Jean Bernard. Medicine, Science, Humanity

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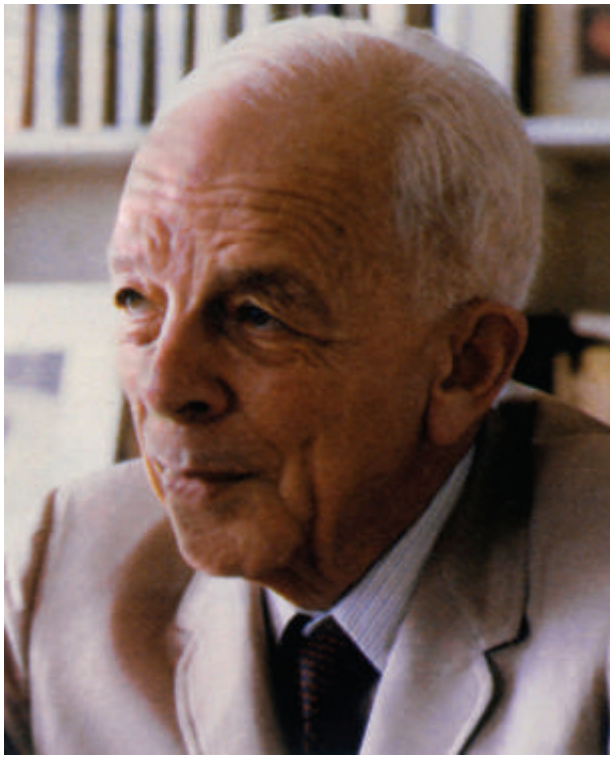
Jean Bernard is quoted as saying "*More progress has been made in medicine during the past 30 years than in the past 3000 years*". This evolution is particularly obvious in the field of hematology. For over 30 years, Jean Bernard acted not only as a participant, but also a promoter, a guide and a reference in hematology. His life was dominated by three poles of interest: - medicine, science and humanity- in the perspective of joining these three aspects and skills in the treatment of patients. His life represents a lesson which is currently applied by all hematologists.

Jean Alfred Bernard was born on the 26th of May, 1907, in Paris. During the first World War, he moved with his family to Couëron, a village close to Nantes, where he attended primary school in a small school that had only one teacher to instruct pupils of all ages. After the war, he returned to Paris, where he attended the *Lycée Louis le Grand*, a famous French secondary school. After hesitating between literature, his hobby, mathematics, becoming an engineer like his father, and a career in medicine, being shocked by the premature death of his mother when he was 13, he decided to become a physician in the belief that medicine is an *"alliance between humanity and sciences"* (C'est de l'homme qu'il s'agit, Ed. O. Jacob, 1988. p. 57).

At that time, hematology was associated with cardiology. In 1927, Paul Chevallier created the French review *Le sang* as a rival to the journal *Archives du coeur, des vaisseaux et du sang*. Jean Bernard's choice for an unknown discipline, with various unexplained and incurable diseases, was influenced by Paul Chevallier. As proof of the fact that luck often plays a role in career choice, the candidate selection for medical residents classified them into three categories; very few were selected, most were rejected, and others with high scores close to the selected group become residents for one year and were obliged to present themselves as candidates a second time the following year. This was the case of Jean Bernard. He chose to be a resident in a small outpatient unit in order to have enough free time to prepare the following year's examination. By coincidence, the unit was led by Paul Chevallier, one of the very rare physicians working on blood and blood diseases. Jean Bernard was fascinated both by his mentor, an eccentric and brilliant man, and by the discipline. Considered by professionals as a minor field with disputes on taxonomy and on the origin of cells, Jean Bernard rapidly understood that the accessibility of blood, and the severity of the diseases, could be the key to the treatment of cancer. In this perspective, his thesis demonstrated the relationship between leukemia and cancer caused by injecting tar (a carcinogenic bitumous substance) into the bone marrow of rats (1933). Paul Chevallier, *"refused official and dogmatic arguments which delayed innovations"*. Jean Bernard learned his lesson and was often charmed by the innovative and anti-dogmatic results and personalities which contrasted with his conventional and punctual demeanor. After the second World War, in which he played a role as a resistant fighter, he was confronted by the contrast between children cured by the recently discovered antibiotic drugs and children with leukemia who died shortly after their diagnosis in distressing conditions. Working as a pediatrician and hematologist with Marcel Bessis, Jean Bernard obtained the first complete remission for two months of a 6-year old leukemia patient through *exsanguino*-transfusion (1947). The leukemia was severe with a white cell count of 86,000, an enlarged spleen, several enlarged lymph nodes and bleeding. This first contested approach brought hope for the treatment of leukemia patients, demonstrating that the evolution of the disease could be reversible. Jean Bernard considered the application of new approaches, development of research and experimental works to be a duty, an obligation and an obvious necessity. Professor of Medicine in 1949, Jean Bernard moved from the *Hôpital Hérold* to the *Hôpital des Enfants Malades* (1951) and then to the *Hôpital Saint Louis* (1957), with a chief nurse Maria Surtel an expert in morphology, inviting Georges Mathé, Michel Boiron, Maxime Seligmann, and Jacques Caen to join the new center for hematology. On the 8th of March, 1957, in an article on the front page of a French newspaper, a journalist reported "*an emotional call from Jean Bernard: it is possible to cure cancers and leukemias. Research is slowed down by the lack of resources*". The Minister of Education, through negotiations conducted by Jean Dausset, decided to build a new institute for blood diseases. The *Centre Hayem* was opened in 1961. Patients were treated on the ground floor close to Jean Bernard's office. On the first floor, biological applications such as nuclear medicine were located. The higher the floor, the further the topics were from being related directly to patients, with animal research being kept on the top floor.

Jean Dausset joined the center, followed by Yves Najean, Jacques Louis Binet, Geoges Flandrin, Marie Thérése Daniel, Claude Jacquillat, Georges Tanzer, Jean Paul Levy, Bruno Varet, Gerard Schaison, Eliane Gluckman, and several other physicians who wished to combine medicine and sciences and who were attracted by this new adventure. I personally spent almost 40 years in the center and I remember the extraordinary variety of skills and the magisterial role of Jean Bernard linking clinical medicine and research, being at the head of both activities. The center was an empire driven with humanity and respect for each participant, whatever their position in the center. Several discoveries testified to the success of assembling various and complementary skills: genetics of histocompatibility, antinuclear antibodies, alpha chain disease, the first successful bone marrow transplantation, cloning and sequencing of hepatitis B virus, cord blood transplantation and differentiation and targeted therapy in acute promyelocytic



leukemia. The major, sole and obsessive goal for Jean Bernard was to cure incurable diseases - the hematologic malignancies - as a model for the treatment of cancer. He personally promoted chemotherapy and demonstrated the marked sensitivity of acute promyelocytic leukemia to anthracyclines. Several young hematologists from Europe, Canada, South America and the Middle East, in particular Lebanon, spent one or more years in the center. Jean Bernard was a mentor for them mainly in clinical fields. He visited all the patients twice a week in the morning, discussing every case with his collaborators, after having met with their families at 7:00 a.m. All of us who worked with him and those who visited the center saw in him a very wise person. His agenda was always full with numerous appointments, some of which only lasted five or ten minutes; however, his timetable was meticulously followed and he was never late for a *rendez-vous*.

During ward rounds, group discussions, staff meetings and more political encounters, he always asked the participants for their opinion in a rather ceremonial manner. At the end of the round table, he repeated chosen words from each of the participants and proposed a consensual conclusion oriented towards his point of view. Everyone felt that he or she had personally played an active role and agreed with Jean Bernard's decision. Jean Bernard admired the images of blood cells, their artistic shape, often made by his close friend Marcel Bessis. He described the morphology and clinical features of a platelet disease with Jean Pierre Soulier (Bernard-Soulier disease). He also liked the history of medicine, in particular the emergence of hematology, reminding everyone that the first description of leukemia was made by Alfred Donné who described the over abundance of white blood cells due to an arrest of differentiation (1844), before the debate between the German Rodolphe Virchow –white blood (1845) - and the British John Hughes Bennett – purulent matter in the blood (1845). His speeches were given without the help of any notes or support; they were carefully divided into three key parts and often punctuated with intriguing stories.

Jean Bernard was a pragmatic visionary, a clear sighted pioneer, who committed himself to the problems of the nation. He decided to create a group of physicians willing to promote the sciences in medicine (Club of 13). He actively and discreetly participated in the planning of research in France, appointed by General de Gaulle (Club of 12 wise persons). He answered the questions of Presidents about future long-term changes due to the sciences first for Georges Pompidou (*Club perspective 1985*), then for Valery Giscard d'Estaing (*Mouvement Universel de la responsabilité scientifique*). Jean Bernard was a government consultant on hospital and university reforms, as well as on addictions and other problems of public health. He was recognized as a wise man by officials, despite his humble behavior.

He was attracted by the demonstration of individuality, "*each person is unique*". He admired the results obtained by Jacques Ruffié on the biological diversity of humans, in various parts of the world, and often reported the evidence of the singularity of each human brought about by studies on the polymorphism of HLA by Jean Dausset. He always respected every single person, not showing emotion, in the face of distress. His emotion and personal points of view were never explicit in his speeches, petitions or even discussions. He rarely expressed his feelings and never showed pain or suffering. However, Jean Bernard and his thoughts can be discovered in the almost fifty books he wrote, which reveal a very sensitive and emotive man. The quill or the pen alleviated his modesty.

The search for the individuality of human, body and spirit, always respectable, led Jean Bernard to create the first Advisory National Committee of Ethics for sciences of life (1976), one year after the Asilomar conference. He defended his opinions at the Academy of Medicine, Academy of Sciences and Academy of France. He was fond of literature, books and writers which explained his assiduity to the Academy of France, a *rendez-vous* of France's most eminent and highly selected authors.

Jean Bernard was the founder of the French school of hematology, with several disciples around the world, the promoter of a successful alliance of science and medicine, mixing scientists and physicians, initiating physicians to have a scientific background. He was also the face of human medicine. He died on 17th of April, 2006. His life is a symbol of the alliance between medicine, science and humanity and a model for future generations. He leaves us a testimony of real values. Hematology will continuously expand with the memory of a pioneer, a founder, and a master: Jean Bernard.

The effect of zoledronic acid on the function and differentiation of myeloid cells

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Background and Objectives. Bisphosphonates are widely used for treatment of osteoporosis and metastases of the skeletal system. Recent data suggest that bisphosphonates may not only reduce bone loss but also exert direct anti-tumor, anti-angiogenic and γδ T-cell activating effects, properties which depend at least partially on their affinity to phagocytosing and antigen-presenting cells (i.e. osteoclasts and monocytes). The latter represent the major source of dendritic cells (DC). Thus, we determined the immunomodulatory properties of zoledronic acid (ZA), a member of the latest generation of bisphosphonates.

Design and Methods. Primary human monocytes, macrophages, immature and mature dendritic cells were incubated with increasing doses of ZA for subsequent analysis of cell surface marker expression and cytokine production. In addition, phagocytic and allo-stimulatory properties, differentiation capacity, and NF-κB activation were determined.

Results. Therapeutic doses of ZA inhibited the *in vitro* generation of DC from monocytes, as shown by an impaired up-regulation of maturation markers. In parallel, ZA also impaired lipopolysaccharide-induced activation of NF-κB, which represents a critical factor for DC differentiation. Accordingly, the activation of allogeneic T cells by ZA-treated DC in a mixed-lymphocyte reaction was significantly reduced. Finally, ZA inhibited the production of tumor necrosis factor-α in monocyte-derived cells and impaired the phagocytic capacity of macrophages and immature DC.

Interpretation and Conclusions. Therapeutic doses of ZA modulate monocyte, macrophage and DC function and might thereby modulate immune function.

Key words: monocytes, dendritic cells, zoledronic acid

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Bisphosphonates are analogs of endogenous pyrophosphates in which the central oxygen atom is replaced by a carbon atom. This chemical modification renders these compounds resistant to hydrolysis and allows two additional chains to be substituted. One of the chains generally contains a hydroxyl moiety that has high affinity for calcium crystals of the bone. The other is responsible for the pharmacokinetic potency of the drug. Newer generation bisphosphonates, such as zoledronic acid (ZA) are 10,000 to 100,000-fold more potent than the older generation bisphosphonates.[1]

Bisphosphonates are currently widely used for the prevention and treatment of osteoporosis as well as skeletal metastases in patients suffering from malignant diseases, such as breast cancer or multiple myeloma, both of which are characterized by osteolytic lesions within the skeletal system. In addition, recent pre-clinical *in vitro* and *in vivo* models provided evidence that high doses of bisphosphonates may not only reduce bone loss by inhibition of osteoclast activity, but may also exert direct anti-tumor and anti-angiogenic effects.[2-4] Bisphosphonates and their metabolites have been shown to share structural homologies with recently identified γδ T-cell-ligands, leading to potent activation of γδ T-cells.[5,6] These effects may represent a potential novel anti-tumor mechanism induced by aminobisphosphonates, which has been linked to the selective expansion of Vγ9Vδ2 T-cells. Indeed, Vγ9Vδ2 T-cells exert potent anti-tumor activity *in vitro* by killing malignant plasma cells isolated from patients with multiple myeloma.[7] In support of this concept, it was found that the combination of pamindronate and low-dose interleukin-2 induced the *in vivo* expansion of Vγ9Vδ2 T-cells in a small cohort of patients with non-Hodgkin's lymphoma.[8] A recent study further demonstrated that application of ZA is able to induce γδ T-cell expansion and function in patients suffering from epithelial malignancies.[9]

Both the anti-osteolytic as well as the T-cell activating properties of biphosphonates have been shown to depend at least partially on the affinity of these drugs for phagocytosing and/or antigen-presenting cell types, such as osteoclasts and monocytes.[10,11] The latter represent key players in the regulation of the immune response and are the major source of dendritic cells (DC). Hence, it is tempting to speculate that ZA, a widely used member of the latest generation of bisphosphonates, exerts immuno-regulatory properties by modulating monocytic cell function and differentiation. The aim of this study was to investigate the effects of therapeutic