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REVIEW ARTICLE

George Cotzias' achievements and levodopa therapy: Their contribution to medical science

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Abstract

George Cotzias was a tireless physician who conducted a variety of studies, focusing mainly on neurological diseases. After leaving his medical studies to serve the Greek army voluntarily, Cotzias was relocated to the United States of America where he continued his studies at Harvard University. His first research was on hypertension, metabolism, and energy balance issues. Later on, he became the chief director of a project on chronic manganese poisoning. It was there that he identified the common characteristics between chronic manganese poisoning and Parkinson's disease, which led him to be referred to the cyclotron. Furthermore, he noted the presence of dyskinetic, motor fluctuation abnormalities, and hypersensitivity caused by levodopa (L-DOPA). He was a pioneer in demonstrating the revolutionary practical benefits of L-DOPA therapy. This accomplishment was a consequence of his patience and insistence to monitor closely, even with cinematographic recording, the health condition of his patients while modifying the L-DOPA dose for optimal health benefit. Cotzias also developed drugs combining L-DOPA and dopamine agonists, defined the phenomenon of the brain's ability to store chemical memory, and established the correlation between L-DOPA and cancer. His work significantly improved the lives and longevity of many individuals. Before his death from cancer in 1977, Cotzias received numerous distinctions and awards for his outstanding contributions to medicine. After his death, his legacy was honored through the establishment of various scholarships, professorships, conferences, and a movie dedicated to his medical achievements.

Keywords: Cotzias; Levodopa; Parkinson's disease; Neurodegenerative diseases; Neuroscience; Neurology; Medicine

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1. Introduction

The investigation of Parkinson's disease (PD) began in 1817 when James Parkinson first described it as a separate neurological disease.[1-9] People with PD experience many endogenous and exogenous irregularities.[10-17] PD is estimated to be the second most prevalent neurodegenerative disease.[18-25] Its characteristic pathological features include injury to the substantia nigra (SN), neuronal loss, neuromelanin depletion, and dopamine deficiency within the SN.[21-33] The most widely recognized movement distortions of PD are bradykinesia and rigidity.[34-42] Yet, numerous other voluntary and involuntary movement impairments have also been documented.[43-51] The presence of gait

disturbances represents another hallmark characteristic of PD.[39,42,44,47,51] These motor deficits affect the patient's quality of life (QoL).[20]

George Cotzias was born in Greece.[1,7,33,38] Cotzias studied at leading educational institutions in Greece and the United States of America (USA).[7,33,38,46] His first distinction was at Harvard University as one of the top graduates.[1,7,33,38,46] He received specialized training at New York's leading hospitals.[1,7,38]

Cotzias emphasized the importance of existing knowledge on levodopa (L-DOPA), identified novel L-DOPA-related properties, and developed combination therapies involving L-DOPA and dopamine inhibitors. He became the pioneer in uncovering the practical therapeutic effects and previously unrecognized side effects of L-DOPA in the treatment of PD.[52-56] Before Cotzias, many physicians have tried to translate the theoretical benefits of L-DOPA into clinical practice through extensive studies, but all had failed.[41,47,55-58] Cotzias used science and art to be sure and precise about L-DOPA features.[2,3,7,8,19,21,26,33,47,59] It was because of Cotzias that the resistance to neurodegenerative PD treatment was addressed.[1,7,30,33,46,55,60]

The conclusions of Cotzias on L-DOPA were verified by many other scientists.[61] L-DOPA was proven to be the standard, cheapest, and most successful PD therapy.[35,42,62-67] Providing L-DOPA to Parkinsonian patients has been proven to be a synonym for longer life expectancy and improved QoL.[35,37,66,68,69] It was a great gift for medicine, the health condition, and the lives of many PD patients.[46,66,68,70-72] They were "awakened" and found themselves from being breathing statues to having the ability to perform daily activities.[73,74] Oliver Sacks named his book "Awakenings" after being impacted by Cotzias using the term "awakenings" to describe L-DOPA's effect.[74] At present, the movie "Awakenings," based on the book by Oliver Sacks, reminds laymen of the importance of translating L-DOPA from theory to practice.[75] Certain allegations about the neurodegenerative and toxical properties of L-DOPA were not substantiated.[17,22,37,41,69] Another unique achievement of Cotzias was the formulation of carbidopa/L-DOPA medicine.[1,3,7,19,32] Within a year Cotzias published the results of carbidopa/L-DOPA, the first oral formulation of this therapy became commercially available.[3,5,32] Its efficacy in treating PD and gastroenterological problems led to the development of an intestinal gel formulation in Sweden.[5,10,19]

Later, a skin patch option of carbidopa/L-DOPA was produced.[2,5,8,32] Beyond its use in neurological disorders, L-DOPA was also effective in curing other diseases.[56,72] It was an essential tool for a further explanation of other illnesses, not always neurological.[7,56] At Brookhaven National Laboratory (BNL), where he focused on cyclotron research,[7,38] Cotzias began studying manganese poisoning[7,38,45,46] and catecholamines.[7,38,53] Cotzias discovered the ability of the brain to remember the chemical content of a drug and respond to it upon reintroduction.[7] Even while struggling with cancer, Cotzias never stopped working on challenging research studies.[7,46] He stated that L-DOPA deficiency could be an early indicator of future breast cancer.[7]

Cotzias received numerous international awards and distinctions.[1,2,7,38,46] After his passing, his body was returned to Greece,[3,46] where state-organized funeral was held.[46] Greece further honored him by issuing a commemorative stamp bearing his image and his name.[1,7] Nowadays, many academic courses, events, and scholarships are named after him.[7] The current article was written to provide a concise biography of George Cotzias as a mark of honor to his memory and all his great novel achievements. Furthermore, this article intends to provide a comprehension of how Cotzias created the successful formula of L-DOPA, the revolutionary therapy. The article also explores how Cotzias leveraged the new research models to combine L-DOPA with other substances, extending its application to the diagnosis and understanding of other diseases. In addition, this work seeks to highlight the significance of detailed scientific observation in achieving medical breakthroughs. Another aim of this article is to have a better comprehension of the nervous system and consider seriously the possibility of restoring health in PD patients. Finally, the article provides a comprehensive review of PD and its evolving treatment modalities, from past to present.

2. Brief history of PD

PD named Kampavata[1-3] was first mentioned in Ayurvedic texts between the 5th and 12th centuries.[1] However, James Parkinson, through his book "An Essay on the Shaking Palsy" published in 1817, was the first to define the standard symptoms of PD. His work also introduced the pathophysiological framework that was recognized by the medical community, classified PD as a distinct neurological disease, and inspired many researchers to pursue further investigations on the disease.[1-9]

PD is characterized by internal as well as external disorders.[10-17] Affecting no fewer than 10 million people globally, it was defined as the second most common and progressive neurodegenerative disorder.[1,18-25] The disease impacts the patient's QoL.[20] The distinguishable internal abnormality and the most studied and strongly damaged part of the brain in PD are the SN, a component of the basal ganglia.[5,11,15,21,26-28] The SN is composed of neuromelanin, over 1,200,000 neurons, and high levels of dopamine - a

neurotransmitter crucial for regulating movement, which becomes dysregulated in PD.[10,17,18,23] Therefore, a wounded SN is accompanied by loss of neurons, neuromelanin, and dopamine within the affected region.[1-4,8,9,11,13-15,17-21,23,28]

The classic external features of PD are bradykinesia and rigidity.[34-42] It is important to address the existence of other voluntary and involuntary movement disorders, including tremors.[43-51] In many cases, the presence of gait complexities was also noted.[39,42,44,47,51] Many PD patients estimated rigidity to be the most disturbing symptom because it affects their daily activities, often more so than bradykinesia and dyskinesia.[12]

3. The young Cotzias in Greece

George Cotzias (Figure 1), the renowned pharmacologist and neuropathologist, was born on June 16, 1918, in Crete, Greece.[1,7,33,38] He was the eldest child of Caterina Stroumboli Cotzia and Constantinos Cotzias. His mother was a victim of cancer.[3] Unlike his mother, his father, Constantinos Cotzias, was continuously absent from home. The latter was a famous, successful, and courageous journalist, politician, lawyer, and businessman who supported the king of Greece during World War II.[7,38,46] In Athens, there is still a square named after Constantinos Cotzias, along with a statue of him.[7,38,46]

From his earliest years, George Cotzias, otherwise called "Zorba of Science"[1, p.10], studied at the leading educational institutions of Greece.

He began his medical studies in Greece.[7,33,46] At the age of 22, when Greece was defeated, he did not hesitate to risk his life.[1,7] It was at this age that his training under the supervision of the professor of surgery Xenophon Kondiades was interrupted because his application to serve as a sergeant volunteer of Greek army was successful.[1,7,33,38,46] In the Greek army, he again met Kondiades after Kondiades requested to collaborate with him at a hospital near the Albanian frontiers.[38] He had a brief military experience as his father could not reject the proposal from the King of Greece to represent the Greek government in the USA after Germans bombed a hospital when all the staff was inside.[7,38] Thus, all the family of Constantinos Cotzias had to travel to the USA.[7,38]

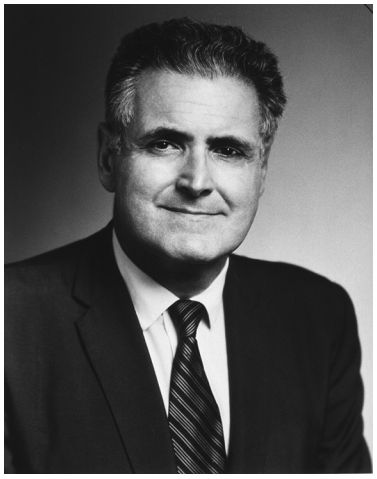

Figure 1. George Cotzias
Source: https://collections.nlm.nih.gov/catalog/nlm: nlmuid-101441400-img (Public Domain).

4. Cotzias in the USA

4.1. Early studies and collaborations

The life of Cotzias in the USA began in August 1941, when he intended to continue his medical studies. He submitted applications to several New York universities, including the University of Cornell, but all were rejected.[7,33,38] The universities rejected his applications citing Cotzias' low level of English language and insufficient knowledge of biochemistry, pharmacology, and physiology as reasons.[7,33,38] The rejections led Cotzias not to ignore his father's advice to apply to the top university in New York.[7,33,38] Thus, Cotzias applied to the Harvard University. Among the application procedures of Harvard University was an interview that Cotzias gave in fluent German with the Harvard medical professor and German refugee Soma Weiss.[38] Finally, Cotzias was accepted as a 3rd-year student at the medical school.[38] When Cotzias graduated as the second-best student of his class in 1943, he received the Summa Cum Laude distinction.[1,7,33,38,46]

In 1945, when his family went back to Athens, the physician stayed in the USA.[38] His first specialization as a pathologist was at Brigham Hospital.[7,38] He then pursued training in neurology at Massachusetts General Hospital, where he worked from 1944 to 1945 and collaborated with the hospital's chief specialist, Dr. Lewis Dahl.[1,7,38] In 1946, Vincent P. Dole decided to employ Cotzias as a researcher, after Dahl's positive recommendation, in the newly established research department at Rockefeller University.[38] During this collaboration, Cotzias added to his scientific portfolio by contributing to the studies on hypertension, exploring links between hypertension, salt metabolism instability, and energy balance.[3,7,38]

4.2. Steps toward the discovery of the distinguished therapy

In 1954, supported by the director of Rockefeller Hospital, Thomas Rivers, Cotzias and Dahl joined Van Slyke's research team in BNL.[7,38,46] It was there where Cotzias began his main studies, which led to the invention of L-DOPA.[38] He had his own research space and worked for 10 years as a senior scientist and head of the Department

of Physiology.[7,45] Cotzias had knowledge of common precursors of dopamine and neuromelanin – one of which was L-DOPA.[7,38] This knowledge was informed by earlier findings: in 1951, Raab and Gigee identified catecholamine in humans, and in 1957, Kathleen Montagu's landmark paper in *Nature* first documented the existence of dopamine in the brain.[1,3,7,16,33,52] Knowing the presence of catecholamines and their function in humans, Cotzias began his studies on them. He suspected that catecholamine and vasomotor action were affected by diamine and histamine.[7,38] Cotzias detected the connection between catecholamine, manganese, and L-DOPA in the brain and opined that catecholamines, diamines, and histamine had vasomotor action.[38,53] In addition to linking angiomotor action with hypertension, Cotzias also focused on enzymes that limit their biological activity by oxidation.[7,38] These foundational studies prompted Cotzias to begin his first research on L-DOPA, laying the groundwork for his groundbreaking discoveries.[7,38]

When Cotzias accepted the proposal of the World Health Organization, he remained in BNL, but from 1963 and for the next 7 years, he and the professor of the Catholic University of Chile, Ismael Mena, were chosen to be the head chiefs of a scientific research team established in the Catholic University of Chile.[7,46] The team's primary objective was to conduct a longitudinal study investigating chronic manganese poisoning in Chilean miners.[38,45,46] The study included 13 adult miners, all under the age of 56.[45] The duration of manganese exposure among participants varied between 6 months and 21 years, while the onset of manganese intoxication varied between 3 and 25 years.[45] All participants experienced positive effects when treated with L-DOPA, also known as the amino acid L-dihydroxyphenylalanine.[7,8,10]

In the meantime, Cotzias considered seriously the relationship between the detailed activation of metal traces in tissue and blood samples using high-energy neutron beams.[7,38,45,46] As part of the longitudinal study, he identified common neurological factors – including injuries in SN due to reduced neuromelanin – between PD and manganese toxicity.[3,7,19,38,46] Later, Cotzias completed several studies explaining the distribution, absorption, kinetic elimination, and probable function of manganese.[38]

During this collaboration, Cotzias also identified the common neurological symptoms between PD and manganese toxicity, such as rigid facial expression, clenched hands, speech difficulties, balance disorders, hand tremors, facial rigid expression, slowed movements, speech tremors, lack of coordination, and difficulty in maintaining balance.[7,19,38,46,54]

5. The outstanding therapy

5.1. The discovery

Cotzias discovered a method to study manganese distribution in human tissues.[7,45] Despite the failure of previous researchers who focused on dopamine levels as a treatment for PD without demonstrating the practical therapeutic efficacy of L-DOPA,[41,47,55-57] Cotzias recognized the potential benefits of L-DOPA for PD patients. However, at the time, its utility was limited to theoretical dimensions due to its inability to cross the blood–brain barrier.[1,3,7,33,38,41,47,55,58] His incorrect – as he later self-acknowledged – hypothesis that the increase of neuromelanin levels in SN could ameliorate the health of Parkinsonian patients was the motivation to initiate the study of L-DOPA.[1,7,19,33,45] Thus, in 1966, Cotzias commenced a research project in BNL investigating the oral use of D-DOPA or otherwise named D, L-DOPA in 17 Parkinsonian patients treated in his clinic.[3,7,8,21,33,47] Cotzias was closely following the health progress of his patients.[2,3] He made a twice-per-day assessment and a cinematographic recording of the patient's health condition.[2,3,7,26,59] He began to increase the dose every 2 h over the course of several weeks until signs of health amelioration were observed.[2,7,38,41] The highest dose administered was 16 g/day.[4,5,14,17] The findings and characteristics of D-DOPA were presented in his article "Aromatic amino acids and modification of Parkinsonism," published in the *New England Journal of Medicine*.[7]

Cotzias also found that the inactive isomer, D-DOPA, which constituted 50% of the administered dose, caused toxicity and intense gastrointestinal and hematological injuries while lacking any therapeutic properties.[7,8,32,33,56] Driven by a priority to alleviate his patients' pain, Cotzias considered pain relief to outweigh concerns over potential drug dependency.[13] In 1967, knowing that L-DOPA did not cause toxicity, Cotzias initiated a study involving 28 adult participants diagnosed with PD.[2-5,7,19,32,33,35,38] The highest dose of L-DOPA administered to the patients was 8 g/day.[17,19,32,33] Cotzias attributed the success of this therapy to the gradual increase of the final high doses of L-DOPA and the continuous observation of his inpatients for months.[7,19] This marked the first successful attempt to achieve practical therapeutic results using L-DOPA. The participants of Cotzias' study became the first individuals to overcome the refractory nature of PD, which, until that time, had been unresponsive to all other treatments.[1,7,30,33,46,55,60] Although its curable features, Cotzias assessed L-DOPA not as a treatment *per se*, but as a step toward developing a definitive treatment.[38]

[1] He persuaded doctors to give morphine (a significantly addictive substance) to his mother till she would have a relief from severe cancer pain.[3]

His paper "Modification of Parkinsonism: chronic treatment with L-DOPA" published in the *New England Journal of Medicine*, in 1969, presented the findings of the study.[3,7,16,34] As Oliver Sacks mentioned in his book "Awakenings," it was in 1969 that Sacks, at the Mount Carmel Hospital, administered L-DOPA to his patients.[73] Sacks vividly described the unexpected and valuable impact of L-DOPA on the patients' health and lives.[73,74] He dedicated the book to the effects of L-DOPA, even choosing the title "Awakenings" in reference to Cotzias' use of the term to describe the transformative results of the drug.[74] The significance of L-DOPA eventually reached the cinema. In 1990, the movie *Awakenings*, based on Sacks' book, which was directed by Penny Marshall, with a screenplay written by Oliver Sacks and Steven Zaillian, was released to the public.[75]

The article and the study's video recordings by Cotzias fascinated Melvin Yahr to such a degree that in 1969, he and his research team started a study on L-DOPA therapy.[1,2,7,19,33] Yahr's study was the most important research of that time because it comprised the first prospective, double-blind, controlled clinical trial, which included a placebo to emphasize the effect of L-DOPA.[1,2,7,19,32,33] The study enrolled 60 patients,[1,2,7,19,33] of whom 56 were diagnosed with idiopathic PD, three with postencephalitic parkinsonism, and one with probable progressive supranuclear palsy.[2,7,19] The study clearly indicated that the beneficial dose of L-DOPA could vary between 3 and 8 g/day, dyskinesia was an inevitable side effect, while cardiac arrhythmia, vomiting, nausea, and hypotension were defined as self-limited adverse effects of L-DOPA.[2,7,19] Furthermore, according to the study, L-DOPA had unique positive results that a placebo could not provide.[7] At least 80% of the participants significantly benefited,[1,7] and more than 90% of the patients had at least 20% improvement not later than 4 months of treatment.[7,33] The conclusions of Yahr's study confirmed the positive therapeutic effects of Cotzias' earlier study.[1,7,19,21,29,32,33,61] After confirmation from Yahr and other scientific studies, L-DOPA was recognized as the most effective treatment for PD at all stages.[7,25,33,60] While it does not impede the progression of the disease,[35] in at least 50% of cases, it can significantly improve the patients' QoL.[20,35,37,66] L-DOPA remains the standard therapy for PD.[52,54,59,60,62-67]

In 1970, the Food and Drug Administration approved L-DOPA therapy.[3,7,19,28,32,34]

Cotzias *et al.* classified the invention of L-DOPA as "the most significant contribution to the medical treatment of neurological examinations in the past 50 years."[46] Nowadays, it is the cheapest and most prescribed antiparkinsonian drug (Figure 2).[42]

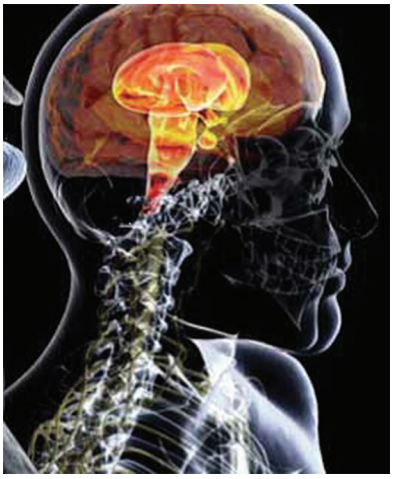

Figure 2. Internal L-DOPA and PD image. Copyright ©[2015] [Dr Dr Mylonas Anastasios][82]. Reprinted with permission of Dr Dr Mylonas Anastasios.

5.2. Further benefits of L-DOPA

Responsiveness to L-DOPA is considered a hallmark of PD diagnosis.[28,54] It was the only treatment that filled the dopamine gaps in the brains of PD patients.[46] It is worth noting that Cotzias himself in his scientific study had shown that L-DOPA has the capacity to stop the progression of PD.[35] L-DOPA helped millions of Parkinsonian patients worldwide.[7,46] Levodopa had impressive results, especially in the early stages of PD in improving tremor, bradykinesia, and rigidity.[4,34,66] Commencing L-DOPA since the early stages of PD means living a better and longer life because it offers a greater improvement in the 1st year of the disease, without side effects on later years, and keeps the subject active, physically and mentally, which means middle-age prepared for older.[68] L-DOPA was proven to be non-toxic, easy to administer, and a better-tolerated therapy, which could also ameliorate the health condition of manganese-poisoned people with no impulsive movements.[3,8,32,46,69] Another precious characteristic of the therapy was the ability to alleviate the consequences of PD, which, in certain cases, have been proved fatal.[7,15,18,41,50] In other words, L-DOPA saved the lives of many people with PD. Even though previous studies, with doubtful results, claimed that there were cases in which the use of L-DOPA therapy caused deterioration of neuronal degeneration and toxicity, there was no strong evidence to support their hypothesis.[17,22,37,41,69] Moreover, none of these studies failed to emphasize the positive influence of L-DOPA on Parkinsonian people's health and lives.[25,28,37,41,69] It has been proved that the revolutionary and the most effective therapy for PD, L-DOPA, possesses neuroprotective abilities and can halt the progression of the disease.[2,4,7,8,21,34,35,70] Yet, the unsatisfying L-DOPA response

is not because of the drug *per se*, but due to other factors independent of it, like gut abnormalities, the presence of protein, and other pharmacokinetic or pharmacodynamic disorders.[28,36] In cases where the faster deterioration of PD after initiating L-DOPA therapy was attributed to the drug, several factors, like assessment of intestinal disorder, the neuroimaging before and after beginning L-DOPA therapy, protein accumulation, and many other factors, were overlooked.[20,66]

In many cases, there was the same death percentage in PD patients receiving L-DOPA and PD patients not receiving L-DOPA.[35] Indeed, the longevity of the patients who received L-DOPA was equal to the normal population.[34] In addition, in other cases, the patients with L-DOPA therapy lived longer than those who did not have the therapy.[17,34,37,69,71] Its impact on the conceptualization of neurodegenerative diseases and other neurological illnesses was more than significant.[7,56] Its therapeutic properties were also extended to non-neurological diseases.[56,72]

6. Cotzias' achievements

While being in BNL, Cotzias accomplished new studies on cyclotrons[7,38] and discovered a method to study manganese distribution in human tissues.[7,45]

In his 1964 and 1967 studies, it was obvious that rats receiving the high concentration of dopamine experienced a 50% longer lifespan compared to those without the treatment.[68] In September 1967, when speaking at the Second International Congress of Neurophthalmology in Montreal, Cotzias gave the first scientific findings on the practical therapeutic impact of L-DOPA for PD patients.[7] Cotzias was also the first to prove the emergence of dyskinetic and motor fluctuations as negative features of L-DOPA.[49,50,53,56,70,76]

Cotzias holds the title of the pioneer of the practical potency of L-DOPA, marking it as the first long-term treatment capable of crossing the blood–brain barrier and restoring dopamine deficiency in the brains of Parkinsonian patients.[7,19,34,46,76] Cotzias was also the first to prove that L-DOPA could defeat PD, whether it was caused by idiopathic, post-encephalitic, or manganese factors.[7] At this point, it is worth noting that Cotzias, in his cutting-edge scientific study, had shown that L-DOPA could stop the exacerbation of PD symptoms.[35] He was the first to establish the role of dopamine and L-DOPA in cerebrospinal fluid, and the interaction between L-DOPA, aging, and fertility, as well as identify the presence of dyskinesias linked to melatonin and growth hormone in patients undergoing L-DOPA therapy.[7] Furthermore, Cotzias proved that L-DOPA could improve the health of people suffering from chronic manganese poisoning without causing any involuntary movements.[3,46,69]

A lesser known but significant achievement of Cotzias was the discovery of severe L-DOPA-induced dyskinesia (LID), which, although not present in all cases, emerged as a consequence of nigrostriatal lesions and high doses of L-DOPA.[39,43,67,70,76] Other factors contributing to the development of dyskinesia were unconscious movements.[7] The fluctuation of the movements depended on the dose of L-DOPA.[7] The dyskinesias disappeared in the absence of L-DOPA and came back after restarting the therapy. It was Cotzias who proved that LID was a phenomenon related to the drug's chemical memory storage in the brain.[7] Cotzias, in collaboration with Lily Tang, named the mechanism of this phenomenon "L-DOPA-induced super-sensitivity."[7] This concept formed the foundation for understanding the "priming" phenomenon, initially named "neuroleptic-induced dyskinesias," which was later studied extensively to explain the molecular events that caused dyskinesias.[7] It is now obvious that dyskinesia is a common disability that comes as a consequence of excessive dopaminergic action in therapy.[23,65,66,77] Therefore, when Cotzias' patients used L-DOPA, it caused a high dopaminergic response. Cotzias was the first to note practical benefits from L-DOPA and no one had recorded the presence of dyskinesia before him. This suggested that dyskinesia was a reaction of the brain to the drastic change from dopamine depletion to dopamine adequacy, causing an intense dopaminergic response. In addition, the absence of dyskinesia corresponds to the ineffectiveness of L-DOPA.[36] The main factors that affect LID are the presence or absence of tremor as an initial manifestation of PD, disease duration, the age at onset, the duration of PD before treatment, the equivalent daily L-DOPA dose, the initial dose, dose duration, disease severity, the presence of motor fluctuations, and the severity of motor symptoms, especially those caused by prolonged L-DOPA therapy.[13,28,39,40,42,77]

Dyskinesia's presence was noted even in therapy change from dopamine agonist medicine to L-DOPA.[20] Yet, many physicians refuse to propose L-DOPA as a treatment for PD due to its side effects, ignoring the fact that even dopamine agents, which these physicians prefer, possess serious complications too.[28] Since dyskinesias is also present when treated with dopamine agonists, it is the dopamine stimulation that causes dyskinesias and not L-DOPA *per se*.[13] Another explanation for dyskinesias is that their occurrence can be influenced by the method of administration.[17] While LID can affect the QoL and, in many cases, increase the risk of falls,[42] it does not always affect QoL to a significant degree, though it can lead to increased healthcare costs.[13]

LID has led to disruptions of carbidopa/L-DOPA therapy and it has been the factor limiting the clinical use

of L-DOPA.[28,39,78] It is suggested that the presence of resting tremor may be associated with secondary compensatory mechanisms that could mitigate LID, even with L-DOPA treatment.[76,79] In some cases, LID occurs as a progression following other motor fluctuations.[13]

Moreover, lower-than-expected rates of LID were observed when low daily doses of carbidopa/L-DOPA were administered.[39] The pathophysiology of L-DOPA-associated response fluctuations is complex and not yet fully understood.[28] Indeed, it is understood that choosing L-DOPA as a first-line therapy results in significant functional improvements for patients, particularly in terms of symptomatic relief, during the early years following the onset of PD.[28] During the final years of his life, Cotzias provided significant data on the relationship between cancer[7] and the features of L-DOPA.[7]

7. Development of new drugs by Cotzias

Although the adverse effects of L-DOPA therapy were significant, they could neither win over the exceptional potency of the therapy nor deter Cotzias from using L-DOPA to treat his patients.[3,7] On the contrary, the side effects of L-DOPA became a strong motivation for Cotzias to create new medications combining L-DOPA with various adjuncts like dopamine agonists – substitute compounds capable of crossing the blood–brain barrier without being converted by local enzymes.[3,36,38] The new drugs led to a reduction in the required L-DOPA dose and minimized irregularities associated with its use.[3]

Cotzias recommended the use of apomorphine, the dopamine agonist that could pass the blood–brain barrier without being converted by local enzymes. When selected as a treatment option, apomorphine stimulated all dopaminergic receptors, exhibited antidyskinetic evidence, and demonstrated an efficacy nearly equal to that of L-DOPA in improving PD symptoms.[7,32,38]

Apomorphine was a reliable substance to assess the dopaminergic receptor responsiveness and the presence of dyskinesia.[7,80] It cured various stages of PD before functional neurosurgery and was used as a treatment for patients who became disabled following deep cerebral stimulation or pallidotomy.[7,32,80] Later, the use of apomorphine was permitted in European countries and Canada.[80] Furthermore, it was estimated to be a successful drug for patients resistant to other therapies experiencing motor distortions during the last stages of PD.[3,7,80] At present, a sublingual form of apomorphine is available.[64] Moreover, apomorphine can serve as a temporary perioperative treatment during abdominal surgery for patients with PD.[80] An important parameter to assess the efficacy of dopamine agonists was the patient's reaction to L-DOPA.[80]

The efficacy of apomorphine as a treatment was closely linked to the patient's response to L-DOPA; only if the health condition of the patient was getting better by the use of L-DOPA, there would be amelioration by the use of apomorphine.[80] In addition, N-propylnoraporphine was shown to minimize certain L-DOPA-related adverse effects, though it was ineffective in reducing dyskinesias when their underlying cause was not L-DOPA.[7]

Moreover, the suspicion that carbidopa might be effective in the treatment of chorea led Cotzias to pioneer the revolutionary carbidopa/L-DOPA combination, also known as the peripheral amino acid decarboxylase inhibitor (DDI) medication.[1,3,7,19,32] This therapy is primarily used in the early stages of PD.[25] Cotzias tried for the 1st time the synthesis of this drug in 1968 by adding carbidopa to the already administered L-DOPA.[3,7]

The benefits of this medicine were reduced doses of L-DOPA,[1,5,8,23,28,32,36,48] faster efficacy of L-DOPA, and milder harms caused by the latter.[28,32,33,40,48,60] In 1972, Cotzias published the study of DDI in a scientific article.[7,48] The therapy's results were so extraordinary that the first oral form of the DDI, marketed under the trademark Sinemet, was released in 1973.[3,5,32]

Since then, various research studies have confirmed the valuable impact of the new formula on Parkinsonian patients.[5,17,23,36] Carbidopa/L-DOPA increases the level of L-DOPA in the brain from 1% in carbidopa's absence to 10% in carbidopa's presence.[23] L-DOPA/carbidopa is considered the most efficient symptomatic treatment for PD, the easiest drug to source, the most affording drug and can be easily monitored.[39] To address the issue of gastrointestinal problems, in the 1990s, the compound was released in Sweden as an intestinal gel.[5,10,19] This formulation has since become a cost-effective therapy not only for gastroenterological disorders but also for patients with acute abnormalities.[20] The gel formulation maintains nearly stable plasma concentrations of L-DOPA, contributing to its effectiveness.[28] It is commercialized in Europe under the trade name Duodopa™[28] and is considered safer and better tolerated compared to the immediate-release form of carbidopa/L-DOPA.[24] In 2006, an oral solution of carbidopa/L-DOPA was commercialized in the USA.[17] In addition, a skin patch of carbidopa was developed for patients with metabolism dysfunction, overcoming the skin barriers and improving the drug's duration and concentration.[2,5,8,32]

At present, carbidopa/L-DOPA is defined as the most impactful oral medicine in PD.[81] It is the most prescribed treatment as it improves PD symptoms, especially at the early stages of PD.[23] It offers mild and infrequent side effects, including dyskinesia, as well as a positive influence on the

QoL of PD patients.[24,28] In certain cases, it could have no adverse, including dyskinesia.[24] The efficacy of carbidopa/L-DOPA is not typically questioned. Any inefficacy observed is often related to an individual's tendency to overproduce aromatic L-amino acid decarboxylase (AAD) enzyme activity, rather than an issue with the drug itself.[36]

Another alternative formulation of carbidopa/L-DOPA involves nanoparticles (NPs) – small colloidal particles ranging from 10 and 200 nm.[23] These NPs can help overcome challenges related to drug delivery and potentially reduce toxicity.[23] The intranasal delivery of NP-encapsulated L-DOPA provides a non-invasive delivery strategy that is easy for PD patients to administer themselves.[23] Its use resulted in reduced adverse effects, minimized L-DOPA dose, fewer treatments, and better drug delivery to the central nervous system.[23]

Despite their efficacy, all the dopamine agonists and PD medication could not replace L-DOPA therapy.[7,11,19,25,34,47,52]

8. Awards received and the involvement in cancer research

In January 1977, when Cotzias traveled to Greece to help his colleagues, he was already a renowned figure.[7,46]

It was in 1954 that George Cotzias received the A. Cressy Morrison Award in the Natural Sciences.[38] In 1969, Cotzias was given an honorary degree from the Santiago Catholic University and the Albert Lasker Award in Clinical Medical Research.[1,2,7,38,46,82] The next year, came another honorary degree for Cotzias, this time from the Women's Medical College of Pennsylvania.[38] In the same year, he was elected to the American Academy of Arts and Sciences.[38] In 1971, he was awarded the Honorary Degree of St. John's University, New York.[38] The next year Cotzias was awarded the Borden Award of the American Medical College Association, while the Harvey Society honored Cotzias for his discovery that some or all of the main symptoms of PD could be reversed with dihydroxyphenylalanine (dopa).[7,82] Indeed, the Harvey Society defined the discovery as one of the greatest therapeutic contributions of that generation.[7,82] In 1973, he was elected to the National Academy of Sciences.[7,38] In 1974 came the annual prize from the American College of Physicians and the honorary degree from the National University of Athens.[38,82]

Cotzias was ranked among the great personalities in American medicine.[46] He has a distinctive place in the global history of 20th-century medicine.[82] The American medical journal *Family Health* classified Cotzias among the first 100 most famous leaders in the World of International Health.[82]

In 1973, Cotzias was diagnosed with lung cancer and battled with the illness till the last moment by continuing to visit the hospital.[1,7,46] Despite his personal struggle, cancer became a source of inspiration for Cotzias, prompting him to initiate scientific research on the disease.[7,46] His studies proved that depletion of dopamine-stimulated adenylate cyclase activity in the brain, which minimized spontaneous motor activities and motor responses to intravenous L-DOPA, could be important indicators of a high probability of future breast cancer.[7] Two years later, Cotzias was employed by Cornell University Medical College and Memorial Sloan-Kettering Cancer Center.[7,46] He even hypothesized that the proper dose of DOPA could cure cancer.[3]

9. Death of Cotzias

Cotzias died on June 13, 1977, at the age of 59 in New York.[1,7,38,46] The Sloan-Kettering Memorial Cancer Center arranged for his body to be sent to Greece.[3,46] His state funeral took place in Greece.[46] The next day, The New York Times published a commemorative article about Cotzias.[46]

10. After death

Six months after his death, the New York Scientific Community Establishment and the Memorial Sloan-Kettering Cancer Center organized an event in Cotzias' honor.[1,7] High-society members were present at this ceremony. Among them were Laurence S. Rockefeller, the permanent representative of Greece to the USA, and many Greek ambassadors.[1,7] The Archbishop of the North American Greek Orthodox Church was also present.[1,7] To honor Cotzias' memory, Greece issued a commemorative stamp in his name (Figure 3).[1,7]

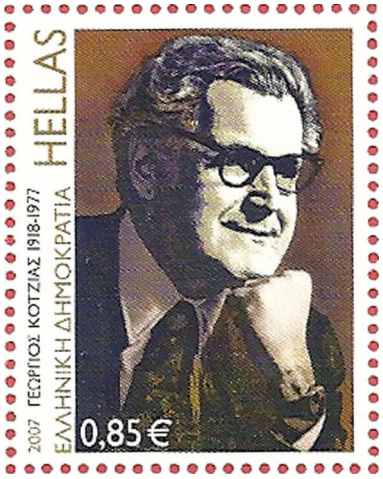

Figure 3. A commemorative stamp with a picture of George Cotzias. Copyright ©[2015] [Dr Dr Mylonas Anastasios][82]. Reprinted with permission of [Dr Dr Mylonas Anastasios].

To the memory of his brilliant achievements, the American Academy of Neurology added the "George Cotzias Lecture" to its annual meeting, and the American Parkinson Disease Association founded the "George C. Cotzias Memorial fellowships."[7] The Cornell Medical Center created the "George Cotzias Distinguished Professorship," and the Memorial Sloan-Kettering Cancer Center added the "G.C. Cotzias Neuro-oncology Division".[7] In Europe, the Spanish Neurological Society established the "Cotzias Lecture" at its annual meeting.[7]

11. Discussion

George Cotzias, a brilliant physician from Greece, stands as a great figure in the annals of international medical history, notably for his pioneering work in PD.[7,46,82] Being the son of highly educated parents, he had eminent academic qualifications and accomplishments.[7,38,46] His studies journey commenced in Athens and culminated at Harvard University.[7,33,38,46]

Cotzias' groundbreaking discovery on the therapeutic implications of L-DOPA for PD and manganese poisoning has been of enormous international benefit.[7,8,10] His methodology, encompassing innovative techniques like cinematographic recording and meticulous patient observation, was revolutionary in its own right.[2,3,7,8,19,21,26,33,47,59] Such techniques ensured accurate assessments of L-DOPA's efficacy and provided deeper insights into the disease progression and treatment response.[7,19] In addition, his revelations about the dyskinetic distortions associated with L-DOPA therapy and its potency on individuals poisoned with manganese comprise significant milestones in neuroscientific research.[7,8,10]

Each medication he formulated provided much-needed relief to patients grappling with PD, a disease once deemed refractory. In this light, L-DOPA stands as a pivotal stepping stone in neurology's evolution.[7,46,56] Cotzias demonstrated the brain's ability to retain the chemical "memory" of a medication.[7] It is noteworthy that Cotzias viewed L-DOPA not as an end but as a significant milestone in the journey toward a comprehensive solution for PD.[38] Given the invaluable impact of L-DOPA, bringing longevity[17,34,37,68,69,71] and alleviating the suffering of PD patients,[4,20,28,34,35,37,66] his vision of transforming PD into a mild, non-lethal ailment seems not only hopeful but also attainable. Beyond L-DOPA, Cotzias' endeavors led to the genesis of a new generation of drug synthesis to combat PD. To date, carbidopa/L-DOPA is the most effective and well-developed medication among the available opti ons.[2,3,5,8,10,17,19,23,32,39,81]

His battle with cancer, while tragic, did not defeat his research spirit. Until his last breath, he remained an insistent seeker and established the connection between cancer and L-DOPA.[3,7,46]

His outstanding career, marked by numerous awards and recognition of his great achievements, is a priceless gift to science and many patients worldwide.[1,2,7,38,46,73-75,82] Today, his legacy endures, with numerous institutions worldwide hosting academic events bearing his name,[7] celebrating the indomitable spirit and unparalleled contributions of George Cotzias to medical history.

George Cotzias's legacy, along with the practical application of L-DOPA, stands as a testament to his immense contributions to the world of medical science.[73-75]

12. Conclusion

The Greek doctor George Cotzias started his medical studies in Athens and accomplished them at Harvard University. He had an extraordinary career in the USA and left an important scientific route behind. The immense discoveries of Cotzias were the practical and remarkable therapeutic use of L-DOPA in treating PD. Cotzias proved the efficacy of L-DOPA using tools that no one has used before, including cinematographic recording to closely monitor the patient's reaction to the therapy and adjust the L-DOPA dose. He also discovered new dyskinetic abnormalities associated with the therapy and demonstrated the therapy's positive effect on individuals poisoned by manganese. L-DOPA was a common substance in all the complex and beneficial drugs composed by Cotzias for PD patients. No one before Cotzias provided an impactful treatment for PD. L-DOPA was a hallmark in the advancement of neurology. Successfully advancing to this stage not only extended life expectancy but also made PD a more manageable condition. The hypothesis that future therapies could transform PD into a common, mild disease – one that no longer causes suffering or death – may not be an exaggeration. Cotzias died from cancer while conducting original scientific research on the disease. He received many awards in recognition of his contribution. Many academic events and awards have since been named in his honor at several institutions worldwide. In addition, a fictional movie illustrates the valuable influence of L-DOPA.

This paper gives a concise but clear image of George Cotzias' great achievements and the tools that could lead to breakthrough research in neuroscience, brain function, and brain response.

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Conflict of interest

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