



## Laudatio for Centenary of the Birth of Luigi Di Bella, MD, PhD

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On the centennial of the birth of Luigi Di Bella, the desire to memorialise, at least in part, his thoughts has prompted us to write this tribute, in the hope that one day his dreams may come true.

Throughout his research for a treatment of cancer, he deemed it necessary to employ a complex array of substances that, by acting centripetally on neoplastic cells, could in turn be capable of affecting, either simultaneously or sequentially, the myriad of biological reactions supporting their lives. Hence, not a substance but a method (Di Bella Method, DBM).

These brief hints at some aspects of Prof. Di Bella’s multifaceted scientific vision are aimed not only at reasserting the truth, but also at giving a modest contribution to a novel and free direction in experimental and clinical science.

**Key words: DiBella Method; melatonin; retinoids; somatostatin**

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Neuroendocrinol Lett 2012; **33**(3):247–248 PMID: 22635077 NEL330312L01 © 2012 Neuroendocrinology Letters • [www.nel.edu](http://www.nel.edu)

**T**he desire to memorialise, at least in part, his body of thought has prompted us to write this tribute on the hundredth anniversary of the birth of Luigi Di Bella (1912–2003).

In order to successfully treat cancer, he deemed it necessary to employ a complex array of substances that, by acting centripetally on neoplastic cells, could in turn be capable of affecting, either simultaneously or sequentially, the myriad of biological reactions supporting their lives. Hence, not a substance but a method (Di Bella Method, DBM).

The DBM is characterised by a rigorously physiological and neurophysiological approach. It is to be recalled that the term “biological therapy of tumours” was first used at the Second International Symposium on Somatostatin held in Athens, June 1–3, 1981.

Premise of his understanding is to consider cancer as a form of life and a phenomenon bordering with life’s mystery: a life he defined as “potent, overpowering, parasitic, anarchic”. The first con-

sequence arising from this assumption is that the guiding role of Physiology must be asserted when studying the complex and multiform problem of cancer, from a perspective both investigative-experimental and clinical-therapeutic.

The DBM’s approach to cancer devotes the same attention to healthy cells as to neoplastic cells, thus diverging, since the very beginning, from the cytotoxic principles. We deem it expedient to present, as especially suggestive of his vision, some of the very concepts exposed by the scientist on various occasions.

*“...I have focused on the principle of promoting the biological conditions conducive to preventing further proliferation of neoplastic cells without destroying the pre-existing ones. Hence a hostile biological environment, but not a toxic pharmacological environment. I have arrived at the conclusion that there is not and there will never be one substance alone capable of curing a tumour.*

...One of the means on which I rely is the elimination of growth factors. One of the most potent of these factors is the growth hormone of the anterior pituitary. Therefore, I propose the use of substances that block the production of growth hormone. But one has to employ multiple therapeutic agents.

...As it proceeds, the life itself of the tumour changes. Treating the tumour without taking the evolution of its biochemistry into account is incorrect. If one's vision of the life and physiology of the tumour is not exquisitely dynamic, one is always at risk of being mistaken in the formulation of the therapy, because tomorrow's tumour will not be the same as today's.

...The oncologist ought to be an internist among the most endowed one can imagine, because he has to be able to unveil and interpret what happens in the organism of the patient.

...With the administration of the DBM drugs one acts not on the diseased cell, but on the process leading to the formation of cancer cells. Precisely the opposite of current practice... One of the core principles of my method hinges on the fact that the destruction of neoplastic cells takes place thanks to the competition instituted between the healthy cell, which grows, and the inability of the neoplastic cell to exploit the resources available. In other words, the aim is to re-establish an equilibrium between the healthy cell sector and the neoplastic one. It is by stimulating healthy growth that one blocks the growth of neoplastic cells: not by destroying them. (April 4, 1998. Conference, Teatro Regio in Parma)".

His first experimental studies date back to the years 1939–1946, and were published in the most important Italian scientific journals of that time (Archives of Physiology and Bulletin of the Italian Society of Experimental Biology). The concept was then conceived of an interrelation between axerofol/betacarotene and growth phenomena. To the sixties dates back the clinical use of retinoids, which was supplemented, as early as 1969, by melatonin (complexed with adenosin) on haematologic patients (*Bull Sc Med.* 1974, **145**: 1–3).

...We should connect hemopathies with the stimulation of habenular ganglia on the one hand and with increase in the platelet count on the other. Whereas stimulation of habenulae leads to an increase in the number of platelets, melatonin does not seem to exert a comparable effect. The reason might be that platelets, at the time they are produced, could elicit phenomena capable of overlapping with and/or reversing the action of melatonin. The overall result is dose-dependent and tends to run out after just 72 hours, at which time it can be masked by a rebound in thrombocytosis (*Arch Fisiol.* 1972, **69**: 129–130; *Boll Soc It Biol Sper.* 1974, **50**: 250; *Int Symp on Melatonin, Bremen, Germany, Sept 28–30, 1980*; Gupta et al. editors. *The pineal gland and cancer. Brain Research Promotion.* 1988, p. 183–194).

...Melatonin, as released from platelets in soluble form thanks to its adenosine complex, does not have in and by itself an antiproliferative action. If and when, however, MLT binds to ATP, ADP, nucleic acids, then it is at this level that it exerts an antiproliferative action (*Boll Soc It Biol Sper.* 1976, **52**: 157; *Symp on Melatonin and the Pineal Gland, Hong Kong, July 25–27, 1988*).

...The high transmembrane permeability of MLT-nucleotide complex allows the MLT to play an active role in the transport of nucleobases and in nucleic acids metabolism, by participating in the reactivation of damaged polynucleotide chains. (*Prog Brain Res.* 1979, **52**: 475–478)".

Di Bella briefed also Russel J. Reiter, who went to Italy in 1979 to confer with him at the University of Modena, and was highly impressed by the results obtained, as documented by clinical records: "... Di Bella et al. (1979) [*ibidem*] in Italy has been using melatonin to treat human subjects with various types of malignancies for a number of years. In the publication cited and in a personal interview with the present author he claimed rather remarkable success in the treatment of blood dyscrasias especially... (Gupta et al. editors. *The pineal gland and cancer. Brain Research Promotion.* 1988, p. 54)".

Likewise, somatostatin was first used by the scientist in oncology and haematology by the mid-seventies, when he could obtain the first samples of the substance synthesized by Serono of Freiburg. The relevant observations were published some years later (*Boll Soc It Biol Sper.* 1977, **53**: 42; *2nd Int Symp on Somatostatin, Athens, Greece, Jun 1–3, 1981*).

...Always loyal to the principle of "hypotheses non fingo" ["I feign no hypotheses"] on the grounds that "metuendum est semper, esse cum tutus velis" ["if you want to be safe, be always on guard"], I can only verify the basic principles on the highest possible number of cases, strictly faithful to the maxim of "primum non nocere" ["first, do no harm"], while harbouring the belief that the medical art would certainly improve if the physician could deal not only with the sick, but also and especially with his/her colleagues. Yet, love of one's neighbour, striving to slowly transform the expression of pain into the image of an acceptable prognosis, would be enough to achieve the goal. It is no exaggeration to expect from the doctor the highest level of general ethics...".

These brief hints at some aspects of Prof. Di Bella's multifaceted scientific vision are aimed not only at reasserting the truth, but also at giving a modest contribution to a novel and free direction in experimental and clinical science.