

The father of hematologic oncology Jean Bernard (1907-2006) and his contribution to the research and treatment of leukemia

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Summary

Through his medical research and scientific work Jean Bernard dominated for half century in medicine and literature and he was honored as no other scientist. He excelled in

different medical fields and is rightly considered as the founder of hematology, oncology and bioethics.

Key words: Jean Bernard, leukemia, hematology, oncology, psycho-oncology

Introduction

Jean Bernard, member of three French Academies and of several foreign ones, was placed for almost a century in the centre of hematological and oncological research. Among his other successes included is the cure of acute promyelocytic leukemia in children. He excelled also at bioethics, history of medicine, poetry and literature.

became secretary of the French Hematological Society, the first hematological society of the world and in 1936 he obtained his doctorate [2]. In 1939 he participated in

His life and carrier

Jean Bernard was born in Paris on May 26th, 1907. He completed his elementary studies in the municipal school of Couëron (commune in the Loire-Atlantique department). In 1927 he was appointed as an external attendant in the hospitals of Paris and particularly in the Surgical Clinic of Professor Antonin Gosset (1872-1944), Salpêtrière hospital. In 1931 he married Amy Pichon, passed successfully the internship exam and had his first child, a daughter named Antoinette. In 1929, in his first exam for internship (one could present 5 times) Jean Bernard failed for three quarters of point and he started his medical carrier as temporary internal doctor. Planning to compete again, he chose to work at Beaujon hospital; head of department was Paul Chevalier (1884-1960), hematologist, who influenced profoundly young Bernard to become a hematologist [1]. In 1932 he started his doctorate thesis in the research of an experimental model in leukemia (Photo 1). The same year he



Photo 1. Resident in Saint-Louis Hospital, 1932.

the World War II and in 1940 he took part in the French Resistance (one among the 500 Resistance fighters of 1940). In 1943 he was captivated in Fresnes. In 1949 he became associate Professor in the Faculty of Medicine and in 1956 he was named Professor of Oncology. In 1961 he was assigned Professor of Hematology. In 1962 he took the direction of the Institute Georges Hayem of the University of Paris. From 1968 to 1970 he has been Dean of the Faculty of Medicine Lariboisière-Saint-Louis. In 1975 he was elected member of the French Academy; in 1972 member and in 1982 President of the Academy of Sciences. In 1973 he became member of the National Academy of Medicine. From 1983 to 1992 he has been President of the National Consultative Committee of Ethics. He was also an associate member of several foreign academies and he was proclaimed doctor *honoris causa* in several foreign universities.

His scientific work

Jean Bernard's scientific work is immense. It contains, except medicine, history of medicine, bioethics, literature and poetry. In medicine, his work is abundant in the fields of hematology, oncological hematology and oncology.

In this article we shall present Jean Bernard's contribution to the research and treatment of leukemia.

1. The acute childhood leukemia

In his experimental work, Jean Bernard concluded that leukemia was a kind of blood cancer or, more precisely, of blood-forming organs. In his clinical department at Hérold hospital, he had been struck by the "dramatic difference between the possible cure of children affected by meningitis or serious infections and the lethal evolution of those affected by leukemia. The dogma was that leukemia is an irreparable and irreversible disease" [3]. Physicians could only relieve the pain and watch the children dying. However, certain improvements that gave hope in children suffering from acute lymphoblastic leukemia had been noticed after blood transfusions that intended to correct anemia. On October 2, 1947, Jean Bernard and Marcel Bessis applied this method to a 6-year-old child affected by acute leukemia. The first *ex-sanguino* transfusion led to an important improvement of the child's health status. The second *ex-sanguino* transfusion was carried out a few days later. The peripheral blood examination became normal and the leukemic cells disappeared [4]. Two months later a relapse occurred. This first attempt allowed to conclude that complete remission was not synonymous to cure

and underlined the cruel side of reprieve obtained after a transient return to normal life.

Between 1947 and 1960 the complete remission was a rare and brief phenomenon. The therapeutic arsenal was completed with the introduction of cyclophosphamide, vincristine [5], anthracyclines later in 1966 [6], cytosine arabinoside [7] and L-asparaginase in 1969 [8]. After 1960, Jean Bernard and his collaborators reported 50 cases with a survival rate more than 5 years. These cases contained real cures, long-lasting complete remissions with late relapses or they were cases of multiple relapses with a fatal outcome. These long-lasting remissions occurred due to the introduction of new drugs and the use of a reinduction method applied at Saint Louis hospital since 1965. The maintenance treatment was interrupted with periods of aggressive treatment similar to the induction treatment. The long-lasting remissions that were transformed later into cures were still rare.

Jean Bernard had the merit to realize national protocols and particularly he was the first in 1972 to describe prognostic factors for acute leukemia; at the beginning he included the patient age, the number of white blood cells and the tumor volume. The 1974's protocol was the first to take into consideration these factors: the purpose was to erase the negative elements by adjusting the drug doses. So, children without unfavorable prognostic factors received a treatment with drug dosage reduced by one-third, while those having at least 2 adverse prognostic factors received the same treatment increased by one-third. The results of the protocol, which included 450 patients, confirmed the value of the prognostic factors and demonstrated that it was justified to modify the intensity of treatment according to the initial risk. The application of this method improved to a significant degree the results in severe forms of disease [9]. Jean Bernard's team proved that it was also possible to shorten the duration of treatment. Previously indefinite, it was then limited to 5 years and, at present, to 3 years. Also, new prognostic factors were added: biological, cytological, immunological, chromosomal detected by karyotype or by molecular biology techniques. Very important was the effectiveness of the initial treatment detected by molecular biology and realized at the end of the induction chemotherapy. Moreover, the use of bone marrow transplantation, thanks to Jean Dausset's work (Photo 2), allowed "to catch up" the premature relapses, frequent in high-risk disease. So, the survival rate without relapse in the French protocol passed from 54% in 1983, to 74% in 1983, to 74% in 1993, and to 82% in 2000.

Should the cure of the leukemic children be attributed only to Jean Bernard and to his collaborators than to their successors? Certainly not.

Each of the big teams brought progress. Leukemia



Photo 2. With his colleague and friend Jean Dausset (Nobel Prize in Physiology or Medicine in 1980) and Madame Jean Dausset, 2003.

did not become curable overnight. In this fight against malignant diseases, Jean Bernard played a determining role as researcher, clinician and leader of school.

2. Forerunner in psycho-oncology

In 1998, Jean Bernard was wishing to take something with him for his last journey: “I shall take the smiles of children leaving the hospital in their mothers’ arms” [10]. Bernard’s visionary spirit permitted the first research over the psychological impact of acute leukemia and its treatment on children. He was preoccupied, even from the first therapeutic attempts, for the psychological consequences of the therapeutic and prognostic revolution that he introduced. The first article appeared in 1955 [11] and was a historical scientific event as it was the second world article on this subject dealing with all the psychological problems caused by this serious, always fatal at that time, disease. In his department Jean Bernard included into his clinic psychologists and psychiatrists. It was necessary to be two in order to undertake research and therapeutics.

It was the therapeutic progress that allowed the evolution in psychology. And it was both a revolution and an adventure for those patients who had the privilege to survive from leukemia. This evolution had been achieved in 10 years thanks to Jean Bernard and his collaborators. Three articles brought to light the progress: the first one in 1956 described the mechanisms of defense of these children in front of death. This first article facilitated the integration of a psychiatrist and psychologist with the medical team [12]. The second article in 1967 suggested major changes: efficient treatments did exist along with specialized centers, remissions were long-lasting, death was pushed away, cure was evoked. The psychological work was not consisted

in enumerating the defence mechanisms against death but in preparing the parents and the children to find a life as normal as possible during the remission periods [13]. The third article in 1971 described the psychological defence mechanisms of parents and children and the contribution of psychotherapeutics. It allowed the construction of a branch of psychology that studied the mechanisms of defence of the children and families facing a serious illness, its treatments, and possibility of cure [14]. Jean Bernard with his pioneer study at Necker hospital and then at Saint Louis became the founder of the psycho-oncology. He was the first to anticipate the psychological consequences of the intense treatments, the situations of doubt and hope created by disease remission, the long and sometimes difficult adaptation and the cure of a previously fatal disease [15].

3. The acute promyelocytic leukemia

The history of treatment of acute promyelocytic leukemia is associated with the name of Jean Bernard and the Institute of Hematology that he was in charge. From his first years of studies in hematology, Jean Bernard becomes interested in acute promyelocytic leukemia that he described meticulously along with its cause [16]. He described the coagulation disorders (in 1957 and 1959) [17,18]. His name is associated mainly with the high remission rates of acute promyelocytic leukemia and with the first cures after the administration of daunorubicin in 1973 [19]. Jean Bernard always supported the toxic origin of leukemia. In 1950 he injected tar into the bone marrow of rats, and found that this caused leukemia. From then on, leukemia was viewed as a disease of the hematopoietic system rather than of blood. His students followed the road that he had drawn.

4. The chronic myeloid leukemia

Let’s follow Jean Bernard’s own reflection about the behavior of this disease: “Certain chronic leukemias evolve constantly towards death after several peaceful years. The indications and the right timing of a bone marrow transplantation are at present discussed. Is it necessary to interfere early, to risk the accidental death due to transplantation while death due leukemia is not imminent and while the progress of other therapeutic measures can occur during the next years? Is it necessary to wait with the risk of failure if the transplantation is attempted in the terminal stage of the disease?” [20].

Chronic myeloid leukemia is considered as being fatal before the introduction of bone marrow transplantation [21-23]. However, very rare cures were reported after the administration of busulfan [24,25]. Jean Ber-

nard was the first to have cured in 1956 a 3-year-old child with busulfan, who is still alive.

5. *The Foundation of the Medical Research*

“There is no French medical research anymore “ noticed sadly Jean Bernard during the World War II. His critical analysis was more general in fact, embracing the whole clinical medicine of the time, directed on clinical diagnosis to the detriment of biology and therapeutics. Very fast, along with his student Jean Hamburger, he rebelled against this unacceptable situation. He gathered a group of almost 10 doctors, all motivated by the same desire for the renovation of the French medicine. He named this group that became quickly famous as “The club of thirteen ” with the entry of Gabriel Richet and Maurice Tubiana and launched a whole series of studies which were going to form the groundwork of the new French medical research. In a few years they created the Claude Bernard Association, the National Institute of Hygiene which became the National Health Institute of Medical Research and also the Foundation of Medical Research.

Conclusion

In a period where scientific morality, academic dignity and real culture are deprived, the presentation of certain aspects of life and work of Jean Bernard, the leading French doctor and humanist, is imposed.

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