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GEORGE CONSTANTIN COTZIAS

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A Biographical Memoir by
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Biographical Memoir

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George I. Coburn.

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BY VINCENT P. DOLE

GEORGE CONSTANTIN COTZIAS was born in the city of Chania on the island of Crete, the eldest child of Constantin and Catherine Stroumboli Cotzias and the grandson of George J. Cotzias, a wealthy merchant in Athens. His father, Constantin George Cotzias, a lawyer and journalist, had recently been banished from Athens because of political activity in support of the king. He was arrested by the fascist government of Eleftherios Venizelos and exiled to Crete to limit his political influence, but he was able to return to Athens eighteen months later. Soon after returning he established an influential newspaper and an advertising agency. Twelve years later, in 1932, he became president of the Greek chamber of commerce and in 1934 was elected mayor of Athens.

As mayor and later in the expanded role of governmental minister for all municipal activities in the region of Greater Athens, Constantin Cotzias shaped the political structure of the modern city of Athens. He reorganized its government, initiated programs of health and public works, rebuilt the municipal hospital, paved roads, created parks, supported young artists, and established a new municipal symphony orchestra.

This productive period was terminated abruptly by the invasion of Greece in 1940. After an intense but brief resistance, the Greek armies were defeated. The prime minister, Alexandros Koryzis, refusing to acknowledge defeat and collaborate, committed suicide. In this extremity, King George of Greece asked Constantin Cotzias to go to the United States as ambassador-at-large representing the Greek government in exile.

George and his family arrived in New York in August 1941, financially destitute after a desperate four-month journey through warring countries. They remained in New York until the defeat of the Axis powers in 1945 made it possible for his parents to return. To complete this account, Constantin Cotzias was reelected mayor of Athens by an overwhelming majority in the first postwar election (1951), but he died shortly afterwards of a heart attack at the age of fifty-nine while resuming his municipal duties. Cotzias Square, next to the town hall of the city of Athens, bears his name.

As the eldest son of a leading citizen of Athens prior to these events, George Cotzias had a privileged early life, attending the best schools and associating with the most stimulating intellectuals of the city. Reflecting George's mother's interest in literature, the Cotzias home was a meeting place for leading writers of prewar Athens and, of course, as the mayor's residence, it was at the epicenter of public policy.

At the age of twenty-two, within one year of graduating from medical school, George apparently was on his way to an uneventful career as a medical practitioner in Athens, specializing in surgery. He had become an assistant to the professor of surgery, Xenophon Kondiades. However, the invasion of Greece changed all plans. George immediately volunteered for military service, although as a medical stu-

dent he was exempt from the draft. At the request of Professor Kondiades, heading a surgical team at a hospital close to the Albanian front, he was assigned to this unit, but while he was in transit the hospital was obliterated by bombing, which killed the entire staff. Military resistance collapsed before the advancing German army. George made his way back to Athens, rejoined his family, and left Greece with them.

After arriving in New York in 1942, George applied for admission to medical school to complete his studies. The rejection by Cornell was unequivocal; not only was he found to be deficient in English, he was told that his education in Athens had provided inadequate training in basic biochemistry, pharmacology, and physiology. He would need further premedical training even to be eligible for admission to the first year of medical school. Applications to Columbia, New York University, Johns Hopkins, and Pennsylvania were equally fruitless.

Reminiscing in later years, George recalled critical advice that his father gave him at this low point. "When I ran for the office of councilman, I was defeated. So I ran for mayor and was elected. Choose the leading medical school in the country and apply there." With this advice George applied to Harvard Medical School and had the good fortune to be interviewed by Soma Weiss, a brilliant professor of medicine and himself a refugee a decade earlier from Nazi oppression. After a long conversation in German, which George spoke fluently, Weiss recommended that he be admitted conditionally to the third year of study at the medical school. Two years later he graduated from Harvard cum laude. He then trained as an intern in pathology at Brigham Hospital, as an intern in medicine at Massachusetts General Hospital, and was a resident in neurology at Massachusetts General Hospital.

This brings the story to the point at which I first knew George Cotzias. During the four years of World War II, it was my good fortune to be assigned to a naval medical research unit based at the hospital of Rockefeller Institute (now Rockefeller University) and to work in the department of D. D. Van Slyke. With the end of the war and demobilization, I left Rockefeller and returned to Massachusetts General Hospital, where five years earlier I had trained in medicine. Shortly afterward to my great surprise and delight, the director of the Rockefeller Hospital, Thomas Rivers, invited me to return to Rockefeller. He asked me to form a new department, replacing that of Van Slyke, who planned to move to Brookhaven National Laboratory the following year.

My first act was to invite Lewis Dahl to join me; Dahl, a scholarly physician and friend, who was completing a tour as senior medical resident at Massachusetts General Hospital, agreed. Within the hour George burst into my office and announced explosively, "I'm coming, too." This unusual application could have been counterproductive, but fortunately Dahl had worked with Cotzias and gave him an enthusiastic endorsement. Immediately I had two talented associates with whom to start the department, the only difficulty being there was no space for the new laboratory immediately available at Rockefeller. At Rivers's suggestion, my two associates were assigned to Van Slyke's group during his final year (an invaluable experience for them), and I started my new career as department head with a year's sabbatical in Europe.

The five years after my return were busy ones. We studied hypertensive patients, looking for clues to the nature of this disorder in disturbances of salt metabolism and energy balance. George, in addition to loyal work as a team member in the clinical studies, became interested in the me-

tabolism of amines in the tissues. He reasoned that catecholamines, diamines, and histamine have powerful vasomotor effects that might be relevant to hypertensive disorders. In particular, he directed his attention to the enzymes that limit their biological activity by oxidizing them.

George thus initiated studies that led him some fifteen years later to the demonstration that L-DOPA (the amino acid L-dihydroxy phenylalanine) was effective in giving symptomatic relief to patients with disabling Parkinsonism. The most important of these studies were conducted after he left my department in 1954. Dahl left at the same time, both having outgrown the limited opportunities for advancement at Rockefeller. They transferred their work to Brookhaven National Laboratory, where Van Slyke meanwhile had established a strong medical division and was able to provide space and support for each to develop an active, independent laboratory.

The move to Brookhaven also provided George with a new resource for metabolic studies, namely a cyclotron. When activated by a beam of high-energy neutrons, trace metals in samples of tissue and blood can be determined with unprecedented sensitivity and specificity. George seized the opportunity. In a series of basic studies over the following decade, he elucidated the distribution, absorption, elimination kinetics, and probable function of manganese. At the same time he became interested in its toxicity, manifest especially in the neurological symptoms of Chilean miners excavating manganese ore. As a neurologist he was impressed by the similarity of the symptoms to those of classical Parkinson's disease (rigidity, retardation of motion, tremors, lack of coordination), and as a pathologist he was attracted by the opportunity to correlate specific structural lesions made by a known toxin to disturbances of brain function. In both disorders the main lesions found in the

brain involve the substantia nigra, a region made conspicuous by a deposit of dark melanin pigment. It was known that this region of the brain is rich in the neurotransmitter dopamine and also that both melanin and dopamine are derived from common precursors. Further, it was known that this region is deficient in both substances in patients with Parkinson's disease.

A possible remedy, as was evident to several investigators at the time, is to increase the supply of dopamine to the neurones in this region. However, dopamine administered as a medication (orally or by injection) cannot reach the site in significant concentration because it does not pass the blood-brain barrier. As an alternative, one can look for precursors of dopamine that are not excluded by the barrier, administer them in large doses, and hope that when the molecules arrive at the critical site enough will be converted into dopamine to have a therapeutic effect. Other investigators had pursued this idea with little success, although the validity of the approach was shown by the transient benefit seen after injection of the precursor, dihydroxyphenylalanine (DOPA). But this effect was only of theoretical interest. It was not of practical value as a treatment because of the severe toxicity associated with the injection.

Cotzias, at this point, made a critical observation that converted the transient response into a successful, large-scale treatment. By starting with very small doses of DOPA, given orally every two hours under continued observation, and gradually increasing the dose over a period of several weeks as permitted by the development of tolerance, he was able to stabilize patients on large enough doses to cause a dramatic remission of their symptoms. He further improved the treatment by utilizing the active isomer, l-DOPA, recognizing that the inactive isomer, d-DOPA (which constitutes 50 percent of the dose in a racemic mixture) is

responsible for 50 percent of the toxicity but contributes nothing to the therapeutic result.

The result was soon confirmed by other investigators and has now become the standard treatment for Parkinsonian symptoms. To his credit, Cotzias realized that this success was only one step toward a definitive treatment. After having a remission, many patients show a disturbing tendency to relapse, even with continued treatment, or to develop movement disorders. He therefore was engaged during the last decade of his life in testing supplementary treatments, especially those utilizing structural analogs of dopamine (like apomorphine) that could penetrate the blood-brain barrier and substitute for dopamine without having to be converted by local enzymes. By a remarkable coincidence, his early interest in the function of bioactive amines in tissues and his subsequent investigations of the toxicity of manganese converged on this problem. Cotzias was at work on the development of new medications when his career was terminated by lung cancer. Like his father, he died at age fifty-nine, before his work was finished.

George was a large man physically and intellectually—restless, fiercely loyal, informed, intuitive, quick in conversation with an infectious laugh that began as a furtive chuckle and grew into a roar. Basically he remained the intense young medical resident who burst into my office in 1946 announcing, “I’m coming, too.” He is survived by his widow, Betty, and a son, Constantin George Cotzias.

Among the honors and awards received by George Cotzias were election to the National Academy of Sciences (1973), election to the American Academy of Arts and Sciences (1970), the A. Cressy Morrison Award in Natural Sciences (1954), the Albert Lasker Award in Clinical Medical Research (1969), the Borden Award of the Association of American Medical Colleges (1972), and the annual award of the

American College of Physicians (1974). He received honorary degrees from Catholic University, Santiago (1969); Women's Medical College of Pennsylvania (1970); St. John's University, New York (1971); and the National University, Athens (1974).

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