THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 14 Issue 1

REVIEW ARTICLE

The Oncoming Hydrogen Era and The New Paradigm of Cancer and Neurodegenerative Diseases Based on the Hydrogen Ion Dynamics on Cellular Homeostasis and Metabolism - from Etiopathogenesis to Treatment

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OPEN ACCESS

PUBLISHED
31 January 2026

CITATION
Harguindey, S., Reshkin, SJ., et al., 2026. The Oncoming Hydrogen Era and The New Paradigm of Cancer and Neurodegenerative Diseases Based on the Hydrogen Ion Dynamics on Cellular Homeostasis and Metabolism - from Etiopathogenesis to Treatment. Medical Research Archives, [online] 14(1).

ISSN
2375-1924

ABSTRACT

This brief review addresses cancer and human neurodegenerative diseases (HNDDs) from a unified perspective, entirely different from that of current medicine, oncology, neurology, and neuro-oncology. It is based on the classical concepts of homeostasis and allostasis of Walter Cannon and Hans Selye, as well as the extraordinary discoveries of Otto Warburg in the field of cancer biochemistry. Drawing on numerous publications from our group and thousands of other recent high-impact publications, the main objective of this article is to summarize and update what is already known as "The New Anticancer Paradigm." Recently, this perspective on cancer, centered on altered pH, or H^+ dynamics as underlying all the various cancer stages from initiation to metastasis to therapy, has been broadened to include the study of etiology, pathogenesis, and treatment of HNDDs under the same comprehensive and unified approach. At the same time, another positive effect of this conceptualization is to introduce and inaugurate the novel interdisciplinary concept of “The Approaching Hydrogen Age” or “A New Hydrogen Era”.

Keywords: pH abnormalities in cancer etiology - Warburg effect today - Distinctive features of cancer - Therapeutic implications of pH-dependent homeostasis and allostasis - New anticancer paradigm.

Introduction. The New Hydrogen Era.

It is evident that, in its various forms in nature (H+, H1, H2, H3O), hydrogen plays a fundamental role in many aspects of human and animal life (living matter), as well as in the entire planetary ecosystem (inanimate matter). It has been postulated that hydrogen was the first molecule detected after the Big Bang, a simple product that can be easily transformed into other energy compounds. From the field of nuclear physics, we know that a hydrogen bomb would have a much greater destructive power than its atomic counterpart. Other destructive aspects of pH-mediated environmental damage include acid rain and ocean acidification. Conversely, positive news comes from hydrogen-based technologies, which promise to obtain unlimited quantities of clean energy with minimal, or even zero, environmental damage. In this regard, hydrogen obtained through the splitting of water using renewable energy sources, such as solar or wind power, is transformed into clean, waste-free energy as a fuel. Since this methodology uses the most abundant raw material, namely water, it can accumulate large amounts of energy with a very low environmental impact.

In this review, we will introduce and discuss hydrogen dynamics in the context of cancer and then broaden it to include its specular role in human neurodegenerative diseases (HNDDs).

I. The New Anticancer Paradigm: meaningful integrations

> *"Now, all diseases have the same form, but their seat varies. Thus, while diseases are thought to be completely different from one another, due to the difference in where they settle, they all have the same essence and cause. I will try to explain what this cause is in the discourse that follows these words."*
>
> Hippocrates

a) The main topics covered in The New Anticancer Paradigm, are:

a) To advance towards a unified and comprehensive understanding of the essential role of hydrogen ion dynamics [H+] in all areas of modern cancer research and HNDDs [1-5].

b) To synthesize the seminal and latest information on the selective abnormalities of cellular homeostasis and allostasis in cancer cells, primarily represented by profound alterations in intracellular and extracellular pHs (or hydrogen ion concentrations, or H+) [5].

c)To understand their role in the comprehensive and definitive etiology of malignant tumors and the role of oncogenes and growth factors in cancer [6-27].

d) To propose new therapeutic targets, more specific anticancer treatments, as well as less toxic than the current ones, to achieve the induction of selective apoptosis in malignant tumors and leukemias [28-33].

e) To therapeutically exploit the concept that both the intracellular alkalization and extracellular acidification pathognomonic of all malignant tumors ("cancer proton reversal", or CPR) are not simply consequences of abnormal cancer metabolism but rather constitute highly selective biological signals ("hallmarks") of the intimate nature of malignancy. In turn, this CPR has very significant effects on the key processes that determine the initial malignant transformation, the natural history of tumors, their local invasion and the metastatic process [34-36].

B) The main topics that our group has worked on during the last decades are:

1. The Integral and Final Cause of Cancer in the Post-Warburg Era from the beginnings of metabolic cancer research [1-3, 34-51].
2. A New Comprehensive Approach to the Etiopathogenesis and Therapy of Breast Cancer Based on Hydrogen Ion Dynamics [52-60,64].
3. An Integral protocol Based on the New Paradigm to Address the Treatment of Breast Cancer and Other Solid Tumors [51-52, 64,67].
4. The New Anticancer Paradigm in the Etiopathogenesis and Treatment of Malignant Gliomas, Environmental Carcinogenesis and Multiple Drug Resistance (MDR) [28,29,61-81].
5. Hydrogen Ion Dynamics as a Fundamental Link Between HNDDs and Cancer. Its Application to the Treatment of Neurodegenerative Diseases with Emphasis on Multiple Sclerosis [28,29].
6. Curing cancer? Present and future of the New Anticancer Paradigm Focused on the Cellular Homeostasis and Allostasis of Malignant Tumors. Its extension to the Pathogenesis and Therapy of HNDDs and other medical pathologies [32, 49, 60,64 82-87].

II. The Final and Integral Cause of Cancer in the Post-Warburg Era from the Perspective of the New Anticancer Paradigm.

The origins of the integral "New pH-centered Anticancer Paradigm" date back more than three decades [45,49]. From a classical genetic perspective, cancer is thought to include a multitude of diseases requiring a wide variety and combination of different toxic drugs to eliminate each neoplasm. However, from a phenotypic point of view, cancer is a highly organized and uniform disease having tightly and robust "hallmarks and/or cardinal characteristics" independent of genetic and tissue differences. This is logical, since all tumors share most molecular, metabolic, biochemical and pathophysiological characteristics, which are independent of their genetic makeup [44, 45, 54-602-60]. Thus, it can be stated that their main differences are in the cell of every tumor origin and where they settle.

Also in this line, hydrogen ion (proton or H+) dynamics are a more realistic way to express changes in pH and/or acid-base homeostasis, as well as their pathophysiology. Here we summarize the latest advances in this energetic and metabolic paradigm, a rapidly growing model in improving our understanding of the intimate nature of cancer and its treatment, as well as in other scientific and medical areas outside oncology [80-87].

Regarding the etiopathogenesis of cancer, we have previously published the existence of a general

mechanism that underlies all malignant transformations, local growth, progression, invasion and the metastatic process of any tumor. This mechanism, related to H^+, constitutes a well-organized, hierarchical and chronic destructive process, which fully agrees with what Otto Warburg once said: "***The causes of cancer are countless, but they all work through the same mechanism***", an observation with which these authors fully agree. In this sense, the search for a unifying theory of cancer etiology has recently been reconsidered. While numerous intermediate causes of cancer have been discovered and well identified from a metabolic point of view, it can be shown that they all act through the final and integral cause represented by an increase in cellular pH. It is worth noting that an infinite number of intermediate causes of cancer of multiple origins and natures ("driving or triggering factors") are carcinogenic via a single common final pathway: a pathognomonic intracellular alkalosis mainly mediated by the upregulation of the membrane-bound sodium/hydrogen Na+/H+ and exchanger isoform 1, or NHE1 (see Table 1), but also other antiporters and H+ extruders like proton pumps. Indeed, recent publications from three different laboratories have concluded that the Warburg effect can be fully explained by a pathological increase in cellular pH and the consequences of this alkalization on the activation of aerobic glycolysis [34,35,51].

Table 1. Intermediate Causes or Drivers that are Carcinogenic Through Increased Cellular pH and/or Overexpression of the NHE1 Exchanger.

Viruses: human papilloma virus (HPV)
Genetic products: Bcl-2, Bax
Oncogenes and viral products: HPV-E7 in cervical cancer, and Ha-ras, v-mos and c-myc oncogenes in different tumors
Overexpression of other H^+ transporters (PT) and proton pumps (PP)
Chemical carcinogens: arsenic salts in groundwater and polycyclic aromatic hydrocarbons
Chronic and intermittent hypoxia
Aging. What Warburg called "time causes cancer"
Various mitogens: VEGF, EGF, interleukin isoforms, TGF and platelet-derived growth factor (PDGF)
Hormones and cytokines (growth hormone, prolactin, glucocorticoids)
Glucose overload
p53 gene mutations
pH-dependent immune evasion due to acidification of the interstitial tumor microenvironment (TME)

*Modified from reference No. 51.

III. On cancer metabolic pathophysiology.

"We will never cure what we cannot understand first".

Otto Warburg

Nowadays, it is well known that the pathological allostatic situation of cancer cells is characterized by a steady state of metabolic alkalosis, sometimes mild (pHi: 7.3-7.4), but at other times so pronounced that it is hardly compatible with life (pHi: 7.7-7.8) (Table 2) [4]. This is the opposite of what Otto Warburg believed, who assumed that malignant cells exhibited acidosis due to their exaggerated production of lactic acid [1-3]. Furthermore, the specific cellular alkalosis of cancer cells is exactly the opposite of the significant tendency toward intracellular acidosis characteristic of HNDDs [28,29,32].

Table 2. pHi and pHe in Normal Cells, Neurons of Human Neurodegenerative Diseases (HNDDs) and Cancer Cells During Apoptosis and Antiapoptosis.

NORMAL CELLS	NEURONS IN HNDDs	CANCER CELLS
pHi < pHe	pHi and pHe (Acidic)	pHi > pHe
pHi: 7.0–7.1	pHi: 6.2-6.8 (Acidic) (↓pHi pathological apoptosis)	pHi: 7.3-7.8 (Alkaline) (↑pHi pathological anti-apoptosis) (CPR)
	pHe: 6.0-6.8 (Acidic) (↓pHi pathological apoptosis)	pHe: 5.0-6.8 (Acidic) (↓pHi therapeutic apoptosis)
Normal pHi/pHe	Acidic pHi / Acidic pHe	Alkaline pHi/Acidic pHe

In the same line, Figure 1 shows cellular alkalization as the *sine qua non* condition for malignant transformation, as well as being the main anti-apoptotic factor, a fundamental characteristic of multiple drug resistance to antineoplastic drugs (MDR) [28,30,35,36]. This alkalization, along with the secondary extracellular acidification of tumors (TME), leads to a proton reversal (CPR), which is pathognomonic of any malignant tumor. The concatenation of these pathological and energetic changes in inducing and maintained a pathological allostasis drives a coordinated cascade of unstoppable progression and metastasis ending up in the death of the patient [47,48,59].

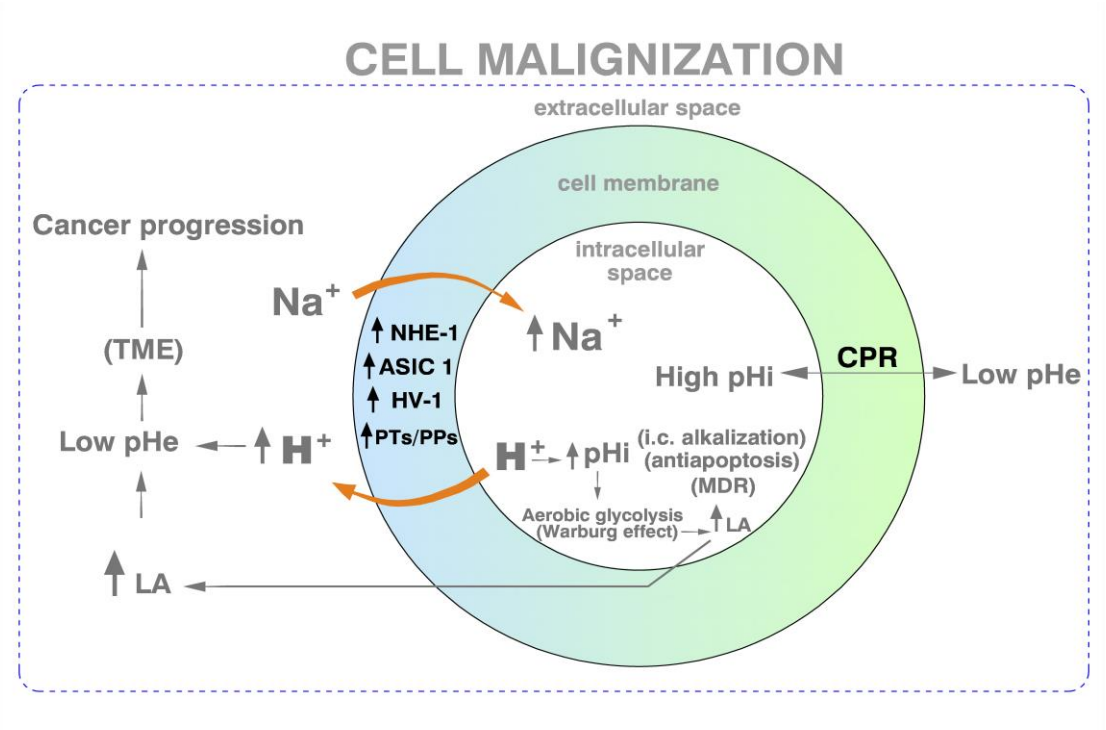

Figure 1. pH-Dependent Interaction Between Ionic Transporters of the Cell in Malignization, Intracellular Alkalization, Tumor Extracellular Acidification (TME), Aerobic Glycolysis and the Warburg Effect.

Legend. Metabolic mechanisms of cellular malignant transformation. Abbreviations: NHE1, isoform 1 of the Na^+/H^+exchanger; ASIC1, acid-sensing ion channel type 1a; Hv1, voltage-dependent H^+ channel isoform 1; PT, proton transporters; PP, proton pumps; CPR, cancer proton reversal; MDR, multiple drug resistance; LA, lactic acid; TME: tumor microenvironment.

IV. Biological Unifications and Therapeutic Implications arising from the New and Wide-Ranged Perspective of Cancer Metabolism. Conclusions and closing Gaps.

This comprehensive perspective of the anticancer paradigm, focused on acid-base energetic homeostasis and allostasis, brings together under a single general concept a biological unification capable of bringing together scientific views until now considered very distant from each other or without any connection between them, like oncology and neurodegeneration [28, 29, 32,45]. These efforts lead to the study of seemingly unrelated phenomena that now present similar metabolic natures, but with opposite and specular pathogenesis.

After integrating the old with the most recent available data on the new paradigm, it can now be stated that the final cause of cancer was never the aerobic glycolysis of malignant cells, or their respiratory impairment, as Otto Warburg defended all his life (1), but rather an essential etiological alkalization [34, 35, 42, 43 47-49, 51,52], a final pathway that also allows a deeper understanding of the most intimate, fundamental and "basic" origin of cancer. Therefore, Warburg's theory of cancer causation is no longer considered the primary cause of cancer, but rather the cellular energy changes related to H+ deficient dynamics and their stimulatory effects on glycolysis [5, 64].

From this broad perspective, it is concluded that the main factor behind the Warburg effect and its aerobic glycolysis, and simultaneously the main cause of cancer, is a selective intracellular alkalization of cells in all solid malignant tumors, mediated by the overexpression of NHE1 or, to a lesser degree, of other cellular proton extruders. In summary, it can also be concluded that this energetic model opens new and unprecedented therapeutic avenues for improving the treatment of cancer [29, 30, 51, 52, 70, 71], and probably also, of certain HNDDs, as it has been considered in recent publications [28, 32 2-60,64]. Indeed, and most recently, complete reviews on the subject of this work [88] fully agree with the parallel pH-perspective of this article as well as with previous publications either of our group or others [28-30, 32,34-36,41,43, 49,51,52,60,64].

Dedication: This article is dedicated to the memory of Alejandra Luna, a brave young girl who died from a glioblastoma multiforme.

Acknowledgments: To the Mercedes Castresana Foundation Vitoria, Spain, for financial help. And to Rebeca Andía Muñoz, for excellent informatic collaboration.

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