

In memoriam Dimitrios Trichopoulos: an argonaut in search of the golden fleece of medicine (1938–2014)

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On December 1, 2014, the epidemiology community bade farewell to one of its most distinguished members. Dimitrios Trichopoulos passed away leaving several colleagues and students in both sides of the Atlantic and all over the world saddened by the loss of a great scientist, mentor and friend. Dimitrios Trichopoulos was Professor of Cancer Prevention and Professor of Epidemiology at the Harvard School of Public Health, Member of the Athens Academy and President of the Hellenic Health Foundation in Greece. He had served as director of the Harvard Center for Cancer Prevention; chairman of the Epidemiology Departments at the University of Athens and at Harvard; and adjunct professor of medical epidemiology at the Karolinska Institute in Sweden. He had published the first study linking passive smoking to lung cancer, had done early work on the association of hepatitis B and C infections and tobacco smoking with hepatocellular carcinoma, and conducted key studies on the role of intrauterine exposures in breast cancer etiology. He received several awards and distinctions, including honorary Doctorates, the Brinker International Award for Breast Cancer Clinical Research, the Julius Richmond Award for the documentation of the role of involuntary smoking in the etiology of lung cancer, and the Medal of Honor of the International Agency for Research on Cancer for his contributions in cancer epidemiology and etiology. He was the teacher and mentor of legions of epidemiologists, medical doctors and other health scientists across the world.

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Dimitrios Trichopoulos was born in the town of Volos, in Thessaly, Greece, close to the ancient Iolkos where Jason and the Argonauts set out from in search of the golden fleece. Son of a surgeon from Minor Asia and a mother who had been raised in Egypt, his Greek family opted to see him succeed his father and take over his clinic and successful surgical practice. He studied medicine at the University of Athens and soon realized that his technical skills would not support a career in surgery. Instead, he set out to study internal medicine and neurology. By a stroke of luck, when he had to cover for his fellow student—later

to be his wife and long life colleague—Antonia in the Department of Hygiene and Epidemiology of the Medical School in Athens, he met Brian MacMahon, Chair of the Epidemiology Department at Harvard, who was then visiting Athens in the context of organizing his international study on breast cancer. As MacMahon and Trichopoulos joked about several decades later, MacMahon discovered in Trichopoulos a trait that most medical doctors lack: the ability to understand logarithms and a sense of numbers.

By now Trichopoulos had realized that his own Argo ship was epidemiology and his golden fleece would be found in medical research. He studied at the London School of Hygiene, Harvard and Oxford University and managed to succeed the unthinkable for the Academic system in Greece: in the early 1970's, he became Professor and Chair of the Department of Hygiene and Epidemiology in the Medical School of the University of Athens at the young age of 33. And he transformed the department into one of the most productive in the world, all without the support of well-funded research infrastructure available to researchers in other settings.

In 1989, when MacMahon stepped down after three decades as Chair of the Department of Epidemiology at Harvard, Trichopoulos took over—his task was not an easy one, for MacMahon had left a heavy legacy. Under the leadership of Trichopoulos, however, the Department evolved into a multifaceted institution that drew heavily on collaborative work, as well as a diversity of new internal initiatives and began an import series of collaborations with investigators in Europe [1]. In 1996, Trichopoulos stepped down and continued to serve at Harvard as Vincent L. Gregory Professor of Cancer Prevention and Professor of Epidemiology. Several years later, in 2013, in his address at the Centennial celebration of the Harvard School of Public Health, he shared his experience of chairing the Epi Department stating that he had served as the least among equals and taking pride in having succeeded and having being succeeded by giants in epidemiology. In this occasion and in the last interview he gave to Michelle Williams, Chair of the Department of Epidemiology at Harvard, for the Voices section of the journal *Epidemiology*, he referred with gratitude, admiration and modesty to several colleagues, with whom he had worked over the years—it was an impressive list of world renowned epidemiologists [2].

Throughout his scientific career, Dimitrios Trichopoulos, in his own words, was taking up “unusual ideas”. His peers would credit this to his original thinking and ingenious creativity, but he would be quick to counter-argue that it was a mere reflection of the constraints of limited resources in Greece which would force anyone to think: “poverty is the mother of ingenuity”. Some examples of his pioneering and innovative work, which is marked by several “firsts”, are listed below.

- He exploited the fact that Greece had a high incidence of hepatocellular carcinoma and studied the role of hepatitis B and C infection, as well as that of tobacco smoking in the etiology of the disease [3, 4]. Notably, in the mid 1970s, it had already been established that hepatitis B virus and hepatocellular carcinoma are positively associated, but what was not known was whether the virus causes cancer or the immunosuppression and hospitalizations associated with hepatocellular carcinoma increase the hepatitis B virus carrier state. With a novel design, Trichopoulos and colleagues addressed this issue and established the directionality of the association and the causal role of the hepatitis B infection [5].
- To this day, Greece has a high prevalence of smoking, but back in the 1970s smoking among women was not socially acceptable. In 1981, Trichopoulos and his colleagues published the first paper on the association of passive smoking with lung cancer [6]. They reported that non-smoking women with lung cancer were more likely to have been wives of smokers rather than non-smokers. Trichopoulos published several other papers on the topic, including one that used an innovative design exploiting tissue samples from autopsies [7]. The documentation of the association of passive smoking with lung cancer did not only establish the lack of a threshold in the effect of smoking on lung cancer risk, but also radically changed the social environment surrounding the smoking habit. For his work on passive smoking, he received the Smoke Free America Award in 1996 and the Julius Richmond Award in 2004.
- It had always been suspected that acute psychological stress may trigger cardiac deaths, but it had been difficult to properly investigate the issue. Trichopoulos and his colleagues exploited the natural experiment created by a major earthquake in Athens and reported an excess of cardiac deaths in the days after the earthquake [8]. This paper has been listed by the Editor of the *Lancet* among the 27 papers deserving to form a Canon for Reading Medicine from antiquity to now [9].
- Though Greece is gradually shifting away from its traditional Mediterranean diet, a large segment of the population still adheres to this diet. In a study he published in the *New England Journal of Medicine* with his wife Antonia Trichopoulou and colleagues, they reported that closer adherence to the Mediterranean diet is associated with longevity and lower mortality from cancer and coronary heart disease risk [10].

A main focus of the work of Dimitrios Trichopoulos had been breast cancer etiology. Among his many important contributions in this field, most notable are the documentation that artificial and early natural menopause reduce breast

cancer risk [11], and the original [12] and repeatedly supported hypothesis that intrauterine and perinatal factors affect adult life breast cancer risk [13]. For these discoveries he received the Brinker International Award for Breast Cancer Clinical Research in 2000 and for his overall contribution in cancer epidemiology and etiology he was awarded the Medal of Honor of the International Agency for Research on Cancer, World Health Organization in 2007.

But over and beyond his accomplishments as a researcher, Dimitrios Trichopoulos was also deeply appreciated and admired as a teacher, a mentor and a friend. He taught in the classroom, but most importantly, he taught outside of it, by example, while doing actual research. His advice to his students was to believe in the work they are doing, be prepared for successes and even more so for failures. He was the first to take the blame for mistakes and the last to place it upon others, firmly believing that the only way to avoid mistakes and failures is by doing nothing—and this was not an acceptable option to him. He repeatedly conveyed the message that there is little variation in intellectual capacity—what makes the difference between success and failure in science is hard work, perseverance and the courage to stand up again after you have fallen. Most importantly, he conveyed enthusiasm and taught kindness, fairness, integrity, generosity and collegiality. I quote his own words: “In science, we need to be kind—disagreement in science requires scientific arguments and not personal hostility and rudeness.” [2]

Dimitrios Trichopoulos remained active, prolific, creative and innovative to the end of his life. He will be greatly missed by many of us.

Conflict of interest The author declares her unconditional respect and profound admiration for Dimitrios Trichopoulos as a person, a scientist and a mentor and wishes to express her deep gratitude to him

for having influenced and shaped her career and life, as he did for the careers and lives of many.

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