and the stimulation of the proliferation of somatotrophs, functional cells with subsidiary actions and capacity for the production of specific mediators.

Growth hormone (GH) actively participates in phosphorylation processes and consequently initiates signaling cascades directed toward the nucleus.

At the tissue level, stimulation appears to be carried out by insulin-like growth factor-1 (IGF-1), which has the ability to bind to six types of proteins.

These bonds regulate direct mutagenic actions 11 either positively or negatively. Related to the above, it has been shown that tumor cells exhibit, among their surface modifications, an increase in the mobility of their transmembrane proteins, an aspect that would strengthen the hypothesis of a super-effect of proliferation-stimulating factors.

The above paragraphs suggest the clinical need to restore the alterations of the hormonal axis referred to and invite basic researchers to illuminate the intimacy of the already well-known communication channels between the cell surface and the nucleus, mediated by membrane flow [14].

This line of research will probably allow us to identify the importance of other structures, processes and subcellular changes such as: surface receptors, intracytoplasmic signaling cascades and subsequent karyotypic modifications.

These events potentially constitute a sequential progression of events, in short a path that both basic and clinical researchers should necessarily follow.

This is an opportune moment for the analysis of the hypothetical causal factors underlying the establishment of the now recognized tumor clone and its characteristic immortality.

One of them, the chronic effect of a noxious stimulus with its consequent and persistent nuclear signaling could induce alterations in both the phenotype and the karyotype.

The identification of such morphological and cytological abnormalities, particularly nuclear changes, has dominated the histopathological diagnosis of cancer for decades and still has certain influences today.

Furthermore, the social behavior of the transformed cell is clearly different from that of its normal progenitor cells. As a result, it bypasses the general mechanisms of homeostasis, essentially apoptosis.

This affirms the presumption of altered physiological phenomena characterized by an "inadequate" response to growth-stimulating factors of autocrine or paracrine origin, individually or in combination.

Furthermore, in tumors, mesenchyme stimulation occurs, leading to neovascularization and an increase in supporting connective tissue, both of which constitute the extracellular matrix of solid tumors.

It is pertinent to remember that neoangiogenesis began a new chapter in molecular therapeutics, thus beginning a line of research that is still active.

Returning to proliferation as a response to an insult, there is a specific bibliographic reference (9); subsequently, another opportune moment to expose that the growth hormone (GH) is also synthesized by mesenchymal cells and macrophages (11), which further supports the possibilities of both autocrine and paracrine actions. Ultimately and coincidentally, such ectopic production is not subject to physiological homeostatic regulations (15).

Acromegaly is a clinical endocrinological entity that constitutes a topic of reflection. These patients have an increased risk (between 3 and 10 times) of developing colon neoplasias and a similar occurrence is observed in familial colonic polyposis (16).

All the above information guides us towards the concept of an altered tissue microenvironment in carcinogenesis, centered on the vicinity of membrane peptide receptors, encompassing both their extracellular aspects and their intracytoplasmic extensions.

Here the signaling cascade (multiple “targets”) would begin, and the origin of second messengers such as cyclic AMP, metabolic alterations of the calcium ion (15), and as already mentioned, mitochondrial alterations; subsequently, with karyotypic modifications, the microenvironmental changes would extend to the

cytoplasmic matrix and to the nucleus itself. Finally, the increase in transmembrane receptors has already been observed in cells of neoplastic tissues (11) .

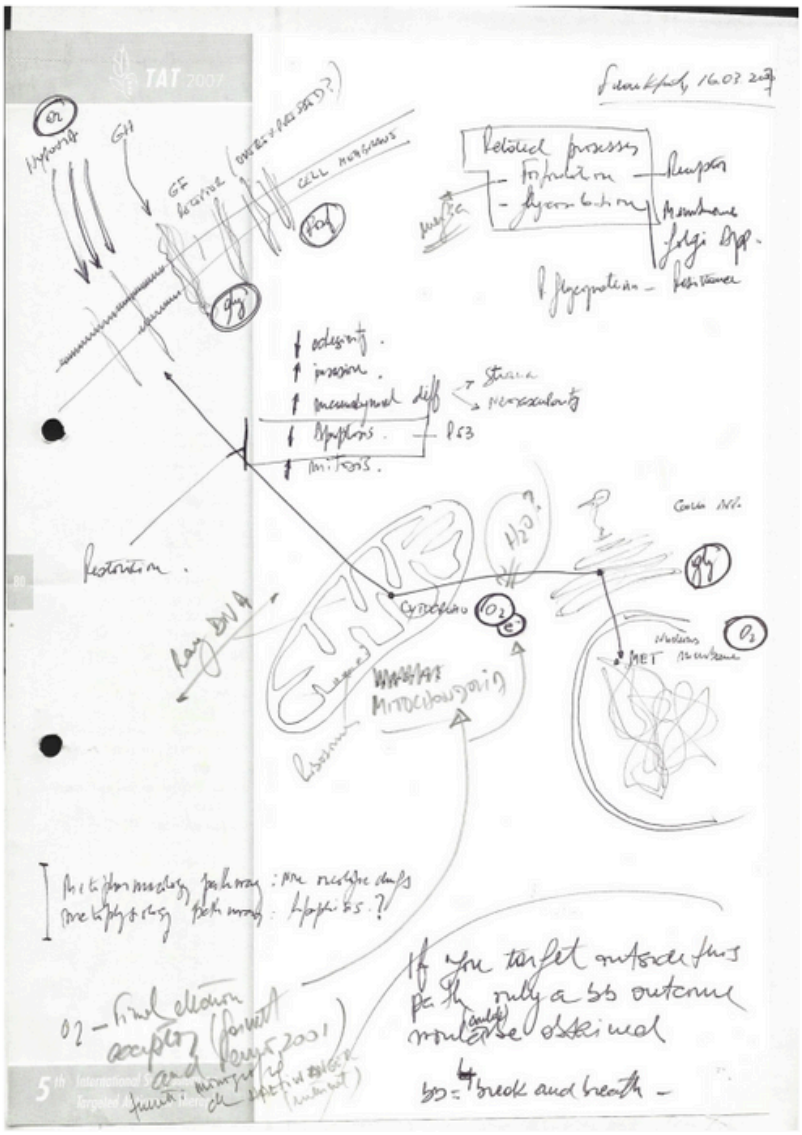

FIG. 1: FROM THE FIRST AUTHOR'S PERSONAL NOTEBOOK, SUBCELLULAR PATHOPHYSIOLOGY OF MALIGNANT TRANSFORMATION. NOTE MULTIPLE STEPS, INFLUENCE OF APOPTOSIS, ENERGY CIRCUITS, CENTRAL ROLE OF MITOCHONDRIA, AND IMPORTANCE OF MEMBRANE STRUCTURES (INCLUDING GOLGI APPARATUS). DATE: MARCH 16, 2007 (CIRCA 5TH INTERNATIONAL SYMPOSIUM ON MOLECULAR-TARGETED ANTICANCER THERAPIES-TAT. AMSTERDAM, MARCH 8-10, 2007).

Thefollowing two images are examples of the transition from handwritten design to the participation of generative AI (perplexity), in all its products errors can occur. Therefore, double quality control is always required. Specifically in images, artifacts and hallucinations are described; however, it is not the only resource available. Other tools can be explored, such as those provided by biorender.com.

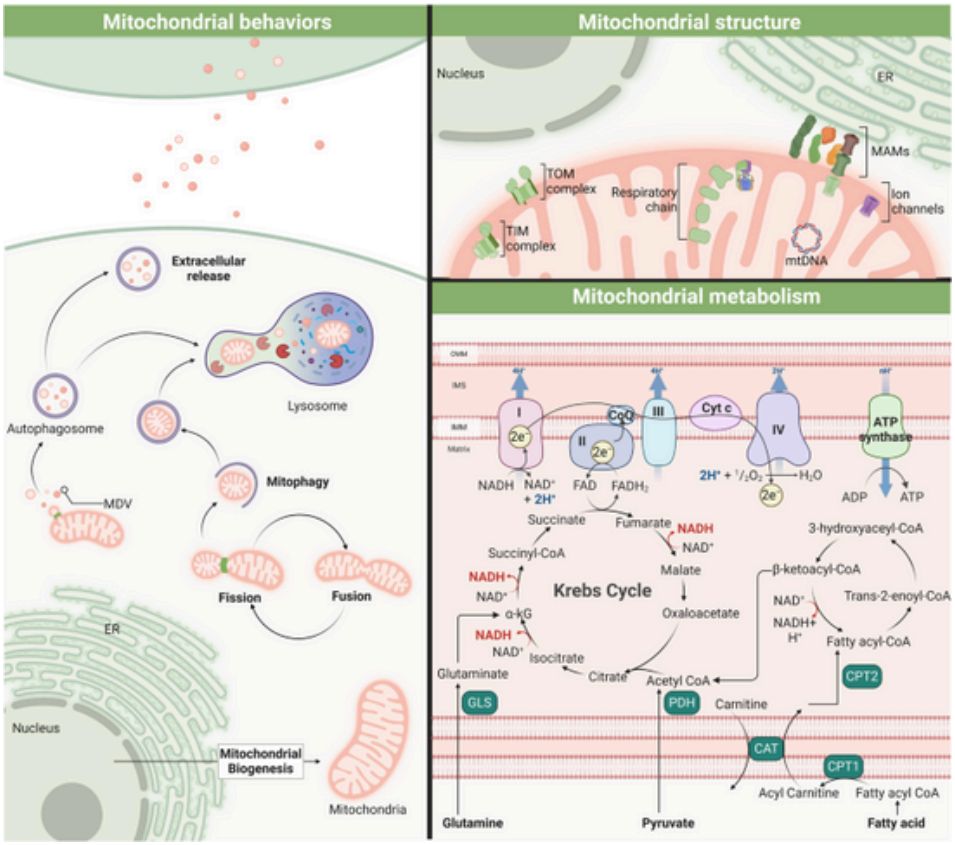

FIG 2. EXAMPLE #1: HOW DOES MITOCHONDRIAL DYSFUNCTION CONTRIBUTE TO NON-HOMEOSTATIC APOPTOSIS OF CANCER CELLS?

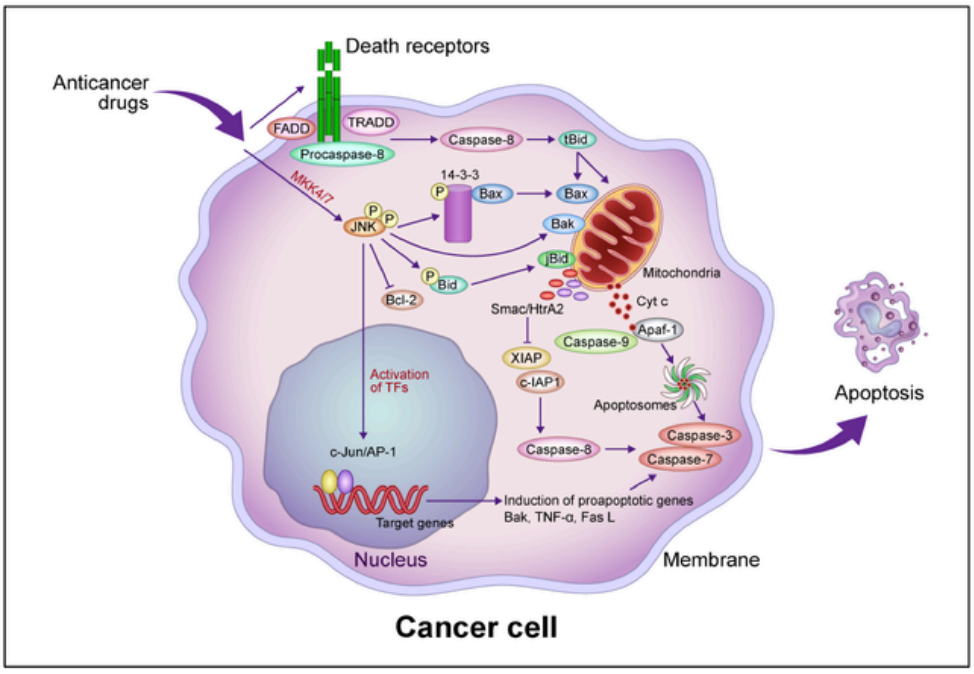

FIG 3. EXAMPLE #2: HOW CAN UNDERSTANDING THEORY IMPROVE CANCER TREATMENT STRATEGIES?

Before the conclusions, a bibliographical citation with its respective link is provided for the greater comfort of potential readers: this is an editorial text that turned out, in the opinion of the authors, to be an essential complement to the possible new theory.

- https://smiba.org.ar/revista/vol_020_04_2024/ (pages 147-150)

CONCLUSIONS:

Thus, with this new physiopathogenic conception of cancer presented and even based on hypothetical terms, new challenges would arise for research, both in its basic aspect and in its clinical counterpart.

This synergistic approach could give a certain degree of reality to the theory and would inspire new lines of action towards innovative lines of investigative therapy protocols that cover multiple objectives (molecular targets), designed with simultaneous or sequential synchronous formats.

The main objective of these efforts is to achieve a greater understanding of the pathophysiological steps throughout neoplastic transformation, in search of reestablishing the normal sequence and rhythm of cell multiplication and thus recovering central homeostatic control of events, with the ultimate goal of neutralizing cell multiplication and the abnormal growth of neoplastic tissues.

In summary, the conception of a transformed microenvironment with the contribution of a local noxa, structural changes in membranes, the erratic modulation of a central hormonal axis, with the production of disruptive signaling from a significant increase in Tyrosine Kinase C and apoptosis inhibited by mitochondrial dysfunction, may trigger new approaches to more effectively confront the disease "cancer", strictly speaking a heterogeneous family of nosological entities.

Finally, the assumptions regarding the beneficial effects of non-specifically oncological drugs - particularly cardiovascular drugs, especially antiarrhythmic and antihypertensive drugs - are not new.

These lines of work have been developed both nationally[17] and internationally[18], in both cases towards the end of the 20th century.

Additionally, it is worth highlighting the interaction with mitochondrial physiology and other molecular effects of certain drugs such as beta 1-adrenergic blockers and angiotensin II receptor antagonists; examples include: the inhibition of respiration of these organelles, their antiangiogenic actions, the inhibition of oxidative phosphorylation of neoplastic cells and the normalization of local energy consumption.

These and other potential future discoveries could provide fertile ground for brilliant laboratory discoveries or luminous epiphanies, which promote innovative scientific research. Here, the participation of Artificial Intelligence with the responsible supervision of Human Intelligence is already an established challenge in the humanized real world of clinical oncology.

In this sense, the previous paragraph could constitute an opportune reference for the epidemiological analysis of the factors of lower risk of suffering from oncological disease in populations of cardiovascular patients undergoing chronic treatments.

Finally, it is appropriate to return to the sources: "Faith and reason are like two wings with which the human spirit ascends to the contemplation of truth." (1)

CONFLICT OF INTEREST:

The authors declare they have none.

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in this case the " Claude " platform was used . Here the first control was fulfilled (the publications are of real existence), the second corresponding to the solidity of the works and their influence on the present writing, was omitted due to the previous elaboration of our article, it already had its own bibliographic foundation and, finally, the original writing constituted the " Prompt " for the present expansion. Without prejudice to the foregoing, a third quality control should not be ruled out.

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