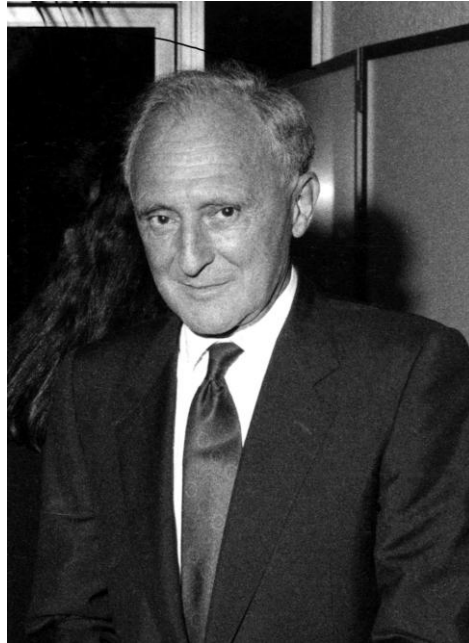


The first Lorenzo Tomatis Lecture



The environmental origin of cancer

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Dominique Belpomme

Professor in medical oncology

Paris V University

Chairman of the Association for Research
and Treatments Against Cancer (ARTAC)

www.arta.info

On Friday 21 September 2007, in Lyon France, we lost Lorenzo Tomatis, a thorough researcher in oncology, a delving scientist, a staunch advocate for public health, a worldwide humanitarian citizen and above all clearly, a true pioneer in primary prevention of environmental cancer.

I would like here to recall some aspects of the career of this giant and trailblazer of environmental health science and public health advocacy, discuss the scientific message he left, examine how we can continue and amplify his work and how we can make new discoveries in the field of cancer prevention in order to bring about an efficient break down of the current growing incidence of cancer worldwide, in close collaboration with national and international institutions.

Let me first remind you how Lorenzo Tomatis reached its reputation as a scientist. Tomatis was born in 1929 and had his early education in Italy. He obtained his medical degree from the University of Turin in 1953. After a brief stint as a medical officer in Alpine troop, he returned to the University of Turin where he specialized in the Department of Pathology.

At that time, like many European fellows, Tomatis visualized exciting research opportunities in the USA and in 1959, because he was perceiving that unravelling the mechanisms of carcinogenesis could be important for public health, he joined the team of Philippe Shubik at the division of oncology, Chicago Medical School, where he was trained in experimental carcinogenesis.

Shubik's group had already established an international reputation in the field of chemical carcinogenesis and Tomatis was rapidly integrated into the team. He published there in 1961 his first paper, which was devoted to urinary bladder and liver cell tumors induced in hamster with O-aminoazotoluene, and in 1962 a second paper on the role of Croton oil in skin carcinogenesis. Tomatis continued to publish throughout his stay in Chicago, but in 1965 his work took a new and very important direction with a publication on the occurrence of tumors in F1 and F2 descendants of pregnant mice injected with polycyclic hydrocarbon and dimethylbenz(a)anthracene, leading to the concept of transplacental and transgenerational effects of carcinogens.

Then he was awarded an Eleanor Roosevelt international Fellowship in 1965-1966 to investigate the response to neonatal exposure to carcinogens. We now know the extreme importance of transgenerational carcinogenesis that Tomatis pioneered, since this aspect has been further developed by several teams in the USA, including Anna Sotgiu and Carlos Sonnenschein's in Boston and is presently extended to pediatrics by Ernesto Burgio in Italy.

By the mid sixties, his scientific papers were well known worldwide. However, coming back to Italy, he realized that his chance to get a position in an Italian research institution was nil. Hence in 1965 his first literary production, *Il laboratorio*, a lucid description of the difficulties through which future academic scientists had to go in Italian universities. It was clear soon after the book's publication that he would never be able to pursue his career in Italy.

Lorenzo Tomatis joined IARC in November 1967 at the age of 38. He created a unit of chemical carcinogenesis and spent his career there developing studies of perinatal, transplacental and multigenerational carcinogenesis, which remained a major goal of his research work. "His pioneering scientific contributions on transplacental carcinogenesis led more scientists to focus on this area of carcinogenesis" said his friend and colleague Takashi Sugimura, director of the national cancer centre in Japan.

Such innovative approach of cancer research was confirmed by Nikolai P. Napalkov, assistant director-general of the WHO, who calls Tomatis' multigenerational studies "some of its greatest contribution in the field of carcinogenesis."

We now know this research area is very important not only for cancer, but also for many other diseases including obesity, type 2 diabetes, allergies, autism and other neurological diseases, which today constitute enormous public plagues in industrialized countries.

An overall objective of IARC is to prevent human cancer and to identify environmental carcinogens as a prerequisite of their removal, i.e. before specific societal measures of environmental primary prevention may be taken.

An important Tomatis' contribution to IARC and to global public health was to promote long-term animal carcinogenicity experiments as valid models for evaluating carcinogenic risks to humans, even in the absence of epidemiological evidence. Hence he considered human epidemiology as a complementary research tool, but not as an exclusive and definitive one, contrary to what some researchers would like epidemiology to be.

As a scientist, I personally agree with Tomatis' point of view on the respective role of human epidemiology and experimental toxicology. Both are essential for the identification of human risks, because both have their scientific specificity, but also their own methodological limits.

Consequently, I disagree on furthering one method upon the other, as it is today the case for epidemiology research, which is wrongly considered by some researchers and politicians to be the best method for establishing human cancer risk.

Tomatis also forecast the need of developing short-term in vitro mutagenicity assays and encouraged research on the role of endogenous detoxification mechanisms of xenobiotics, the interaction mechanisms of carcinogens with DNA and gene-environment interplays in carcinogenesis.

However, during his tenure at the IARC, his major contribution was the creation of what has come to be recognized as the monument of primary prevention of cancer: *the IARC monographs on the evaluation of carcinogenic risks to Humans*.

Since 1972, when the first monograph was published, this series of about 100 volumes has indeed provided objective evaluations of carcinogenicity of agents, mixtures and exposures.

In January 1982, in recognition of his work in cancer causation and prevention, Tomatis was elected by WHO member nations as the second director of IARC. Then he was re-elected and so served overall as director for 12 years.

When he assumed his responsibilities in IARC, not only did he work to further apply and develop his view on an integration of experimental research with epidemiology studies, he also focused his efforts to strengthen the role of IARC worldwide.

Under his personal efforts and actions, IARC was not only identifying cancer risks, but also setting up and carrying out cancer prevention interventions. The Gambia hepatitis intervention study, in order to prevent primary cancer by hepatitis vaccination, is a striking example of what IARC did during Tomatis' management.

And it is not incidental that he gave support to a study in a developing country. Because of his consciousness of the social aspects of cancer throughout the world, he considered cancer not just as a disease to control but as a global public health problem to solve. This explains why he drew attention to the link between poverty and cancer, not only in developing countries, but also in industrialized countries where higher cancer risks are associated with lower socioeconomic class.

In 1990, IARC published a book entitled “Cancer: causes, occurrence and control”, which is a synthesis of scientific knowledge and ideas about cancer causation and prevention at that time. Tomatis, who was the editor-in-chief of this book, set out the two factors he believed to limit the successful development of research in cancer prevention. I quote: “the competition between military expenditure and funds allocated to education and health” and the consideration of basic and applied research as separate competing areas, which he calls “a grave error, which can only serve the purpose of preventing scientists from forming a common front in spending the available resources rationally and efficiently and perhaps obtaining more of them.”

I would add, personally, a third limiting factor i.e. the loss of research independence due to financial corruption in the framework of our current economic system, a consideration that Tomatis had already detected and clearly exposed, when he stated in 2002 that – I quote – “the IARC’s program for the evaluation of carcinogenic risks for humans had to resist strong direct and indirect pressures from various sources to protect its independence.” Such statement appears now more and more evident and reach such a point that several scientists consider that integrity of science is currently under attack.

Over the decades, through his intelligence, cultural and social commitment, as his scientific colleague and friend in Turin Benedetto Terracini stated, I quote “Lorenzo Tomatis was able to recognize the frailty of the mechanisms with which scientific facts are produced, stored and used for public health purposes as well as the vulnerability of scientists and scientific institutions to the flatteries of industrial interests. Over the years, he did not miss any opportunity to point out the blindness, laziness and vested interests leading to ignore scientific findings, which in fact were inadequate to implement preventive measures addressed to environmental carcinogen hazards.

I know that such thoughts about the link between science and the economics may not be well accepted, but as Tomatis wrote in his book, *il laboratorio*, when comparing the situation of research and the role of universities in Italy with the ones in the USA, we need lucid and open critics. As his friends Napalkov and Terracini wrote, Tomatis proved to be so clever that “it was clear soon after the book’s publication, that he would never be able to pursue his career in Italy.” However, what may have been Italy’s loss has certainly been the world’s gain.

Upon his retirement from IARC in 1993, Tomatis served as scientific director of the Institute of Child Health *Burlo Garofolo* in Trieste, Italy, from 1996 to 1999. Shortly thereafter, he joined *the National Institute of Environmental Health* (NIEHS) in North Carolina sharing his experience and writing

important papers on environmental public health and prevention. During that time, he was also the chairman of the Scientific Committee of ISDE, the *International Society of Doctors for the Environment* in Arezzo, Italy.

What lessons Lorenzo Tomatis gave us and what can we do to extend and amplify its pioneering work? The last paper he wrote in 2006, as chairman of the ISDE Scientific Committee, on the identification of carcinogenic agents and primary prevention of cancer, is a clear message he addressed to us. I regret I did not have the chance to meet Lorenzo Tomatis before he died on Friday 21 September 2007 in Lyon. But I consider that I am one of his students. Because following a different way, as a medical oncologist, I came exactly to the same conclusion that cancer is in fact an environmental disease in a majority of cases, and that primary prevention should be considered as a priority avoidance of manmade physicochemical pollution.

There are, I suppose, three main considerations of Tomatis' contributions to the problem of cancer and public health at the period of time we are dealing with.

The first consideration deals with epidemiology. Cancer induction in animals in the absence of epidemiological confirmation (which requires decades) has often been claimed to be no proof of hazard for humans, but epidemiological findings in the absence of knowledge on biological mechanisms have also been considered to be an insufficient proof of causality. We therefore have to clearly reinforce ecotoxicological studies and not to consider epidemiological findings as the sole way to understand what is going on. It is such an approach that we used and still use in Martinique, a French Caribbean island, in which we showed that organochlorine pesticides is probably causally involved in the growing incidence of prostate cancer. Unfortunately, scientific journals with peer review committee are not yet prepared to accept such ecological studies.

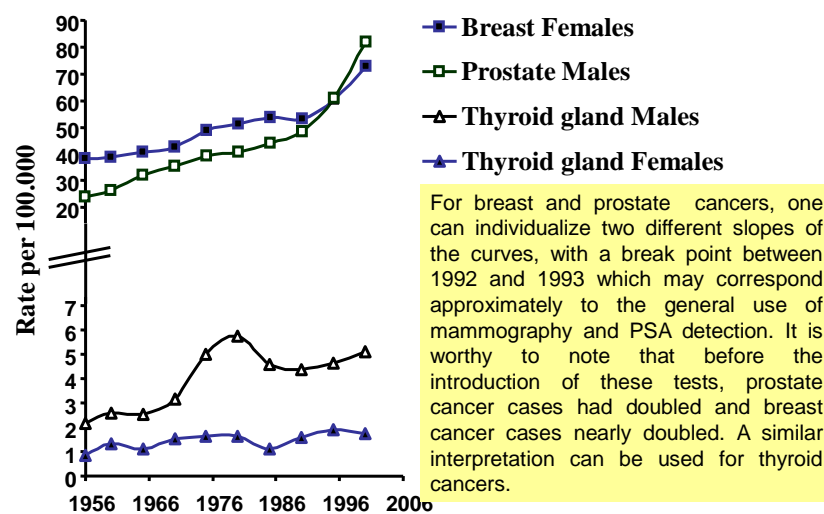
The second consideration: we must realize that governments' decisions (or inertia) often reflect industrial interests (from tobacco multinationals to chemical industries), rather than a will to protect people against environmental risks. This represents both a scientific and societal challenge. In order to promote primary prevention, we therefore need, as scientists to unify our forces and as citizens, to be in close contact with civil society and collaborate with NGOs.

Finally, the third consideration: we must recall that the social and political problems underlying the causes of cancer was a major feature of Tomatis' period as Director of IARC, and remain currently an enormous challenge that we should consider and face. In this context, social inequalities and poverty

associated with cancer remains indeed a milestone, which may explain a large part of the worldwide difference in cancer risk.

A new observation that Lorenzo Tomatis could not have made because of his too early disappearance, is the striking recent growing incidence of cancer in all industrialized countries that neither screening detection nor aging can fully explain. This led us to suspect a possible environmental origin of many cancer cases.

Incidence rates for breast, prostate and thyroid cancers since 1955 in Norway.

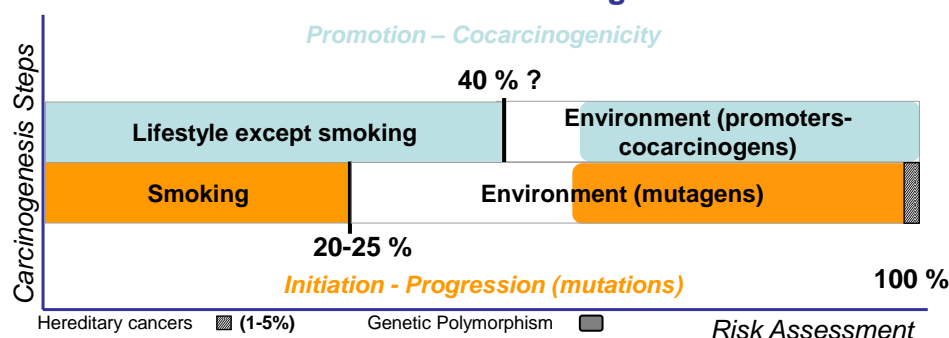


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As reported by my colleague at the ARTAC, Philippe Irigaray, using a method combining epidemiology and experimental data, we estimated the fraction attributable to the environment among overall cancer cases to be in the order of 2 out of 3 to 3 out of 4.

A reappraisal of the risk attributable to environmental carcinogens



Initiators and progressors and more specifically mutators are the main contributors to carcinogenesis, because they allow carcinogenesis to reach an irreversible state. Since less than 5% of overall cancers are estimated to be hereditary and 25-30% causally related to the complete carcinogenic effect of tobacco smoking, we estimate that overall the Population Attributable Fraction (PAF) for environmental carcinogens mutagenic range from 65-75%, while PAF for non mutagenic factors (i.e. for promoters and cocarcinogens), may range from 40-60% according to previous Doll and Peto's estimate.

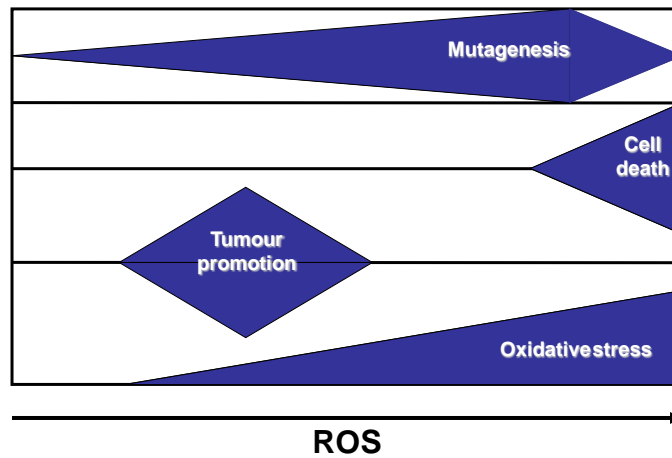
Xeno-chemicals, be they mutators, promoters or cocarcinogens may be therefore involved in the present growing incidence of cancer in high income countries

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Our hypothesis therefore tends to reinforce Tomatis' work attempting to set up an environmental primary prevention of human cancers, especially for children and workers.

In our attempt at explaining the recent growing incidence of cancer, as pioneered by Lorenzo Tomatis, we considered carcinogenic effects of xenochemicals as a priority causal mechanism, and therefore chemical carcinogenesis as a priority process to investigate. But this is not easy, even at the scientific level, because chemical pollution is multiple and diffuse, deals with cocktail effects and involves different types of biological mechanisms.

Representation of a dose dependent hypothetical relationship between oxygen free radicals and cancer genesis



Local doses of free radicals capable of cancer genesis are infratoxic. Doses capable of inducing promotion seems lower than those involved in mutagenesis.



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Hence the Paris Appeal we have initiated in 2004 at the UNESCO's headquarters in Paris, an international declaration on diseases due to chemical pollution, which is now signed by numerous international scientists, several Nobel Prize winners, around 1.000 European NGO's and about 200.000 European citizens. It is also signed by 2 million European doctors represented by the Standing Committee of European Doctors. The Paris Appeal contains 3 articles:

THE PARIS APPEAL: SIGNATORIES

The Paris Appeal has been signed by:

- over 1,000 scientific key figures,
- 1,500 NGOs,
- approx. 250,000 European citizens,
- the Standing Committee of European Doctors which gather all governing medical bodies and other medical organizations, representing the 2 million medical doctors in the 25 EU Member States.



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- **Article 1:** The development of numerous current diseases is a result of the deterioration of the environment.
- **Article 2:** Chemical pollution represents a serious threat to children and to Man's survival.
- **Article 3:** As our own health that of our children and future generations is under threat, the Human race itself is in serious danger.



Protect Women and Children: 2 million medical doctors call out to Euro-deputies

Pr. Dominique Belpomme
For the Paris Appeal Support Committee
www.artac.info (appel de paris)
www.ipetitions.com/petition/paris-appeal

Following Tomatis' gift to humanity, we should unify our forces and bring together scientists to work as one. In this context, we are creating the **European Cancer and Environmental Research Institute** (ECERI), here in Brussels, to foster scientific progress and independence.

Thank you dear Lorenzo Tomatis for your scientific influence, your generosity and compassion, your integrity and sense of ethics. Thank you Delia Tomatis for having encouraged and supported the scientific determination and heroic fight of your husband. Thank you Paolo Tomatis for the help you give us, as a member of ISDE-Italy, to achieve the work of our master Lorenzo.

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The Paris Appeal, International Declaration on diseases due to chemical pollution

<http://www.ipetitions.com/petition/paris-appeal/>