Curriculum of prof. Paolo Bellavite

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Paolo Bellavite was born in Verona on 9 April 1952. He is medical doctor, specialist in hematology, by a.a. 1984/85 Associate Professor of General Pathology at the University of Verona. He holds a Masters in Biotechnology from the University of Cranfield (England) and the diploma of advanced training in health statistics and epidemiology at the University of Verona. The main areas of research of Bellavite focused on molecular and cellular aspects of inflammation, with particular regard to the structure, biochemistry and function (normal and pathological) of granulocytes (neutrophils and basophils) of blood and tissues. He developed numerous micromethods in clinical laboratory to investigate pathophysiology and pharmacology of leukocytes, platelets and free radicals. He carried out scientific research in the context of complementary therapeutic approaches and in particular of high dilutions of agonists and medicines on cellular and murine models. He is coordinating the Observatory for the Complementary Medicines (initiative in cooperation between Ordine of Medicine and University of Verona) and is the delegate for the Veneto Region for these issues. He is the author of over 200 publications including 9 books the last of which is "Complexity in Medicine" (Tecniche Nuove, Milano 2009). 114 his publications are indexed by PubMed.

Website and complete list of publications: www.paolobellavite.it

More specifically, the main issues faced by Bellavite and his research group were as follows (for brevity only 30 publications are cited as representative):

1. BIOCHEMISTRY AND PATHOLOGY OF PHAGOCYTES (NEUTROPHILS, MONOCYTES AND MACROPHAGES).

This is the original and traditional strand of his studies, because since the time of the thesis he has been devoted to the study of the oxidative metabolism of these cells, focusing on the characterization of the systems that generate oxygen free radicals. He pursued the study of molecular bases and signal transduction mechanisms through which the metabolic system of phagocytes is activated, identifying various mechanisms of the functioning of the electron transport chain and by measuring components of the enzyme in neutrophils and macrophages. During the period of employment at the Centre for Biotechnology (Cranfield, England) he dedicated to molecular cloning of the cDNA of a presumably membrane protein associated with the NADPH oxidase complex (Bellavite, Bazzoni et al. 1990). On returning from this period of research, he organized the first unit of active research in molecular biology in Verona. The knowledge gained on systems of activation and transduction metabolism leukocyte contributed to enunciate a unified theory of activation mechanism and the nature of the enzyme NADPH OXIDASE (Bellavite 1988). He showed for the first time that activation systems of adhesion and respiratory burst are considerably separable (Bellavite, Chirumbolo et al. 1992), investigated the mechanisms of priming in leukocyte

responses to agonists and antagonists, physiological and bacterial. Featured also the induced changes in the systems of transduction and in NADPH oxidase by leukocyte migration in vivo into inflammatory with the technique of the so-called "skin" window (Bellavite, Carletto et al. 1994), the effect of leukocyte migration on fatty acid composition of membrane (Bellavite, Guarani et al. 1995).

2. DEVELOPMENT OF NEW METHODS OF INVESTIGATIONOF LEUKOCYTE AND PLATELET FUNCTION.

Continuing a line of research pursued already in the early years of commitment in the laboratory, the author with his group has tried to make increasingly sensitive, reliable and versatile methodologies with assessing, in medical research and clinical diagnostics, the ability of leukocytes to produce free radicals and also to adhere to particular surfaces. He invented and patented a micro-method on whole blood, for measuring simultaneous production of superoxide and opsonizing capacity of plasma (Bellavite, Dri et al. 1983), which is still used by other both in diagnosing both in research in this field. In collaboration with others, but providing a contribution of materials and ideas direct and decisive, has used the technology of biosensors for evaluation of production of superoxide released from NADPH oxidase of neutrophils, the photometry with automated systems for the production of hydrogen peroxide by same cells and a cytometric technology for the measurement of the aggregation and polarization of neutrophils. In his lab Bellavite has developed new and particularly sensitive test (micromethod on 96-well plates) for adhesion ofleukocyte and platelet (Bellavite, Andrioli et al. 1994), with which we have been able to highlight the role of lipoprotein in platelet adhesion (Lippi, Guidi et al. 1998) and who had also many applications experimental clinical and pharmacological field (see below). Still, Bellavite with his group has developed a new methodology for the evaluation of total antioxidant power of plasma (Lussignoli, Fraccaroli et al. 1999). The most recent methodological advancements have occurred due to the set-up, in collaboration with the immunologists, of a cytofluorimetric new approach to the study of activation of granulocytes basophiles of human blood (Chirumbolo, Vella et al. 2008) and a method of analysis-typing of medical parameters of lymphocytes (Ortolani, Bellavite et al. 2010).

3. STUDY OF LEUKOCYTE AND PLATELET FUNCTIONALITY IN SUBJECTS IN DIFFERENT PHYSIOPATHOLOGICAL CONDITIONS.

Bellavite, by activating and promoting many collaborations with various groups of the Faculty of Medicine of Verona and external, has always tried to find the practical applications of laboratory studies and experimental human pathology. The methods of analysis developed by his group have been used in many models pathophysiology and human disease involving the mechanisms of inflammation and/or oxygen free radicals: chronic granulomatous disease, cystic fibrosis, in which he described an increase in enzyme Alpha-glucosidase; leukemias, where it proved the existence of subpopulations immature but functionally active and dysregolated in the production of radicals; severe burns, which are evaluated through ex vivo activation of leukocytes and elastase release; rheumatic diseases, in which he proved the phenomenon of "priming" ex vivo leukocyte metabolism and an increase in migration leukocyte, restricted to the sickness of Behcet disease; leukocyte function in sport or subjects under various test efforts; subjects of different ages and in particular subject very elderly in which proved a desensitization of metabolic response linked to cAMP-dependent signal transduction systems; subjects with chemotherapeutic immunodeficit where he proved a paradoxical risk of pulmonary hemorrhage during the period of

relapse (Todeschini, Murari et al. 1999). Also the cell functionality was investigated with platelet methodology described above in various clinical situations and physiopathological hypotheses, as patients suffering from hypertension, sportsmen, diabetics, those with the genotype PlA2 receptor for fibrinogen (Andrioli, Minuz et al. 2000). Bellavite has always kept aspects clinical-laboratory support research constituted a broadening and deepening of acquisitions of cellular and molecular biology. The experiment of nature constituted by pathology flanked by analysis of molecular and cellular mechanism highlight new phenomena and new mechanisms, such as a form of disease relatively benign chronic granulomatous disease affecting two twins, a form of neutropenia linked to primary increased leukocyte adhesion and pathogenetic mechanism of genetic periodontitis, which has proved the existence of a factor-specific defect in leukocytes (failure or reduced response to fMLP but not to other agonists).

4. STUDY OF THE MECHANISM OF ACTION OF MEDICINES AND OTHER BIOLOGICALLY ACTIVE SUBSTANCES IN MODELS IN VITRO AND IN VIVO.

In experimental models developed by him and above, Bellavite has tested the effects of many types of substances used as probes to identify new drugs and the cellular mechanisms subject to modulation. About neutrophils, he showed the effects of protease inhibitors, inhibitors of prostaglandin metabolism and, in particular, of lipooxygenase, morphine, adenosine, colchicine, pentoxyphylline. On platelets, he showed the effects of Ticlopidine and other inhibitors ex vivo, while in vitro have been detected the paradoxical effects (pro-adhesives) of diclofenac and flurbiprofene and proved that the Nitroderivatives of non-steroidal anti-inflammatory drops have mechanisms of action other than original molecules (Lechi, Andrioli et al. 1996). Also, further studies included in the laboratory of Bellavite cells obtained from healthy volunteers subject to diverse diets for content of nutrients like fatty acids and phospholipids in both neutrophils (Guarini, Bellavite et al. 1998) and platelets (Andrioli, Carletto et al. 1999). More recently, the group showed an effect receptor-specific of quercetin (a natural substance contained in foods) on human basophils, suggesting that it may play a dual role: both of reducing allergy symptoms and of raising defences against infections (Chirumbolo, Conforti et al. 2010). Bellavite and his team paid attention to pharmacogenomics, showing for the first time that platelets of carriers of polymorphism PlA2 have a sensitivity to inhibition by aspirin about 10 times the normal subjects (Andrioli, Minuz et al. 2000). In collaboration with researchers from the Institute of Pharmacology and Immunopatologia of the University of Verona, Bellavite investigated the mechanisms with the induction of tolerance to exogenous antigens in the rat, proving that low doses of Mycobacteria protect against arthritis by adjuvant (Conforti, Lussignoli et al. 1997).

5. SCIENTIFIC BASES OF COMPLEMENTARY MEDICINES

A particular interest of Bellavite and co-workers has regarded the possible scientific bases of complementary medicines like Phytotherapy, Oriental Medicine, Homeopathy, Omotoxycology, a topical for the great interest of the population and the need for qualified health professionals within the SSN. As a result of the work undertaken with the Observatory for the complementary medicines, in 2002 Bellavite was called to take the main report to national Congress of all orders of doctors on the theme of the possible integration of different medical approaches (Bellavite and Pomari 2002). In this vein Bellavite and his group, in collaboration with other researchers, adopted a critical and experimental approach. In particular for homeopathy they contributed to investigate the so-called "law of similars" (Bellavite, Ortolani et al. 2007), revised in a modern laboratory using both cellular models (Bellavite, Conforti et al. 2006b; Chirumbolo, Brizzi et al. 2009)

and animal models (Bellavite, Conforti et al. 2006a; Magnani, Conforti et al. 2010). Very recently Bellavite participated in an international group to outline the relationship between hormesis (positive effect of small doses of toxic substances) and homeopathy, mentioning similarities and differences (Bellavite, Chirumbolo et al. 2010). All experts agree that it is necessary and recommended that this controversial field is engaged by further searches and of higher quality. His expertise in that's also the appointment by the Ministry of health as an expert in National Commission formed in compliance with the data protection act 185/95 to regulate the introduction of Italian Homeopathic Pharmacopoeia. In 2005/7 has published a review on important international journal indexed (Evidence-based Complementary and Alternative Medicine Journal), in six episodes, in which took stock of the connections between modern Immunology and ultra-low-dose pharmacology.

6. STUDY OF FUNDAMENTAL THEMES OF GENERAL PATHOLOGY AND OF THE HISTORY OF MEDICINE

In addition to treat in the form of reviews some topics such as inflammation and cancer, Bellavite has developed a series of theoretical studies and computer models to illustrate typical behaviour of complex systems and far from equilibrium systems (feed-back, networks, chaotic systems and Fractals). With a group of researchers and doctors, academics and extra-University, Bellavite has developed, in relation to these issues, various topics that touch on the history of medicine, ethics and epistemology (Bellavite, Semizzi et al. 2001; A.A.V.V. 2005; Bellavite, Conforti et al. 2005; Bellavite 2009). As the above mentioned, he has also contributed to the founding of the Observatory for the Complementary Medicines (first initiative of its kind in Italy), approved as research by the Institute of chemistry and Microscopy Clinic of the University of Verona on 17 December 1997 and subsequently (2 March 1999) established as an initiative of the order of Medical Doctors and Dentists together with the Faculty of Medicine. The Observatory has edited by UTET a entire book, curated by various authors including Bellavite, with definitions, historical origins and methods of various complementary medicines (Bellavite, Conforti et al. 2000).

In summary, scientific and cultural interests of Bellavite can highlight two aspects, among them strictly complementary and in continuity: a first strand is dedicated to basic studies, with insights on molecular and cellular mechanisms of the pathophysiology of white blood cells and platelets, while another is dedicated to studies of application within the vascular and inflammatory diseases and to attempt to evaluate according to scientific criteria complementary therapeutic approaches.

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