

● History and Heritage

ANTOINE LACASSAGNE

"Cancer is one of the diseases that has benefited most from experimental research which, in turn, has established its peculiar complexity on this object of study."⁹

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Antoine Marcelin Bernard Lacassagne was born on August 29, 1884 in his parents' summer home, in the village of Villerest, near Roanne (Loire), territory of ancient Aquitaine, France. He was the son of Jeanne Madeleine Rollet (1855-1893) and Alexander Lacassagne (1843-1924), a distinguished criminologist and professor of forensic medicine on the faculty of medicine and pharmacy of Lyon. He was the grandson of Joseph Pierre Rollet (1824-1894), a renowned syphilologist and professor of hygiene at the Faculty of Lyon. He had a sister, Jeanne (1883-1972) and a brother, Jean (1885-1960). Lacassagne also had a half-brother, Alexandre, born to his mother in her first marriage to Jean Guillermond. Alexandre Guillermond, became Professor of Botany at the Sorbonne and Member of the French Academy of Sciences. Jeanne Lacassagne married Albert Policard (1887-1972) who became Professor of Histology of the Faculty of Medicine of Lyon and also a Member of the French Academy of Sciences. Inspired by his illustrious ancestors, young Antoine was to dedicate his lifetime efforts to experimental research. He became a pioneer of radiobiology, contributed to the early development of radiotherapeutics, and made seminal marks in the study of carcinogenesis.

Antoine started his elementary schooling in the austere buildings of the Lycée Ampère, on the shores of the river Rhone, in Lyon. In 1892 at age eight, he lost his mother; thereafter, his sister Jeanne became the feminine influence in his life (Fig. 1). His secondary studies continued at the Lycée Ampère; one of his language professors was Edouard Herriot (1872-1957), a notable writer who became mayor of Lyon and Prime Minister of France.³ After high school, urged by his father, Lacassagne spent 1 year in Munich to learn German (Fig. 2).

Upon his return from Bavaria, Lacassagne registered at the Faculty of Sciences of Lyon for studies toward a Bachelor of Letters degree. In 1902 he served in the army establishment located in the city of Vienne (sur Rhone), not far from Lyon (Fig. 3).

Having lived his formative years in the intellectual atmosphere of dedicated physicians and educators, Lacassagne decided to study medicine, not because of any strong attraction, as he explained later, but rather "out of indolence." He completed his pre-medical studies of physics, chemistry, and biology (P.C.N.) and then registered to become a medical student. Concurrently with his medical school curriculum, he prepared for the competitive exercises that qualified a limited number of externs (and later, interns) of the hospitals of Lyon; these exclusive positions assured him of a thorough clinical experience.

During the 4 years of his internship (1908-1912), Lacassagne registered also at the Faculty of Sciences and obtained master certificates in zoology, botany, and geology. These non-medical studies undoubtedly contributed to his eventual strength and originality as a medical researcher.

The Doctorate of Medicine required the presentation and defense of an original thesis. During his internship, Lacassagne sought an appropriate subject for his dissertation. For this purpose, he was presented to the associate professor of histology, Claudius Regaud (1870-1940). There was a fateful encounter, for their characters, talents, and professional activities blended fruitfully in the next three decades and much of their work intertwined. Under Regaud and Thomas Nogier (1874-1947) he became an apprentice, a collaborator, and a coauthor of studies on experimental radiophysiology²⁸; he displayed

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Fig. 1. Jean, Jeanne and Antoine Lacassagne in the company of their father (1895). Courtesy of Madame M. Muller.

a persistent intensity that became his trademark. Regaud had made enlightening observations of the effects of radiations on spermatogenesis; he suggested that Lacassagne study the radiophysiology and the histologic substratum of the effects of irradiation of the ovaries. Regaud also encouraged him to continue preparing for an additional degree from the Faculty of Sciences.

On April 26, 1913 Lacassagne presented his thesis: "*Etude histologique et physiologique des effets produits sur l'ovaire par les rayons X*,"⁴ a work that has never been surpassed. Thus, he was granted his M.D. degree, and in



Fig. 2. Antoine and Jeanne Lacassagne in Munich (1899). Courtesy of Madame M. Muller.



Fig. 3. Antoine Lacassagne in military service (1903). Courtesy of Madame M. Muller.

addition he received a diploma of *Licencié ès Sciences*. As a young scientist full of lofty ambitions, he could not have anticipated the course of his brilliant career.

Pierre Paul Emile Roux (1853–1933), director of the Pasteur Institute, had nurtured the wish to provide Marie Curie (1867–1934) with research facilities worthy of her talents; in 1911 she had received her second Nobel Prize. Working in conjunction with Louis Liard, vice-chancellor of the University of Paris, and thanks to a generous bequest (Osiris), Roux was able in 1912 to make his wish a reality. On a spacious track of land along rue d'Ulm, purchased from the *Dames de l'Adoration*, not far from the Panthéon, the *Institut du Radium* of the University of Paris was to be built. The *Pavillon Curie* for research in physics and chemistry was to be a dependence of the Faculty of Sciences and entrusted to Madame Curie and her collaborators. The *Pavillon Pasteur* for biologic and medical research was to be a dependence of the Pasteur Institute. Roux asked Regaud to accept the co-directorship of the Radium Institute, to be in charge of medical research, with the title of Professor of the Pasteur Institute.

Regaud, although regretful, left the laboratories and the friendly academic support of Lyon, where he had gained strength and prestige as a researcher. In October 1913, barely 4 months after his graduation, Lacassagne accepted an offer from Regaud, to become his assistant with an appointment as fellow of the Pasteur Institute. His decision was frowned upon by relatives and friends, because he was renouncing an academic career that had just started in Lyon.

In Paris, awaiting the construction of the Radium Institute, Lacassagne attended the highly sophisticated course on microbiology, taught by Emile Roux and as-

sisted by Elie Metchnikoff (1845–1916), Charles Louis Alphonse Laveran (1845–1922), and other distinguished colleagues; this course, with its emphasis on laboratory technology, was an enlightening experience. With the Pasteur Pavilion only partially built, Regaud, André Debièrne (1874–1949) and Lacassagne initiated an experimental study of the biologic effects of radon in lower animals. However, when the work had just taken its course, it had to be discontinued in July 1914 as the First World War broke out.²⁵

Madame Curie turned the Curie Pavilion of the Radium Institute into a school for specially trained nurse technologists to serve in a fleet of radiological ambulances. Regaud was put in charge of an evacuation hospital near Baccarat. Lacassagne was attached to the 8th Army Corps that saw action in Sarrebourg and then served on the Meuse and Champagne fronts. In response to a War Ministry call, he volunteered for service in the Orient. He was assigned to the care of Serbian soldiers suffering an epidemic of typhus in a Lazaret, isolated on an island off Corfu: he kept a remembrance of the moving, miserable condition of the Serbian defectors. He later served in Salonica and with the *Chasseurs d'Afrique*.

Meanwhile, Regaud had been recalled to Paris to help in the reorganization of the army medical services. He proposed the creation of a large medical facility near the front, and was appointed director at the village of Bouleuse near Rheims; Colonel Regaud gathered a faculty of the outstanding protagonists of French medicine and surgery.³³ Regaud requested Lacassagne's transfer, to become the bacteriologist of his surgical units. The model medical center was destroyed in one of the last enemy offensives of the war, in 1918.

Shortly after the Armistice, Regaud and Lacassagne were again at work at the Radium Institute. Thereafter, Lacassagne was Regaud's collaborator on every activity (J. Regaud, unpublished data, Dec., 1940). The original scope of their research now included the development of clinical radiotherapy techniques. Regaud's wider professional contacts, during the war, had opened new vistas and opportunities for recruitment: Henri Coutard (1876–1950) was quartered in the basement of the Pasteur Pavilion and put in charge of radiodiagnosis, roentgentherapy and experimental X ray irradiation; for these purposes, he had only one unit but used three different tubes. Regaud and Lacassagne bicycled to the great Parisian hospitals carrying their limited supply of radium needles with which they developed the early techniques of interstitial and intracavitary curietherapy: for cancer of the tongue, the technique of "radiumpuncture," and for cancer of the cervix, the tandem and colpostat.²⁷ Radium was somewhat scarce, so some of Madame Curie's radium was put in solution to collect the radon in an emanation extraction plant; it was then compressed into capillary glass tubes that were placed into hollow platinum needles. Regaud and Debièrne worked out a dosim-

etry system calculated at the source in *millicuries destroyed*.

The rapidly increasing clinical activities required more help. Justin Jolly (1870–1952), a hematologist, took charge of histopathology; he also made interesting experimental observations of the role of blood supply in radiosensitivity. René Ferroux (1892–1954), a physicist trained at Grenoble, was also given space in the Pasteur Pavilion; he designed the first telecurietherapy ("radium bombs") units. Out-patient and hospitalization facilities were available at the Pasteur Institute. Jean Louis Roux-Berger (1880–1957), a dedicated surgical oncologist, took charge of these facilities. Antoine Bécèle (1888–1966), the venerable pioneer of French radiology, became an influential supporter of the clinical activities; he brought Georges Richard (1888–1961) and Mademoiselle Dr. Juliette Baud (1893–1979) as well as Jean Pierquin (1887–1956); they became enthusiastic developers and practitioners of radiumtherapy. Later, a private surgical clinic offered additional facilities, rue Chantin; Octave Monod (1870–1930), a superb diagnostician and internist was put in charge.

Because of an incredible timetable, Regaud and Lacassagne continued their experimental research, making valuable original observations; in 1922 Regaud made his timeless contribution, the greater effectiveness of fractionation.³³ Lacassagne and Monod studied the histopathologic effects of the irradiation of malignant tumors.²² With Madame Lattes and Lavedan, he analyzed the consequences of the injection of polonium in lower animals.²⁴ In doing this work, Lacassagne developed the original technique of *autohistoradiography*.²³ With Coutard, he studied the consequences of the experimental irradiation of ovocytes on fecundity and subsequent pregnancies.²¹ He also wrote on radiotherapy of sarcomas.⁶

The increasing activities and personnel required administration and funds. The authorities of the university and Pasteur Institute, in accordance with Madame Curie and Regaud, decided to establish the *Fondation Curie*. The young Baron de Rothschild was its first philanthropic contributor; André and Christian Lazard were also devoted supporters. Regaud had a bicycle accident: and was forced to accept a chauffeured automobile for his transportation, provided by the trustees of the foundation.

On grounds close to the Radium Institute and accessible through rue d'Ulm, the Foundation erected two unpretentious two-storied stucco buildings. One served as the outpatient clinic with examining rooms, archives of detailed clinical records, laboratory of histopathology and administration; the other accommodated Coutard's expanded roentgentherapy service with eight units and a small addition to the laboratory research facilities (Fig. 4).

The Radium Institute of the University of Paris, what many called the Curie Institute, became a mecca for



Fig. 4. Stucco buildings added by the Foundation Curie (1923). In the forefront the outpatient clinic, on the back the department of roentgentherapy.

those interested in radiotherapy. Visitors were offered a white gown and invited to attend, in silence, the bi-weekly follow-up clinics methodically and didactically conducted by Regaud, Lacassagne or Monod. The examination of previously treated patients gave an opportunity to review details of treatment, sequelae, recurrences, etc. and to discuss causes of success or failure. Those seeking training, mostly foreigners, were required to remain full-time for periods of no less than 6 months, often renewed, and they were rotated through the various services. Lacassagne was in charge of *stagiers*, as the latter were called; interviewed and assigned them. They were among the first radiation oncologists trained in a truly multidisciplinary atmosphere of tumor pathology, surgery, roentgentherapy, curietherapy, radiophysiology and cancer research.³¹ *Stagiers* were required to register and attend the course of several months' lectures and demonstrations, organized by Antoine Bécélère at the Faculty of Medicine. At the end of the academic year, the successful registrants received the *Certificat de Radiologie et Électrologie Médicale*. After obtaining the certificate and completing four additional full-time training periods of 6 months as well as presentation of a thesis, the candidates received the *Diploma de Radiophysologie et Radiothérapie* of the University of Paris.

Regaud and Lacassagne undertook a review of the already extensive literature on radiophysiology and their histologic correlation. They wrote a series of articles on the effects of radiations on the various organs and tissues

with thorough and pertinent references. These articles were published as fascicles issued without regard to regular chronology, and they were eventually gathered into three volumes of *Radiophysologie et Radiothérapie* as the archives of the Radium Institute, edited by them in association with Ferroux and published by the *Presses Universitaires* (1928–1938).²⁷ The publication either reprinted or listed the articles written by members of the staff in various journals. Lacassagne wrote many articles on the result of radiotherapy of cancer.⁵ In 1931 Lacassagne was the chairman of the section on radiobiology of the Third International Congress of Radiology, held in Paris (Fig. 5).

A philanthropist, said to be young and insisting on anonymity, visited Regaud and offered to finance a spacious research laboratory. Adjacent to the stucco structures, a handsome six-storied brick building was completed in 1932 (Fig. 6). The new building provided expanded space for the laboratories of histopathology of Georges Gricouroff (1899–) and his skillful staff, in addition to a comfortable library, a conference room, and radiodiagnostic facilities for Francois Baclesse (1896–1967). One floor of this building was provisionally given to accommodate Regaud's pet project, a clinical study of the possibilities of telecurietherapy. Jean Reverdy was engaged to help in this project. Lacassagne chose to retain his laboratory in the old Pasteur Pavilion.

On October 10, 1932 Lacassagne made a preliminary report to the Academy of Sciences⁷ on the role of female



Fig. 5. Antoine Lacassagne, Chairman of the Section on Radiobiology of the International Congress of Radiology, Paris, 1931.

hormones in carcinogenesis. He was able to produce 100% cases of adenocarcinoma of the breast, by means of weekly injections of folliculine in male mice of a susceptible strain. This work inaugurated the world-wide interest in the use of hormones in investigative oncology. He found that other tumors could be produced by the injection of hormones and also studied the carcinogenic properties of artificial estrogens.⁹ He extended his studies to experiments with the antagonistic properties of testosterone, of the destruction of the hypophysis. For the rest of his life, he retained his interest in hormonal carcinogenesis, alone or in combination with other agents.

The year 1934 was an eventful one at the Radium Institute. Early in January, Irène Curie and Frédéric Joliot, working in the basement of the Curie Pavilion, discovered artificial radioactivity. Thus, they opened the doors of Nuclear Medicine and facilitated biologic tagging as well as the industrial uses of radionuclides.³⁴ Lacassagne and Fernand Holweck (1890–1941) undertook testing the biologic consequences of the notion of *quanta*, the discontinuous absorption of radiations. Using monochromatic radiations, Lacassagne irradiated unicellular organisms, *in vitro*. He observed a variety of effects: instant death due to massive absorption, but also delayed growth, suppressed motility, abortive anomalies of divi-

sion, hereditary malformations, depending on the area of the cell structure hit by the rays.⁸ In the summer of that year, Madame Curie died. Lacassagne recalled his emotion when 20 years previously, he had first been presented to her.¹⁹

In 1936 another important facility was added, the Hospital Curie (Fig. 7). Situated behind the ancient Maronite church, with entrance on rue L'Hommond, the hospital was eventually connected with another structure, rue d'Ulm, across the street from the Institute. The long-awaited hospitalization facilities were complemented by ample operating rooms and accommodated the telecurietherapy service. The new building also offered restaurant facilities to the personnel.

In 1937 Regaud's health started to fail; upon his retirement, Lacassagne assumed the responsibilities that he had long exercised as deputy director. He aimed, however, to rescind all clinical obligations and to confine himself to be director of research. The advent of the Second World War imposed on him the responsibility of all the medical services of the *Fondation Curie*. He was assisted by Mlle. Dr. Baud and by foreign volunteer physicians. Ahead of the Nazi occupation of Paris, Lacassagne and Ferroux transported by automobile eight grams of radium, then worth about one million dollars, to a prearranged cache in a bank at Blois. Upon his return to Paris, Lacassagne renewed his ceaseless activities. The College of France appointed him professor of a newly created

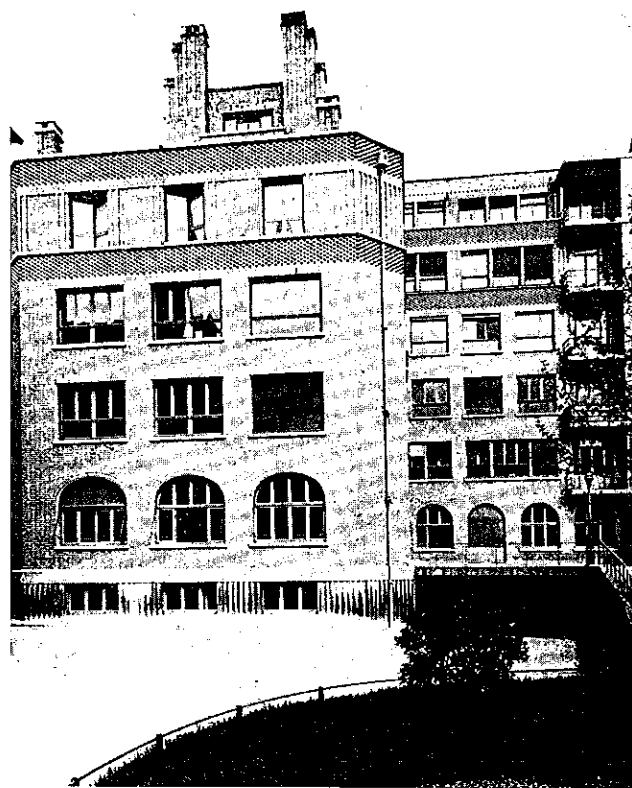


Fig. 6. The anonymous gift for laboratories (1932), now the Claudius Regaud Pevillion.

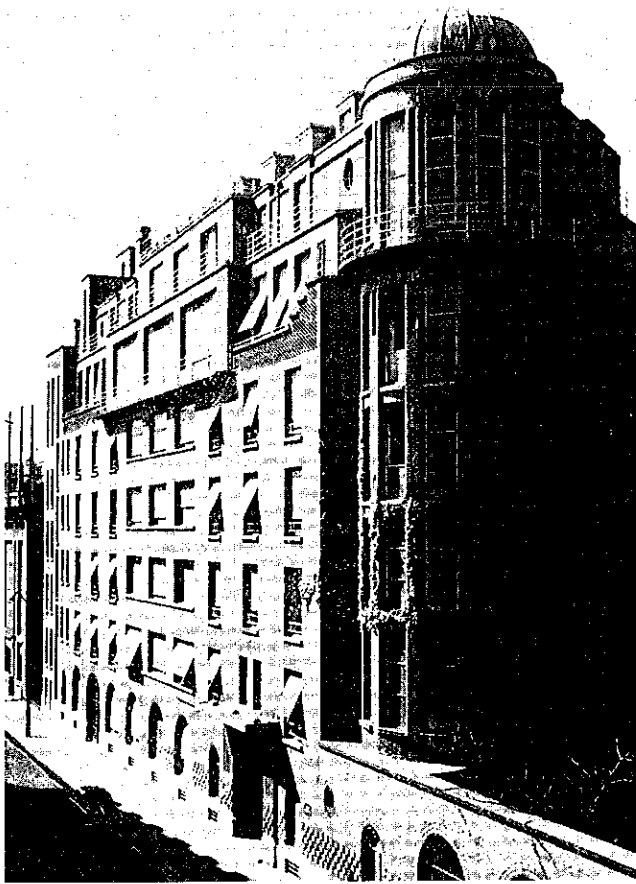


Fig. 7. The Curie Hospital on rue Lhommond (1937).

chair of radiobiology. In collaboration with Joliot, he studied at the College of France the biologic effects of neutrons and continued his studies of carcinogenesis.

The out-of-print volumes of *Radiophysiologie et Radiothérapie* had been in demand, mostly because of their valuable documented review of radiophysiology. Lacassagne and Gricoureff decided to bring its contents up to date in this respect and published (1941) a small volume on the effects of radiations on living tissues.¹⁰ As a valuable publication for residents in training in therapeutic radiology, it was translated into English years later.

Lacassagne first demonstrated *in vivo* (1942) the role of oxygen in radiosensitivity; ingeniously, he showed that newborn mice put into a state of anoxia survived doses of radiations which proved lethal to the non-anoxic control of the same species.¹¹ This laboratory evidence inevitably led to clinical trials of radiotherapy under oxygen pressure.^{15,30}

Beginning in 1943, Lacassagne undertook a long sustained study of carcinogenesis. In 1945 he published an exhaustive study of the carcinogenic effects of electromagnetic radiations.¹² He was impressed by the view of engineer Otto Schmidt of I. G. Farben, who attributed the carcinogenic effects of polycyclic hydrocarbons to the particular distribution of electrons in their molecules.

Lacassagne developed a vast program of research which was, without doubt, one of the earliest examples of sub-molecular biology in the field of experimental carcinogenesis.^{13,26}

After the war, Lacassagne became a titular member of the French Academy of Medicine (1948) and the Academy of Sciences (1949). In 1950 he presided, in Paris, at the Fifth International Congress of Cancer held at the Sorbonne; as a gracious host, he led his colleagues in a visit to a champagne factory near Rheims (Fig. 8).

In 1954, at age 70, Lacassagne accepted the official rule of retirement from his positions as director of research at



Fig. 8. Antoine Lacassagne, President of the International Congress of Radiology, Paris, 1950 and Facsimile of Lacassagne's signature.

the Radium Institute and as professor of the College of France, but he was permitted to keep a small laboratory at the Curie Foundation, where he continued his work. Having worked devotedly in the ranks of the Centre Antoine Bécélère, he was elected its president in 1957. He published (1957) a study of the mechanism of death from total body irradiation,^{14,16} and he continued his work on chemical carcinogenesis.¹³ In 1957 he was elected president of the *League Nationale Contre le Cancer*, and in 1960 he received his nation's recognition as *Commandeur de la Legion d'Honneur*. The American College of Radiology offered him the highest honor in their gift, the Gold Medal (1963) (Fig. 9).²⁹

In his later years, Lacassagne was assisted by his successor, Raymond Latarjet, but also by a host of collaborators in biology, chemistry, physics, and histopathology in a friendly network of affectionate colleagues in various institutions. One of his faithful collaborators, Madame le Professeur Lucienne Corre-Hurst, was director of the Institut Lannelongue, in Vanves, near the *Cité Universitaire* in the Parisian southern banlieue. She offered him advantageous research space in her institution; he was greatly attracted by the surrounding trees and beautiful gardens and accepted with youthful enthusiasm (1965).¹ There, already in his 80's, he created and developed a Research Center which stands to his credit. With the help of private grants and government funds, he equipped the laboratory and continued his research work. He derived justifiable satisfaction from the center at Vanves. In 1969 he received the *Ordre Nationale du Merit* and the *Médaille du Vermeille* from his adopted city of Paris.

For the last 15 years of his life, Lacassagne's attention was captured by the experimental production of cancer

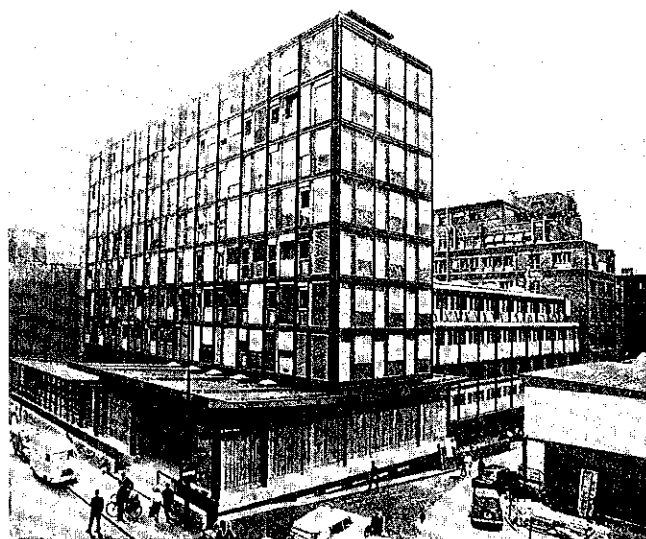


Fig. 9. The Polyclinic, built partly on the grounds of the early stucco structures. On the far right, the rear view of the Claudius Regaud Pavillion.

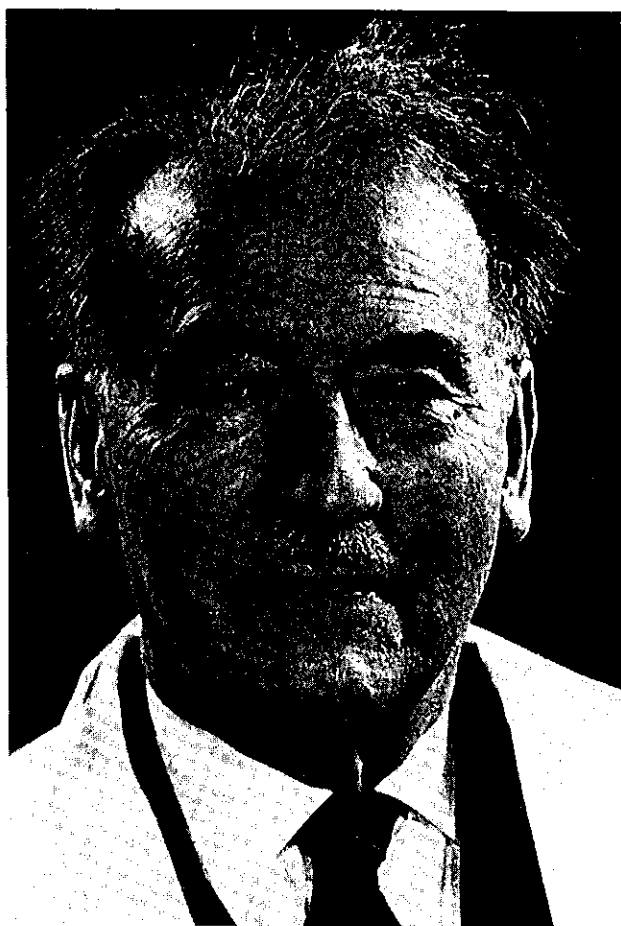


Fig. 10. Antoine Lacassagne, Grand Officer of the Order of Merit (1971), shortly before his death.

of the liver in rats by means of hormones, chemical substances, and combinations of them.¹⁸ The experiments offered the possibility of studying the role of anticarcinogens. He had previously been able to destroy the rats' hypophysis by means of radon. Seeking means of destroying the adrenals, Lacassagne and Hurst decided to use an isomere of dichloro-diphenyl-dichloro-methane (O,P'-DDD), a drug with marked effects on the adrenal cortex; using it in conjunction with carcinogens of the rats' liver, they observed definite inhibitory effects. However, using the drug alone in control rats, they observed after a period of months, the development of adenocarcinomas of the Leydig's cells of the rats' testis.¹⁷ Lacassagne decided to assemble the world's references in the form of bibliography of the experimental production of carcinoma of the Leydig's cells; he finished it in the very last few days of his life. It was published posthumously.²⁰

Antoine Lacassagne was an extraordinary person. In his younger years, his tall slim figure and his expressive face with a small moustache and well-trimmed goatee seemed to be ready to don a cape, wide brimmed, plummed hat, and sword of the *gentilhommes* of a former era. He never married and was, in the words of one

of his associates, a lay monk whose religion was the experimental science at the service of man.³⁵ Throughout his life, there were always ladies who adored him distantly. He was an amiable, kind man with inexhaustible sympathetic tolerance; he showed genuine interest in the views of others and patience with younger men ready to spout their opinions. He lived alone in a comfortable self-styled apartment (Porte Royale Square), within walking distance from the Institute. He lived by his own strict but well balanced rules and took pride in his culinary abilities. He went to bed early but awoke much before dawn, thus increasing the number of hours of daily work. While at home, he granted himself no holidays, but twice a year in the spring and early autumn, he took a short vacation in his *fermette*, near the place of his birth in Villerest. Returning after lectures given or congresses held in foreign lands, he brought seedlings of rare trees that he attempted to transplant to the rather infertile land of his property. Visitors of his laboratory were often surprised to find him watering plants in various places within his laboratory and the garden between the pavillions where Madame Curie shared his interest.

Lacassagne had genuine affection for his family traditions and for the Loire Valley, the region of his origins.

He was fond of history and literature and had great interest in world affairs. He was a true savant and humanist²; he seldom aired his views but was suspected of having liberal ones. He was solicited by a variety of causes, but he gave his support to only a few. In Paris the Salvation Army offered to the *clochards* of the city a bowl of potage and a bunk in a barge on the banks of the Seine. Unsuspected by most, Lacassagne attended the annual dinner meeting of the organization of which he was an Honor Member.³⁵

Monsieur Lacassagne was a passionate doubter with a mystic's respect for the unknown; the search for truth was both his philosophy and his religion. He was a gentle rebel possessed of a wild compulsion to research. An introspective slave of thought, he was subject to its subversive and anarchic influences.³²

Already 86 years of age (Fig. 10) and still impressive by his remarkable memory and intellectual verdancy, he suffered the inveterate tyranny of old age. He hurried to finish his last paper, and as he felt his physical strength relentlessly failing, he wrote brief notes of thanks to his faithful collaborators; principally out of concern for the trouble that he might have caused them, he deliberately abridged his existence on December 16, 1971.

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