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MINI-REVIEW

The Warburg-effects: basic metabolic processes with reference to cancer development and global photosynthesis

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ABSTRACT

One century ago (1920), Otto Warburg (1883–1970) discovered that in liquid cultures of unicellular green algae (*Chlorella* sp.) molecular oxygen (O_2) exerts an inhibitory effect on photosynthesis. Decades later, O_2 dependent suppression of photosynthetic carbon dioxide (CO_2) assimilation (the "green" Warbur geffect) was confirmed on the leaves of seed plants. Here, we summarize the history of this discovery and elucidate the consequences of the photorespiratory pathway in land plants with reference to unpublished CO_2 exchange data measured on the leaves of sunflower (*Helianthus annuus*) plants. In addition, we discuss the inefficiency of the key enzyme Rubisco and analyze data concerning the productivity of C3 vs. C4 crop species (sunflower vs. maize, *Zea mays*). Warburg's discovery inaugurated a research agenda in the biochemistry of photosynthetic CO_2 assimilation that continues to the present. In addition, we briefly discuss Warburg's model of metabolic processes in cancer, net primary production (global photosynthesis) with respect to climate change, trees and other land plants as CO_2 removers, and potential climate mitigators in the Anthropocene.

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Global photosynthesis; cancer; Warburg-effect; photosynthesis

Introduction

In the green cells of cyanobacteria and chloroplasts of algae and land plants (embryophytes), light-driven conversion of carbon dioxide (CO_2) into photosynthetic assimilates is catalyzed by the enzyme ribulose-1,5-bisphosphate carboxylase/oxygenase (Rubisco). However, under current atmospheric conditions (ca. 410 µmol mol^{-1} air CO_2, and about 210 mmol mol^{-1} air molecular oxygen, O_2), the 525-fold higher O_2 level reduces the carboxylase reaction of this key enzyme, resulting in a light-dependent gas-exchange process (uptake of O_2/release of CO_2). This inverse O_2/CO_2-flow is analogous to that occurring during dark respiration, but it does not lead to a net gain of adenosine triphosphate (ATP). In the leaves of plants that display the evolutionary ancient C3 mode of carbon assimilation (sunflower, wheat, rice etc.), this process, called 'photorespiration', leads to a ca. 25% reduction in net photosynthesis (CO_2 assimilation at 25°C). In C4 plants (maize, sugar cane etc.), photorespiratory gas exchange is inhibited by more than 90%, so that net photosynthesis (and the resulting accumulation of carbohydrates) is significantly higher than in C3 species.[1,2]

In this contribution, we summarize the discovery of photorespiration, which can be traced back to Warburg's experiments with suspension cultures of green algae of the genus *Chlorella* (Figure 1). Then we describe the occurrence and significance of this biochemical pathway based on unpublished data obtained on the green leaves of sunflower plants. In addition, we discuss the Warburg effect in cancer research. Finally, we review data on anthropogenic CO_2 emissions relevant to climate change and the role of trees as potential de-carbonizers of the atmosphere.

The Warburg effect in *Chlorella* cells

In order to study the mechanism(s) of photosynthesis, the German biochemist Otto Warburg (1883–1970) introduced a novel experimental system that is still in use today, involving liquid cultures of green freshwater algae of the genus *Chlorella*. In two seminal papers published one century ago, Warburg (1919, 1920) discussed the technical problems associated with the experimental analysis of leaf photosynthesis,[3,4] a process he described as "the photochemical dissolution of carbonic acid." The technique Warburg used in studying photosynthesis consisted of irradiated liquid cultures of *Chlorella* cells (Figure 1) maintained at a constant temperature and provided with a constant stream of CO_2.

It is not widely known that unicellular green algae of the genus *Chlorella* (and related taxa) not only exist in ponds; they also inhabit the bark of trees, from which they can easily be isolated. Figure 2 shows a green leaf of a Californian Cost Live Oak (*Quercus agrifolia*) and a piece of green-colored bark from the same tree. Unicellular green algae can be scratched from the surface and maintained in liquid culture. Hence, Warburg's model organisms (i.e., epiphytic unicellular *Chlorella*-like algae) can be observed as green deposits on the bark of trees and the walls of buildings, etc. Importantly, these *Chlorella* cells[5] perform photosynthesis in the evolutionary ancient C3

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Dedicated to the memory of Winslow R. Briggs (1928–2019), a pioneer in plant photophysiology.

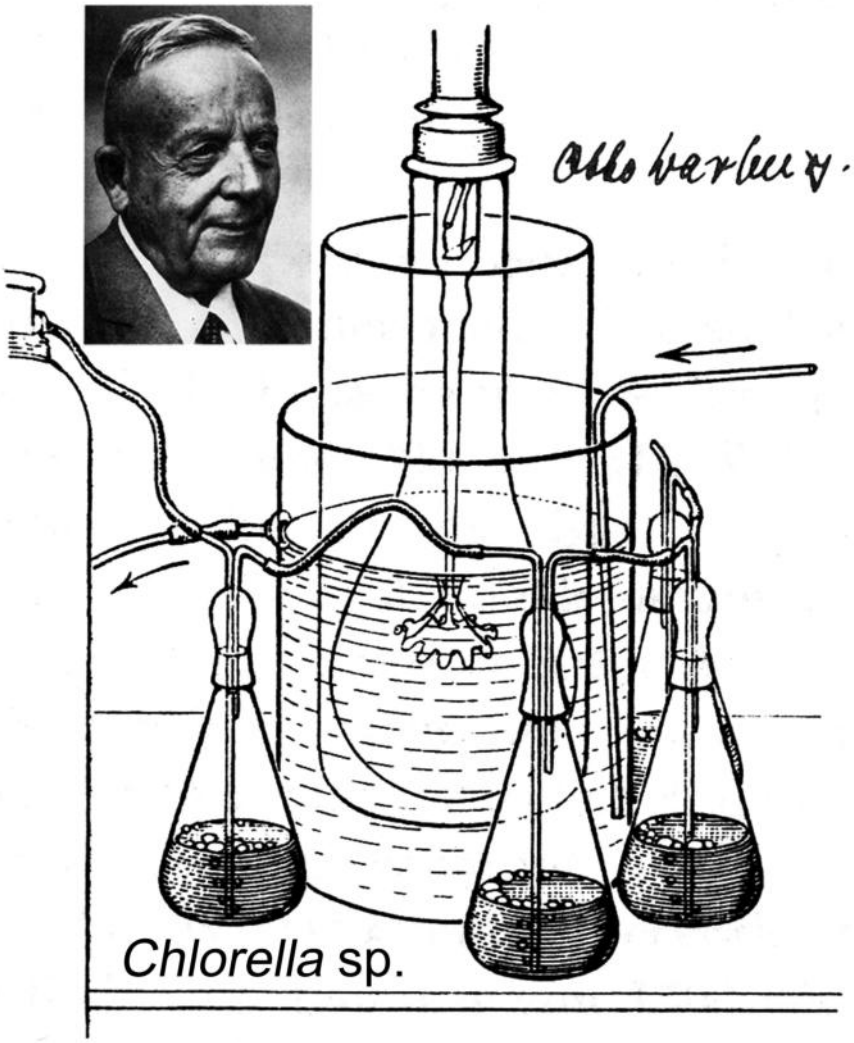

Figure 1. Experimental set-up used by Otto Warburg one century ago for the continuous cultivation of green algae (*Chlorella* sp.) in Erlenmeyer flasks. In the center, a light bulb was arranged in such a way that the cultures received optimal irradiation. In order to achieve maximal assimilation rates, the *Chlorella*-cultures were aerated (O_2 plus CO_2, arrows). The portrait of Warburg (with signature) was added to the image (adapted from Warburg 1919, ref.[3]).

mode, which corresponds to that in the green leaves of sunflower plants and other embryophytes that display this mechanism of carbon assimilation (Figure 3).

Warburg (1920)[4] quantified the atmospheric oxygen (O_2) produced by the *Chlorella* cells in the light (Figure 1) with sophisticated manometric techniques that he invented ("the Warburg manometer"). Using this technique, he made the key discovery that light-mediated (photosynthetic) O_2-production of *Chlorella* cells, maintained at saturating CO_2 concentrations, is inhibited by oxygen.[4]

This "green" Warburg-effect was later confirmed by experiments carried out on the leaves of land plants.[6] *Chlorella* and other members of the Chlorophyta can be interpreted as forming a virtual "evolutionary green lineage", because they are phylogenetically related to land plants (embryophytes).[7–9] Therefore, experiments with green algae are valuable model-studies for the elucidation of C3 photosynthesis. Based on this view, we conclude that "*Chlorella*" is a good proxy for an ancient land plant that employed the inefficient mode of C3 carbon assimilation.

The "Warburg effect" in oncology: peculiarities in cancer cell metabolism

Two years after his second article on "oxygen and *Chlorella*" appeared in print, Warburg[10] published the first of his many papers on cancer metabolism, leading eventually to what is known today in cancer research as the "red Warburg effect". Based on studies of a small number of tissues, Warburg reported that even under aerobic conditions malignant cells tend to produce most (though not all) of their energy through glycolysis, the enzymatic breakdown (fermentation) of glucose to lactate, rather than through more energetically efficient oxidation processes. In essence, in the early 1920 s, Warburg

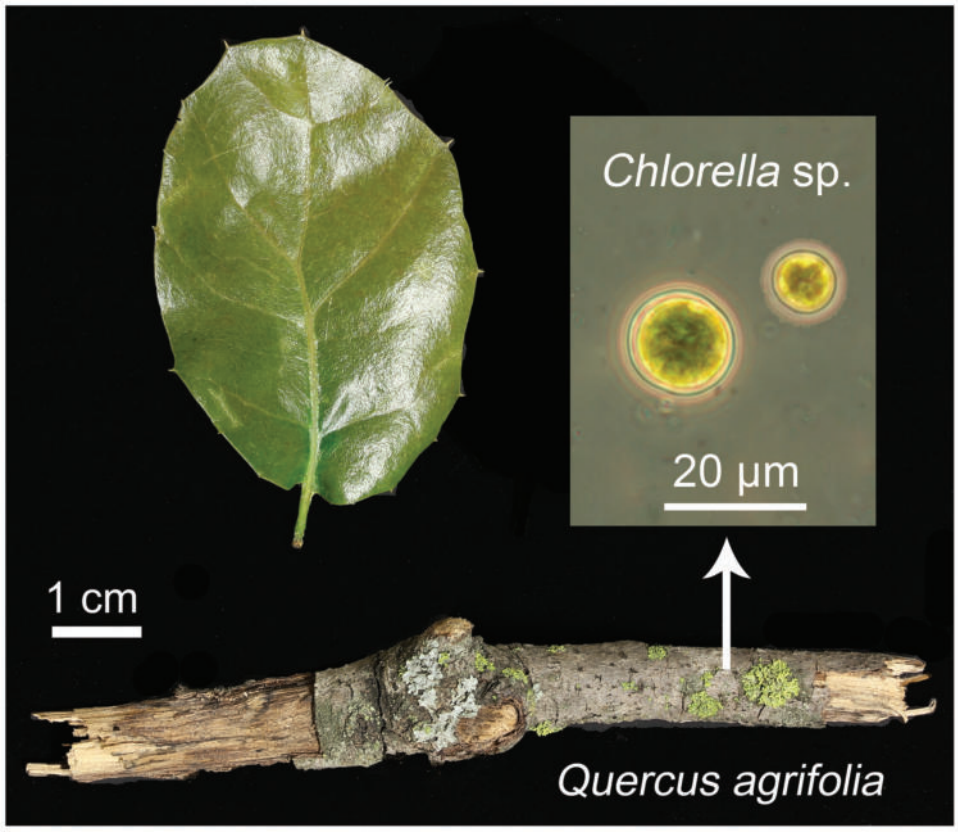

Figure 2. Branch and fully expanded green leaf of a Coast Live Oak (*Quercus agrifolia*), growing in front of the Carnegie Institution, Stanford, California. On the surface of the branch, single-celled green algae can be extracted that, at least in part, belong to the genus *Chlorella* (inset). Epiphytic green algae have been used by Otto Warburg and others to analyze the mechanisms of CO_2-exchange. Note that both the oak and the green algae perform photosynthesis via the C3-mode of carbon assimilation.

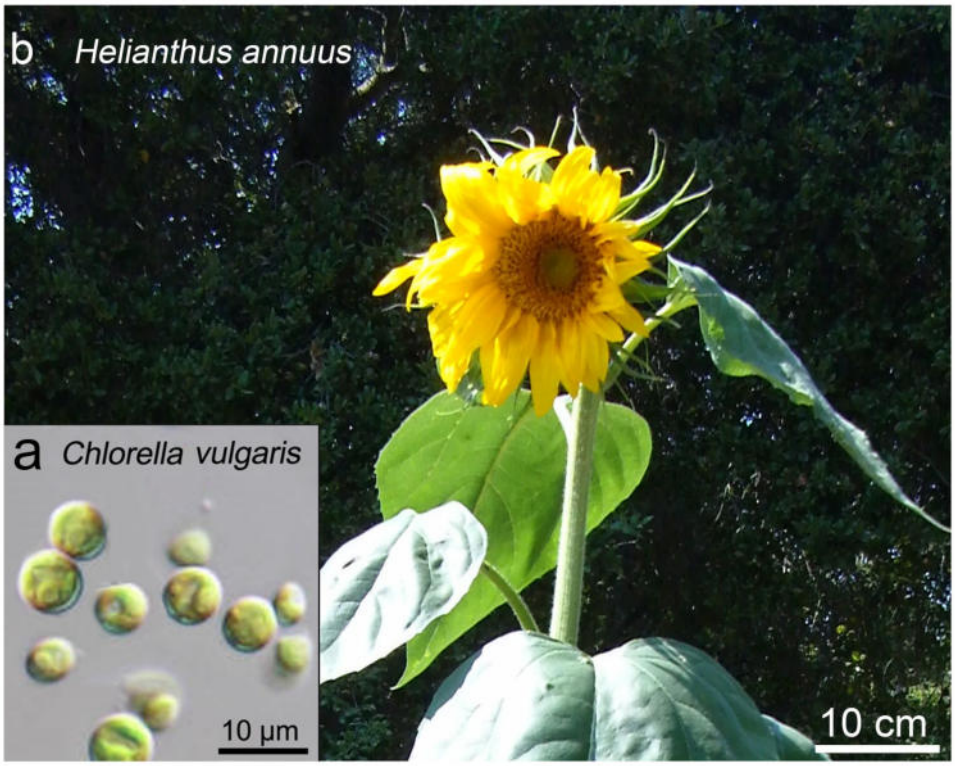

Figure 3. In vitro-system versus intact plant for the study of photosynthesis. Liquid cell culture containing freshwater algae (*Chlorella vulgaris*) (a) and mature sporophyte of a California sunflower plant (*Helianthus annuus* var. Sunspot) (b). Single cells (globules) and intact organs (leaves), respectively, were used for the analysis of the effects of atmospheric oxygen on the rate of CO_2-assimilation.

found evidence in cancer metabolism of violations of the Pasteur-effect, i.e., the expected inhibition of fermentation in the presence of oxygen.

By the end of the 1920 s, Warburg's claims were already being severely criticized by other researchers, including the English biochemist Herbert G. Crabtree (1892–1966), who tested Warburg's findings against a far more diverse sample of tissues.[11] While partly confirming Warburg's work, Crabtree also found high levels of metabolic heterogeneity in cancer tissues, including wide variation in the use of oxidation and glycolysis, even in single cell lineages. He also identified non-cancerous tissues that, in the presence of oxygen, extensively used glycolysis in energy production; and, conversely, malignant tissues that in the same conditions showed profuse signs of oxidation.[12]

In essence, by 1929 Crabtree had turned up early suggestions of metabolic plasticity in both healthy and malignant tissues, many decades before studies of that phenomenon became a major focus of cellular research. Crabtree also noted that Warburg himself had recently discussed healthy tissues that heavily depended on glycolysis in the presence of oxygen, undermining a key claim of the Warburg effect, that was the sole hallmark of cancerous but not normal cells.[12]

For decades, Warburg and his colleagues responded to similar criticism with violent polemics, increasingly arguing against all evidence that heavy dependence on glycolysis was solely found in malignant cells. In a famous 1956 paper in *Science*, aimed at Sidney Weinhouse (1909–2001), who criticized Warburg much more fully than Crabtree, Warburg argued that dependence in cancer on glycolysis was the result of "respiratory damage", which he now claimed as the prime cause of all cancer.[13] He elaborated on this in a lecture given at the Lindau Nobel Laureate Meetings in 1966, further expanded in revised form and published in 1969. By then, Warburg was convinced that the idea of respiratory damage pointed to a method to prevent all forms of cancer.[14] All that was needed was to add sufficient respiratory enzymes to food to assure that "all growing body cells be saturated with oxygen." There was in fact "no other disease whose prime cause is better known" than cancer, and avoiding it could "be accomplished by everybody, everywhere, at any hour. Unlike the prevention of many other diseases, the prevention of cancer requires no government help, and not much money" (ref. [14]).

Warburg's biographers report that in the early 1900 s, while still a student, he decided that curing cancer was his life-long goal.[15] At the end of his life, Warburg had convinced himself and a few colleagues, including Dean Burk (1904–1988), that he had achieved that goal. Given his huge influence as a Nobel laureate and the proclivities of Warburg and Dean to push his agenda polemically, this claim arguably held back progress in cancer research for many decades.[16]

The development of increasingly powerful "omics" tools in the last half decade has led to a massive reassessment of Warburg's work on cancer, approached from the broad perspectives of network models and systems biology. Data in Google Scholar suggests that an astonishing 6,000+ papers were published on the Warburg effect in 2018 alone, over ten times the number published just five years earlier. The most recent are filled with elaborate discussions of plasticity in cancer pathways, tied to nonlinear feedback loops and rapid shifts in gene regulatory networks, that regulate a large number of other metabolic pathways besides just oxidation or glycolysis.[16] As a whole, work in the field today has much more in common with Crabtree's finds of metabolic heterogeneity in tissues 90 years ago than anything found in Warburg's work. Taken together, this fact illustrates how thoroughly systems biology[17] has overturned the reductionism that characterized Warburg's work on cancer by the end of his life.

Björkman's experiments on green leaves

Later attempts to corroborate Warburg's studies in photosynthesis research have also led to new discoveries, but this time in more positive ways. Some of those discoveries have led to increasingly sophisticated views of photosynthesis, critical to modeling parts of climate change. Unfortunately, attempts to use that modeling to build future predictions of global warming are hampered by many of the same kinds of complexities that "omics" studies have brought to cancer research, a topic to which we return at the end of the article.

In one seminal study dealing with Warburg's work, Björkman (1965),[18] focusing on photorespiration in land plants and not algae, compared the rates of photosynthetic CO_2-uptake at saturating light intensities under normal air (21% O_2) and near zero (ca. 2 %) oxygen concentrations. The plants he studied included species from the genera *Plantago, Mimulus, Solidago, Polypodium, Sagittaria*, i.e., taxa belonging to different families living in contrasting habitats. Björkman's results showed that, compared to normal oxygen levels, the rate of photosynthesis in these plants was a remarkable 28% to 33% higher at 2% O_2 than at normal oxygen concentrations. Conversely, CO_2-assimilation was strongly inhibited by 21% oxygen, with an average reduction in photosynthesis of 30% (ref. [18]).

Based on these and other data, Björkman concluded that "at least as far as carbon dioxide fixation is concerned, photosynthesis would proceed at a higher rate if the oxygen concentration of the atmosphere were lower." Moreover, paradoxically, "the present photosynthetic activity of land plants is limited by a product of the photosynthetic process itself" (ref. [18], p. 454). In these sentences, the phenomenon later called the "oxygen paradox" was noted for the first time.[19]

In a later study, Björkman et al. (1968)[20] analyzed the effect of lowered oxygen concentrations (5% O_2 instead of 21 %) on dry matter production in land plants. The plants were grown at 0.03% CO_2 in continuous white light (24°C). Figure 4 shows a representative experiment, using 5-day-old bean (*Phaseolus vulgaris*) seedlings as a typical C3 species. Over a 6-day period, plant growth was strongly promoted by lowering the O_2 concentration from 21% (ambient air) to 2.5% (hypoxic conditions). The dry mass increase of entire "hypoxic" *Phaseolus* seedlings (root, stem, leaves) was about twice as high as in the normal air-control, indicating that net CO_2-assimilation via photosynthesis was suppressed by 21% atmospheric oxygen.

Similar results were obtained when uniform cuttings of Monkey flower (*Mimulus cardinalis*) were studied. As in the case of the *Phaseolus* seedlings (Figure 4), dry matter production was strongly enhanced by low O_2 in this C3 species.[20]

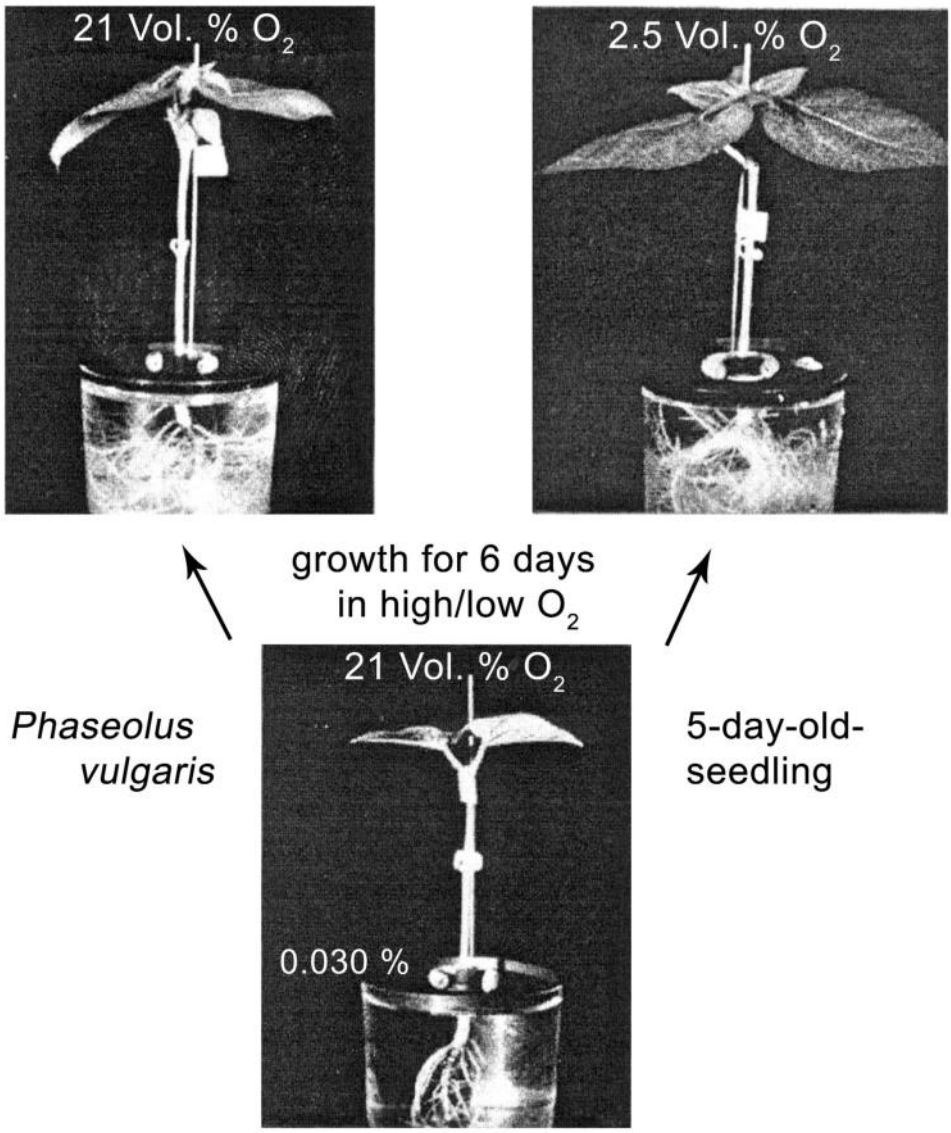

Figure 4. Effect of a reduction in atmospheric oxygen-level (O_2) on growth of the primary leaves, and dry matter accumulation in bean (*Phaseolus vulgaris*) seedlings. The plants were raised in aerated nutrient solution at 0.03 Vol. % CO_2 and 21.0 vs. 2.5 Vol. % O_2, respectively. Note that the primary leaves are much larger in the low oxygen-environment (adapted from Björkman et al. 1968, ref.[20]).

Finally, the authors analyzed the effect of O_2 reduction from 21% to 5% in juvenile maize (*Zea mays*) plants, which perform carbon assimilation via the more complex C4 mode of photosynthesis. In contrast to the drastic effect on CO_2 assimilation measured in *Phaseolus* and *Mimulus*, only a very weak O_2 reduction response was recorded in *Z. mays*, which was found not to be significant.[20] Hence, about 50 years ago, it was discovered that the inhibitory effect of O_2 on leaf photosynthesis occurs only in C3 plants, but not in C4 species, a finding of importance in modeling the differential effects of photosynthesis in various plant species on climate change.

Experiments on the leaves of sunflower plants

The domestic sunflower (*Helianthus annuus*) is not only an important crop species for oil production, but also a model organism for basic plant research. Recently, Kutschera and Briggs[21,22] analyzed phototropic solar tracking in the upper third of the stem of 12-week-old *H. annuus* individuals raised at the Carnegie Institution in Stanford, California (Figure 3 (b)). This study yielded the unexpected result that an optimization of leaf photosynthesis may not be the key selection pressure for the evolutionary development of this unique plant behavior. Rather, a shade-avoidance response may be involved in dense populations.[21,22] While more research is required to corroborate this hypothesis, this work adds new suggestions to other evidence that plant phenotypes arise from complex dynamic interactions of organisms with the environment. Understanding these processes is essential for the advancement of basic plant research and its applications, including those pertinent to parts of climate science.[23]

To achieve this, accurate assessment of rates of photosynthesis are essential, requiring sophisticated tools and protocols, especially under field conditions.[24] Chlorophyll fluorescence measurements are often used to estimate photosynthetic properties by employing, for example, the LIFT approach.[25] Notably,

the combination of chlorophyll fluorescence and gas exchange measurements have recently led to substantial improvements in our understanding of photosynthetic processes. Focusing on gas exchange measurements, an increasing number of scientific publications have made use of portable photosynthesis systems, allowing the quantification of light-driven intra-chloroplastic processes, including photorespiration.[26]

The data shown in Figures 5 to 7 were obtained using the equipment for quantification of photosynthesis (CO_2 assimilation) at normal and reduced atmospheric oxygen concentrations (21% vs. 1 % O_2), as described in a previous report.[25] The photon fluence CO_2 assimilation curve of Kutschera and Briggs[21] shows that, at 500 to 600 µmol photons m^{-2} s^{-1} (i.e., within the linear range of light treatment), sunflower leaves display a strong, suboptimal rate of net photosynthesis. We applied this intermediate level of white light to a representative *H. annuus* leaf and measured (at a concentration of 0.04% CO_2 /21% O_2) a steady carbon dioxide uptake-rate of ca. 16 µmol CO_2 m^{-2} s^{-1}. In the presence of < 1% O_2, the rate of photosynthesis was 33% higher than in the control (Figure 5). Hence, the O_2 effects measured by Björkman and coworkers[18,20] on other C3-dicot species are reproduced here, using *H. annuus* as experimental plant material and more sophisticated methods for the quantification of CO_2-assimilation.

After an abrupt lowering of the light intensity (photon fluence) from 550 to 80 µmol m^{-2} s^{-1}, a new, steady-state level of CO_2-absorption was recorded. Moreover, under "normal" conditions (21% O_2), a "post-illumination CO_2 burst", described for the first time by John P. Decker (ref. [27]) can be detected (Figure 5). As detailed elsewhere, this phenomenon led to the discovery of photorespiration.[6,25]

The compensation point and photorespiration

Twenty-six years ago, Berry et al. (1994)[28] summarized data on the magnitude and significance of the carbon dioxide compensation point in the leaves of C3 plants with reference to the global CO_2-balance. When a green leaf of a C3 plant is placed into a closed plexiglas chamber and illuminated, it either absorbs or releases carbon dioxide until the CO_2 concentration reaches a steady-state value. At this CO_2-compensation-point (CP), net photosynthesis (carbon exchange) is zero. The CP value (ca. 40 µmol CO_2 per mol air at 25°C and 21% O_2) is independent of light intensity (above a threshold value), dependent on atmospheric oxygen concentration and temperature, but largely independent of the (C3) plant species investigated. Figure 6 shows net photosynthesis-values obtained at three different photon fluences as a function of intracellular concentration of CO_2, measured on a leaf of a sunflower plant (Figure 3(b)). The curves at 500, 250 and 100 µmol photons m^{-2} s^{-1} intersect at ca. 38 µmol CO_2 per mol air. This value represents the CO_2-CP in *H. annuus* and is indistinguishable from that measured on the leaves of *Xanthium strumarium* and other C3-species.[28] The dependency of the CO_2-CP on the level of atmospheric oxygen is shown in Figure 7. At 21% O_2, the CP is ca. 38 µmol CO_2 per mol air and there is a linear relationship between CP and a lowering of O_2 levels. At 5% O_2, the CP value is ca. 13 µmol CO_2 per mol air, and at lower oxygen levels the CP of sunflower approaches that of the C4 plant maize (ca. 1–2 µmol CO_2 per mol air; see ref. [25]).

Hence, O_2 appears to compete with the active site of Rubisco, which is in accordance with the fact that this inefficient enzyme confuses its substrates (O_2 for CO_2). These intracellular processes, which evolved as a coordinated biochemical chain of reactions in the

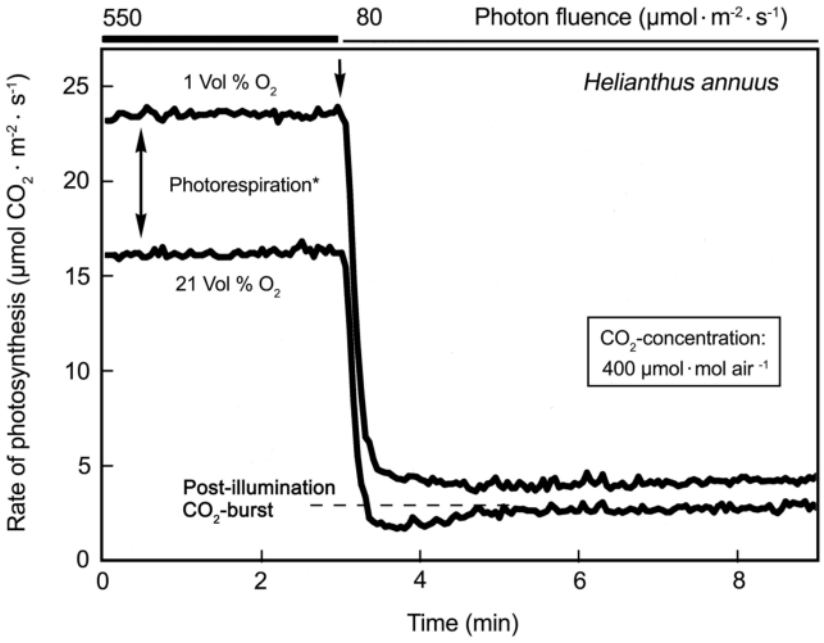

Figure 5. Representative gas-exchange curves measured on an intact leaf from a 4 week-old sunflower plant. The rates of photosynthesis, at 21 vs. 1 Vol. % O_2, respectively, were measured with a LI-6400 Portable Photosynthesis System (LI-COR, Inc., Lincoln, Nebraska) as described by Kutschera et al. (ref.[25]). After 3 min, the photon fluence was reduced from 550 to 80 µmol · m^{-2} · s^{-1}. Note the post-illumination CO_2-burst at ambient O_2-level (21 Vol. %).

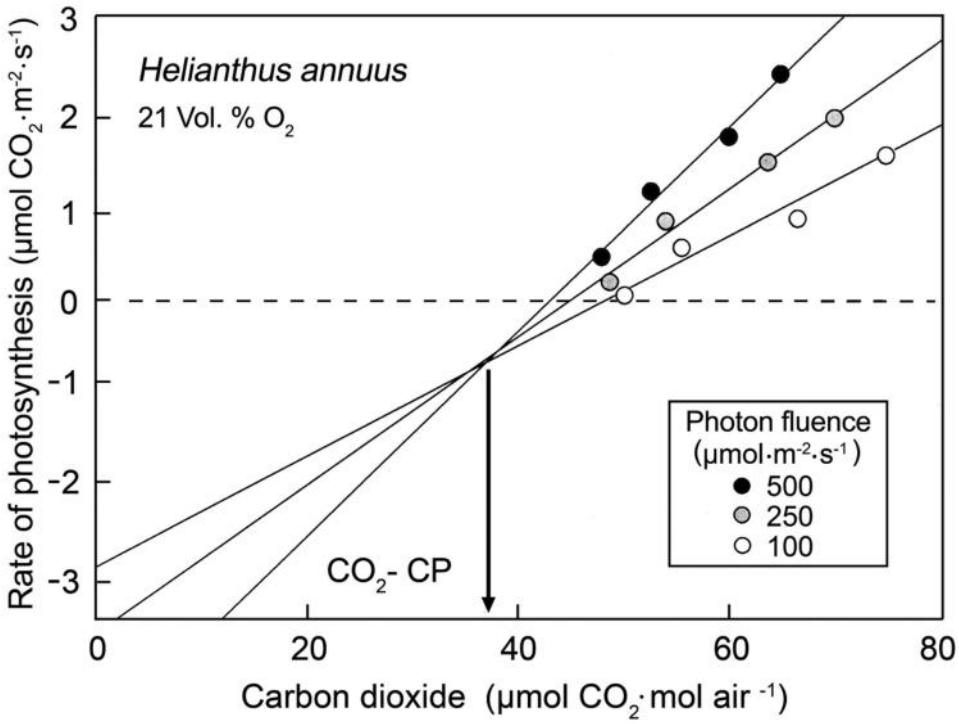

Figure 6. Quantification of the carbon dioxide compensation point (CP) in the leaves of 4 week-old sunflower plants. The rate of photosynthesis was measured at ambient oxygen concentration (21 Vol. %) at three different photon fluences, and the CO_2-CP was determined graphically (arrow).

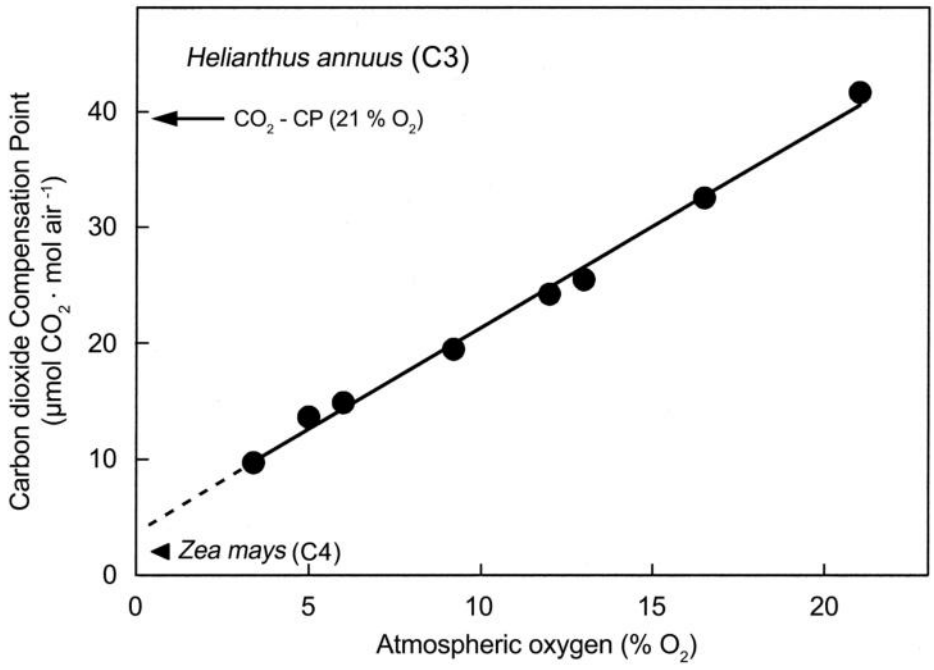

Figure 7. The dependency of the carbon dioxide compensation point (CP) on the oxygen concentration of the air in leaves of 4 week-old sunflower plants. At ambient oxygen concentration (21 Vol. %), the CO_2-CP is ca. 39 µmol CO_2 mol · air^{-1} (arrow). The corresponding value for maize leaves (*Zea mays*) at 21 Vol. % O_2 is indicated (arrow head).

chloroplasts and neighboring organelles (peroxisome, mitochondrion), are depicted in Figure 8. The scheme illustrates photorespiration, with the focus on the exchange of metabolites.

Carbon dioxide enrichment, gross primary production, and global greening

The concentration of carbon dioxide (estimated pre-industrial levels ca. 0.029 %, i.e., 280 µmol CO_2 per mol air, or ppm, see

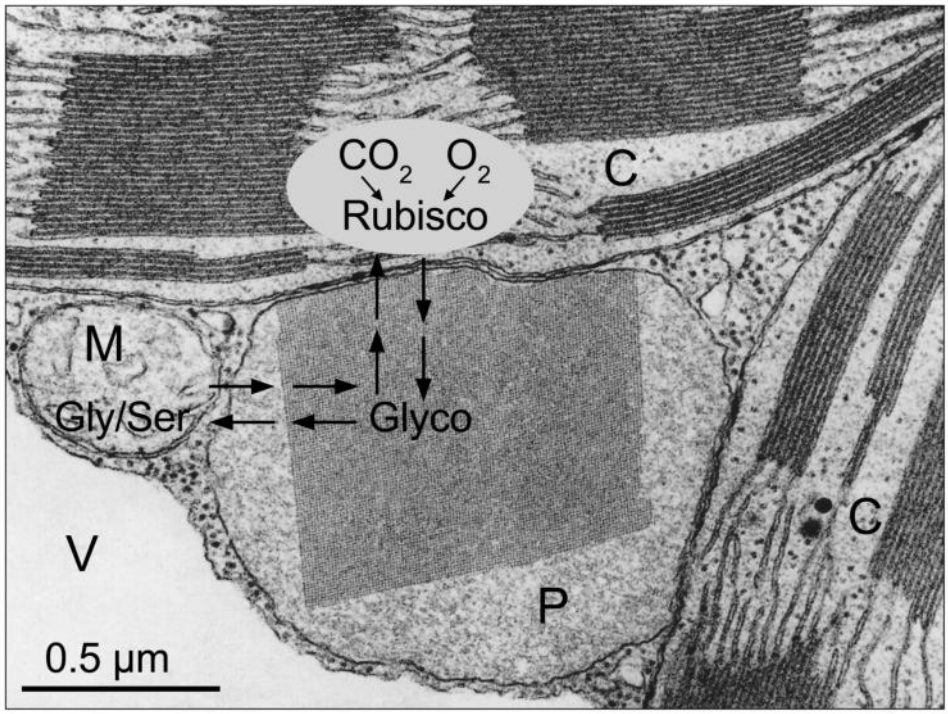

Figure 8. Transmission electron micrograph of the cytoplasm and vacuole of a mesophyll cell of a C3 plant (*Nicotiana tabacum*), showing two neighboring chloroplasts (C), a peroxisome (P, with the enzyme catalase) and a mitochondrion (M). The photorespiratory pathway is indicated. Gly/Ser = Glycine/Serine, Glyco = Glycolate; Rubisco = Ribulose-1,5-bisphosphate carboxylase/oxygenase. Rubisco can bind to the substrates carbon dioxide (CO_2) and molecular oxygen (O_2).

ref. [29]) steadily increased since ca. 1880 to the present. When Björkman et al. (1968)[20] published their seminal article, "normal" CO_2 concentration was ca. 300 ppm; Kutschera et al. (2010)[21] reported an average ambient CO_2 level of 350 ppm; and the experiments described here were performed at 400 ppm CO_2, which approximately corresponds to the value measured in 2020 (see the atmospheric CO_2 measurements at Maona Loa: https://www.esrl.noaa.gov/gmd/ccgg/trends/full.html).

Carbon dioxide enrichment-experiments have shown that in C3 plants, like sunflower, wheat, and rice, etc., elevated carbon dioxide results in enhanced growth, due to stimulation of photosynthetic CO_2 assimilation (dry matter accumulation).[29,30] Accordingly, anthropogenic CO_2 production throughout the 20th century appears to have influenced terrestrial gross primary production (GPP), defined as the amount of CO_2 fixed via Rubisco in the leaves and stored in the woody parts of land plants.

Recently, Campbell et al. (2017)[31] documented a large (31% ± 5 %) historical growth in global GPP since ca.1880, much of it attributed to the rise in CO_2 atmospheric concentrations. Figure 9 shows this key finding, based on a Monte Carlo global modeling approach. These results suggest that the planet's current land plants remove ca. 30% of yearly anthropogenic CO_2 emissions from the atmosphere, storing this extra carbon (corresponding to ca. 5% of the planet's natural occurring CO_2 release each year) in wood, suberin, and other stable biomolecules.[32] These quantitative studies are in accordance with recent satellite data that have documented increasing leaf area of vegetation due to CO_2-fertilization as a result of anthropogenic CO_2-emissions (70 %) and other factors (improvements in human land-use management etc., ca. 30 %). In a detail study, Chen et al. (2019)[33] have shown that, as a result of this "greening of the world", total cereal production in China and India have increased by ca. 43 and 26 %, respectively, during 2000 to 2017. As shown in a Review Article on "global greening", a significant enhancement in the land carbon sink occurred, combined with a cooling of the terrestrial surfaces.[34]

Despite this plant-based CO_2-removal, radical reductions in carbon emissions are necessary, presumably enabled by replacing carbon fuels by large-scale net zero-emissions technologies (NETs) involving wind, hydroelectric, solar, and tidal power, etc., or by proposed artificial photosynthesis methods.[35–37] Far in the future, renewable energy sources could portentially also be combined with a wide range of proposed carbon capture and sequestration methods, most of which sill at the drawing board stage.[38,39]

Conclusions

This article, which commemorates the 100th anniversary of Otto Warburg's discovery of photorespiration (1919, 1920),[3,4] traces the steps Warburg and the many researchers he inspired took in studying key metabolic pathways in plants and animals. Science has changed radically in the century since Warburg's early work; and it would be difficult to name any researcher who has had nearly as

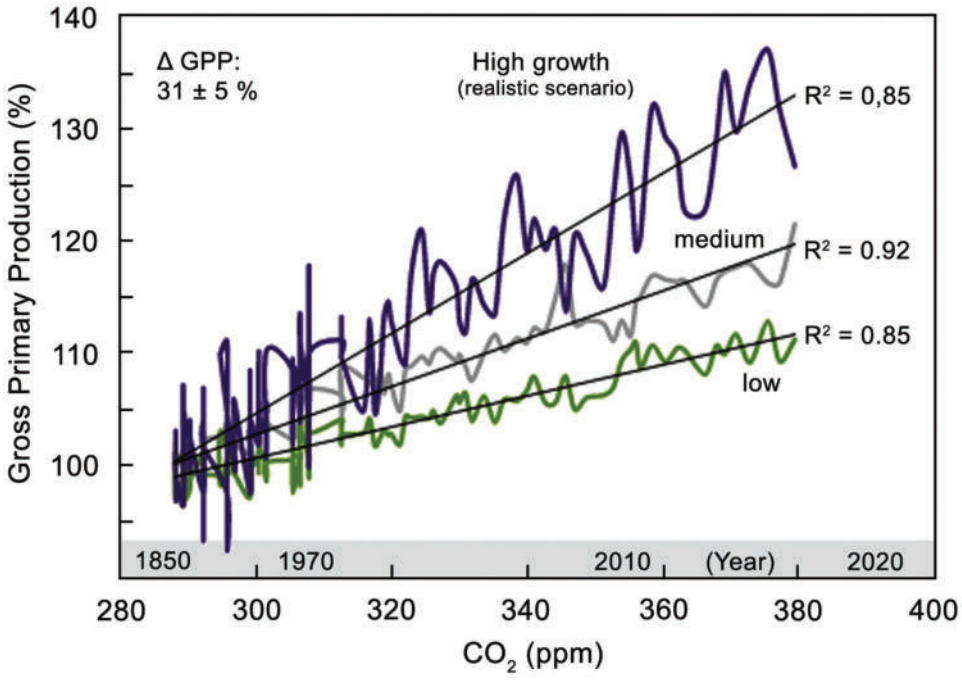

Figure 9. Computer model showing global terrestrial gross photosynthesis (primary production) as a function of the carbon dioxide (CO_2) level of the air. At high productivity (real-world scenario), a ca. 30% enhancement in global terrestrial photosynthesis occurs, which is the result of human-made CO_2 that has been released into the atmosphere (anthropogenic carbon-emissions) (adapted from Campbell, J. E. et al. 2017, supplementing online Figure 6, ref.[31]).

profound an effect on both plant and animal biology as Warburg did in his era.

Reviewing Warburg's work a century later, we can learn as much from his errors as from his discoveries. Biology in Warburg's time was guided by reductionist ideals that above all valued simplicity in modeling reality. Today we know that we inhabit a world that is anything but simple: stochastic and nonlinear processes, regulated by complex feedback mechanisms, can be identified in every field from plant physiology[38] to cancer research[16] to studies of human impacts on ecology, all of which are intimately linked. To ignore these connections and to propose the use of reductionist models to treat disease or mitigate climate change is to ignore the lessons learned from a century of continuous discussions of Warburg's work. The findings from systems biology that eventually dethroned the Warburg-effect in cancer research warn us against taking reductionist approaches to climate change, where miscalculations pose genuine existential risks to billions of humans and countless other life forms, from microbes to land plants and animals, which are our essential companions on the planet Earth.[40]

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