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Francesc Duran Reynals (Barcelona, 1899-New Haven, USA, 1958)

Virus and cancer: a controversial theory

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Francesc Duran Reynals was most likely the first Catalan to become a research scientist of world renown [1].

Around 1900 both science and technology were well represented in Catalan society. But those with the highest profiles were the applied fields, such as industrial technology, medicine, or surgery. The weak initiatives of the Spanish state in this area (demonstrated in, for example, a very small university with no outlets for research) practically prevented the existence of any relevant academic world [2]. At the national level science and higher education policy were centered on the University of Madrid, but in the first decades of the century the establishment of research centers was in fact considered. The Junta para Ampliación de Estudios, founded in 1907, included recognized scientists like Santiago Ramón y Cajal, who won the Nobel Prize in Medicine in 1906, and it established the first governmental research laboratories in the 1910s [3].

Catalonia at this time had a dynamic economy, based on a precociously industrialized textile sector, and highly developed agricultural sector as well, both of which created a demand for applied sciences which was satisfied wither by private initiative or by local entities, such as municipalities or provincial administrations. One of the elements of this demand for science was public health, as might be expected in a highly developed urban and industrial region.

Francesc Duran spent virtually his entire scientific career in the Untied States, but he had been educated in Barcelona, in the scientific milieu just mentioned, and throughout his life he cultivated close ties with the Catalan science community.

Some family history

Francesc Duran Reynals was born into a modest middle class family in Barcelona on December 5, 1899. His father, Manuel Duran Duran, a writer and illustrator, was a nephew of the famous jurist Manuel Duran i Bas (1823-1907), who had been rector of the University of Barcelona and, for a few months, minister of justice of the Spanish government, precisely during the year in which Francesc was born. As for his mother, Agnès Reynals i Maillol, she was a daughter of Estanislau Reynals i Rabassa (1822-1876), also a jurist and an important protagonist of the political organization of Catalan conservatism and of economic protectionism. Francesc's father, Manuel, died prematurely in 1906, just after the death, equally premature, of his wife. Their five sons –of whom Francesc was the youngest-were placed in the care of their mother's three sisters, Paulita, Pilar and Anna Reynals, and their niece, Paulita Farriols i Reynals, who guided them through their education.

A polyfacetic family

Between them, the Duran Reynals brothers covered a broad span of professions or activities in the new century, including literature, architecture, law and industry. The eldest brother, Eudald (1891-1917), was recognized as a promising young writer. His early short stories won him a certain fame, but his brief career ended when he was found dead in a pension in Paris where he was awaiting a lull in the War which would have permitted him to travel on to England. His brother Raimon (1895-1966) also traveled in artistic circles. In his early career as an architect he designed Italian-style neoclassical buildings, influenced by Brunelleschi. Later on, he changed his style and was associated with GATPAC, a group of Catalan followers of Le Corbusier and the Bauhaus. He returned to Neoclassicism during the Franco period, but in the last years of his life, he returned to the rationalist style and is today considered the immediate forerunner of the Barcelona school of architecture [4].

The third brother, Estanislau (1894-1950), was a lawyer and leader of the Catalan nationalist group, Acció Catalana. For that reason, he was not allowed to exercise his profession after 1939, because of the policies of the Franco regime. The fourth brother, Manuel (1896-1946), studied chemical engineering at the Industrial School of Barcelona and spent his career in private industry.

If we add to this portrait the international scientific career of the fifth brother, Francesc, we have a picture of a dynamic, entrepreneurial family group, which can be considered representative of the Catalan cultural and social elite of the early 1900s.

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The staff of the Municipal Microbiological Laboratory of Barcelona in 1918. Left to right: (unknow assistent); Puig de Valls; Pere Domingo; Mrs. Domingo; Ramon Turró (seated); F. Duran Reynals; Miquel A. Baltà; Pere Gonzàlez; Mr. Inglada. (Photograph in L. Cervera, *Ramón Turró*. Lliberia Catalonia, Barcelona, 1926).

The Municipal Microbiological Laboratory of Barcelona

Francesc Duran Reynals began his medical studies in Barcelona in 1916, but did not finish until 1925, nine years later. With six «excellents» in 27 courses, he did not cut the conventional image of an outstanding student with a brilliant career ahead of him. But we know that from his first year of medical school –as he himself stated in 1919– he began to frequent the Municipal Microbiological Laboratory, to take advantage of the opportunities for scientific work there offered by the director, Ramon Turró [5].

Duran's first scientific collaborator seems to have been the physician Manuel Dalmau i Matas (1890-1918), considered the young promise of Catalan biology who died prematurely [6]. Dalmau had gone to Halle with a fellowship from the Junta para Ampliación de Estudios to study with the physiologist Emil Abderhalden, who had proposed an immunological theory similar one devised by Turró. With the outbreak of World War I, he returned to Barcelona and won a new grant, this time to continue his studies in the United States. Between October 1916 and June 1917, he studied with Otto Folin and Walter B. Cannon at Harvard University, while visiting various centers of biomedical research, such as the Rockefeller Institute in New York. When he returned to Barcelona, Dalmau was slated to head a research institute funded by the Mancomunitat de Catalunya. For the time being, however, he was named to the Municipal Laboratory of Barcelona, where he died, a victim of the influenza epidemic of October 1918. We believe that Dalmau's term in the United States either began or consolidated the North American connection later exploited by the Catalan biomedical school. The group headed by the physiologist August Pi i Sunyer, a student of Turró's, would establish over the following years very tight scientific bonds with a number of American institutions [7]. Duran himself was to develop his career there.

Anaphylaxis and immunity

The first research projects of the young Francesc Duran were tightly connected to the lines of research already begun by the so-called Barcelona School of biology, led by Turró and Pi Sunyer, and constituted the point of departure of his research career. In 1919, Duran read his first research paper at a meeting of the Society of Biology of Barcelona. It was just a short note reporting an experiment on anaphylaxis and pregnancy. It was well-known that mothers could induce anaphylactic sensitivity in their babies. What Duran wanted to show was that, once that sensitivity was transmitted, the mother became *desensitized*, which might be explained if anaphylactic phenomena could be associated with some substance, possibly a protein. That was exactly what Turró and his collaborator Pere Gonzàlez had attempted to demonstrate some years before. Duran's note appeared in 1919 in the section of the *Comptes Rendus* of the Société de Biologie de Paris reserved for the Barcelona Society's reports. Thus the beginning of his scientific career was auspiciously announced [8].

Between 1919 and 1925, Duran continued studying the relationship between anaphylaxis and pregnancy, sometimes in collaboration with other workers at the Municipal Laboratory. In 1921 he published an article where he seems to terminate this research problem, after the publication of Auguste Lumière's results on the same question. This well-known and polyfacetic scientist from Lyon –he and his brother were pioneer cinematographers– was at the time a proponent of the colloid theory, a chemical-reductionist approach to biology adduced to explain multiple phenomena, immunity among them, by the dynamics of blood colloids. This theory, which quickly vanished from the scientific scene after 1940 was nevertheless a preeminent theory in the inter-war years [9]. Lumière's findings on anaphylaxis and pregnancy contradicted those of Duran, in that they made clear that the sensitization of the mother had not disappeared, and he proposed a colloidal explanation to prove his contention.

Thus, Duran Reynals had begun his scientific career choosing an avant-guard research program –anaphylaxis– which was, apparently, displaced by a world biomedical leader. Even though some authors have seen in this episode a cause of Duran's demoralization, [10] we are inclined to believe –since we lack's Duran's own assessment– that, to the contrary, he may well have felt quite satisfied that, although only a student, he had made a respectable contribution to a research-front problem, thanks possibly to advice received from Turró or Gonzàlez or Dalmau.

In North Africa, 1922-1923

Duran turned next to a new research problem, that of bacteriophage viruses, a research-front issue in world microbiology, and one which would, moreover, be a powerful determinant in his future course. In any case, between the acts of his scientific career, he lived through a dramatic experience: his six-month stay in Melilla in 1922 and 1923, to aid in the repatriation of Spanish prisoners after the «Disaster»» at Annual. Spain held an occupation zone in North Africa, wherein erupted at the turn of the century, a war which eventually led to the decolonization of the zone (except for the enclaves of Ceuta and Melilla, which continue under Spanish jurisdiction to the present day). In 1920, after a few years of peace, hostilities again erupted, leading to a spectacular defeat of the Spanish army at Annual, in 1921. This crisis was at the root of Primo de Rivera's coup in 1923 and proved to be the prolegomena to the fall of the Spanish monarchy, apparently implicated in the corruption of the Army of Africa [11].

In 1921, because of the crisis, Francesc was obliged to appear daily at his military post in Barcelona, until finally in November 1922 he was sent as a medical officer to Melilla, in Morocco. Soon after an accord was reached with the rebels to free (probably in exchange for money) their prisoners. The latter, many of them wounded, had spent more than a year in camps, without any sanitary conditions nor medical attention. According to the testimony of his family, Duran felt the impact of the Dantesque scenes of these camps and the experience scarred him for the rest of his life.

F. Duran as a soldier in Melilla, 1922-1923 (Duran Family Collection)

The world of the virus

Around 1924, Francesc Duran was very likely the first person to obtain bacteriophage viruses in Barcelona (and, probably, in Spain). That was the recollection of the physician Jaume Sunyer Pi when he wrote the obituary of another veteran of the Municipal Laboratory, Josep Vidal Munné, who died in the same year as: «The Fellows [of the Laboratory included] Armangué, Babot, Amell, and the late Duran Reynals, whom I still recall with a [porcelain] mold in his hand, proudly filtering the first bacteriophage to be isolated in Barcelona.» [12]

Viruses appeared in history associated with the most terrible diseases. One of the first to manipulate them was, of course, Edward Jenner, when near the end of the Eighteenth Century he developed the smallpox vaccine, thus inaugurating a new era in the history of Medicine. More than a century later, the nature of viruses continued to elude biologists, given that they are not visible with an optical microscope. They were called *filterable* viruses because they survived in a culture that had been passed through a porcelain filter. Certain diseases were associated with viruses, such as rabies or tobacco mosaic disease.

The medical world received a jolt in 1917 when the bacteriologist Felix d'Herelle (born in Montreal, but educated in France) revealed the existence of certain viruses which were exclusively parasitical on specific species of bacteria, which they eventually destroyed [13]. (Thus they were called bacteriophages –devourers of bacteria.) D'Herelle demonstrated that these viruses were filterable and were harmless to animals or people and so could be used clinically to combat bacterial infections. This discovery provoked a vigorous and somewhat strident debate among bacteriologists, because it put into play concepts basic to Biology and Immunology.

The controversial nature of bacteriophages was no doubt an important factor attracting Duran to them. In early 1925, he presented a series of studies mainly on clinical applications of bacteriophage against typhoid fever, a disease that was still endemic in Barcelona. The results of those pioneering experiments were inconclusive, but they explored a way to combat bacterial infections in the days before the discovery of antibiotics.

Some researchers at the laboratory of J. B. Murphy in the Rockefeller Institute. We can identify: in the front row, from the left. A. Claude and James B. Murphy beside him. We can see F. Duran behind Murphy in the right. (Duran Family Colletion).

In Paris at the Pasteur Institute

In 1925, Francesc Duran completed his licentiate in Medicine (delayed due to his military service) and he now sought to begin a research career by seeking a fellowship from the Junta para Ampliación de Estudios to continue his training at the Pasteur Institute in Paris. His proposal was to study problems related to anaphylaxis and immunity in the department of Alexandre Besredka, at the time a world expert in this area, and to study bateriophagy with Eugène Wollman. Once in París, however, it appears that anaphylaxis no longer interested him, even though Besredka wrote him a letter of recommendation and included Duran's papers on the subject when he wrote a review article on the subject in 1930.

His collaboration with Wollman (who, like Besredka, was of Russian origin), on the other hand, was intense, at least insofar as laboratory work was concerned, because Duran did not agree with Wollman's eclectic theoretical positions in the ongoing polemic among bacteriologists: he believed that the bacteriophage was a «microbe» –that is, a filterable virus– but he also accepted part of the hypothesis of opponents of that view who held that the bacteriophage was purely a transmissible *autolysis*. Wollman thought the bacteriophage to be the result of a mutation passed on by Darwinian mechanisms from generation to generation [14]. Amidst the welter of conflicting hypothesis, each defended with some passion by the different groups participating in the debate, and in view of D'Herelle's priority in this discovery, Duran began to focus on the characteristics of the bacteriophage viruses themselves. Changing the focus of bacteriophage research suggested the advisability of continuing to work in a similar research-front facility. And so in June 1926 in a report to the Junta para Ampliación de Estudios on the first year of his fellowship he argued the advisability of changing the venue of his research from Paris to the Rockefeller Institute in New York. He justified the change in the following words:

> «Very recent research, in particular that carried out by Professor Alexis Carrel of the Rockefeller Institute in New York has revealed the unsuspected relationship that the problem of cancer (in a newly-discovered aspect which he summarizes from the studies of Peyton Rous) with that of bacteriophagy.
>
> In the critical review of the question which I published in the *Revista Médica de Barcelona* [15] which I include, I attempt to establish the analogies clearly.
>
> Moreover, in the past month I have been studying Rous' chicken sarcoma virus experimentally in collaboration with Mlle Harde at the Pasteur Institute, insofar as the means here permit, and will continue working on this problem until the end of my fellowship [16]».

As he makes clear, Duran had learned, while in Paris, of the discovery that Francis Peyton Rous, of the Rockefeller Institute had published in 1911. Rous described the exis-

A photograph of the Rockefeller Institute in 1928, published in an article on Cancer by F. Duran published in the Catalan journal *Ciència*, December 1928.

tence of a sarcoma –that is, a cancerous tumor– of chickens that was transmissible from one chicken to another. The causal agent was filterable and could thus be presumed to be a virus. In this way, there occurred the possibility of an infectious theory of cancer which then entered into play with the numerous other theories attempting to account for this terrible disease. Duran Reynals was to become one of the most tenacious advocates of the viral theory of cancer.

The discovery of spreading factors

Duran's research in New York yielded a surprising byproduct, one that was tangential to his main research program and which led to an authentic physiological discovery, which Duran called the «T» –testicular– factor, because he first found it in this type of tissue.

When he first arrived in New York, Duran had wanted to work in the laboratory of Alexis Carrel at the Rockefeller Institute, however he soon switched to the laboratory of James B. Murphy, whose approach to cancer was more congruent with his own. There he immediately set to work on Rous' chicken sarcoma. In 1927-1928, while he was working in Murphy's lab on the receptivity of viruses in different tissues and organs in a great variety of conditions, Duran discovered that the addition of testicular extracts to the saline solution in which the infectious material was suspended greatly augmented its spread. The discovery, first communicated the Société de Biologie of París in June 1928, led Duran to suspend his research on cancer, and to begin an important series of experiments on spreading factors [17]. He examined the effect of the factor on a great variety of substances, from venoms to Chinese inks, in order to understand the dynamics of the process. The ink experiments suggested a second effect of the T factor, which increased the permeability of host cells to exogenous factors. He also found great quantities of the T factor in neoplastic tissues, which led him to think that its action might also clarify the mechanism by which normal tissues were invaded by cancer cells.

In a long article reviewing his research published by the Pasteur Institute in 1936, Duran observed that the conjunctive tissues where spreading phenomena took place had never played much of a role in pathology [18]. His 1928 discovery of spreading factors coincided with the end of his Spanish government fellowship. In the same year, however, he was hired by the Rockefeller Institute.

Duran acquired his international reputation between 1940 and 1950 thanks to his research on the spreading factor, without doubt the aspect of his work which attracted the attention of the biomedical community. During World War II Josep Trueta, the exiled Catalan physician then residing in Oxford, was interested in the spreading factor from the opposite viewpoint, that is, the depermeabilization of tissues facing a bacterial invasion. Somewhat earlier, his colleague E. S. Duthie had identified the spreading factor as the enzyme hyaluronidase. Thus the research begun by Duran was extended to include evidence of the relationship between spreading factors and the basic structure of conjunctive tissue which appeared to play a relevant part in bacterial infection. In 1943, Duran published the results of his studies of the relationship between the spreading factor and the ability of a spermatozoon to penetrate the uterus and ovum [19].

In a keynote lecture at a meeting on hyaluronidase in 1948, Duran again summed up the meaning of his discov-

A photograph of F. Durant in 1936 in *La Medicina Catalana, January* 15, 1936, when he was awarded a prize for a cancer report.

ery: this research, he said, «might well provide a lesson for bacteriologists, who are overly focused on the agent of infection and not nearly enough on the problems of the host. Furthermore, they ought to bear in mind that certain diseases, cancer especially, might well be induced by physiological factors which become pathological.» [20] Duran thus used this platform to attack the blind acceptance of endogenous theories of the etiology of cancer which excluded contagion theories.

The Servet Institute

In the fall of 1932, after the onset of the Second Spanish Republic and of Catalan autonomy, Duran began to think of going home and establishing a biomedical research institute in Barcelona. That institution, whose full name was «The Miquel Servet Institute for the Study of Cancer and Other Diseases of Unknown Etiology», was supposed to include a Foundation which would send students abroad for advanced training, which would publish a journal (in French, perhaps in imitation of the journal that Ramón y Cajal published in Madrid) and monographs, which would organize specialized courses and, in Duran's own words, would «raise the cultural level of the medical profession generally». Duran sought financial support not only from the Rockefeller Foundation but also from the municipal government of Barcelona and from the Generalitat de Catalunya, the recently reestablished regional government. Problems arose, however, because his pitch to the Catalan authorities was oriented towards public health, while at the Rockefeller Institute he was known as a researcher, not as a clinician. As a result, he proposed to continue his work on «filterable chicken sarcomas» in Barcelona, as well as other neoplastic processes in mammals (duck and rabbit sarcomas), along with his research on the spreading factor. Miquel Pijoan who, in 1931, was working in the laboratories of Pomona College, California, applied Duran's method to twenty different kinds of bacteria and found that the factor considerably increased the infectious power of all of them. This convinced Duran that a similar research program could be applied to the solution of diseases endemic to Catalunya, like Malta Fever (also called Barcelona Fever) and trachoma.

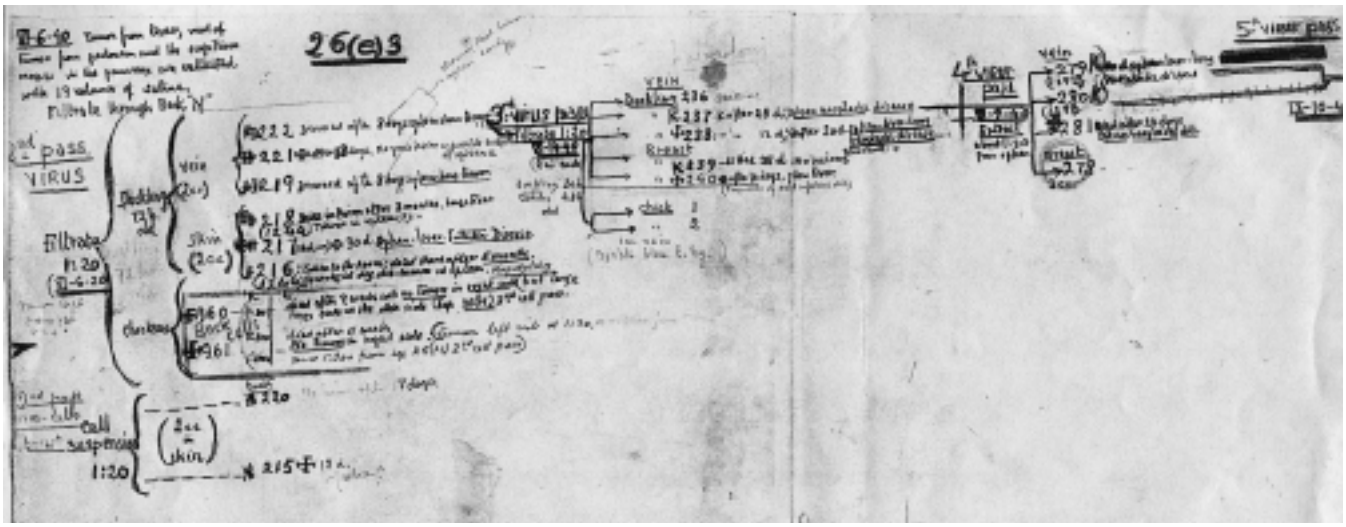
The Servet Institute was supposed to have been associated with a municipal cancer hospital. Duran had, in effect, conceived an American-style plan for the fight against cancer in Catalunya, directed by a research institute and a specialized hospital associated with it. The Rockefeller Foundation, however, was not interested in the project, probably because its clinical orientation was tangential to its objectives of stimulating research and training scientists. Moreover, the Foundation did not approve of the rigidly centralized model that prevailed in Spain and which stressed teaching and pedagogical objectives.

Duran tried to avoid these fears arguing that the plan would be modified by Catalan autonomy and by the new structure of the University of Barcelona. In any case, it is more likely that the Rockefeller Foundation would not approved the kind of cancer research that Duran proposed either. In fact, the Foundation was backing Pío del Río Hortega's histological approach to cancer in Madrid, and was not interested in the virological approach represented by Duran. So Duran wound up isolated, knowing that there was no prestigious institution in Barcelona left to support his views.

In 1934, Pere Domingo, a close friend of Duran's in Barcelona, advised him to renounce the foundation in Barcelona of an institute modeled on the Rockefeller or the Pasteur, and that he advance a more modest project that could fit in the Municipal Laboratory and the University of Barcelona, where Duran could teach Oncology. None of this could come to pass, however, in view of the change in the political scene after the conservative came to power in 1934 and with the revolutionary situation in Asturias and Catalunya in October of the same year.

Nevertheless, in the summer of 1935, Duran reached an agreement with J. M. and M. Roviralta, brothers who owned a construction company called Uralita, towards establishing an institute along the lines of his original plan. As an initial step, he recruited three young scientists who had already been sent to New York to further their training at the Rockefeller Institute: that is, Jordi Folch-Pi, Jordi Casals, and Vicenç Moragues.

In March 1936, Duran married Maria Lluïsa de Ayala, a medical researcher whom he had recruited to work in Alexis Carrel's laboratory. Finally he left his position at the Rockefeller and, in June 1936 arrived in Barcelona to direct the new center. No sooner had he arrived in Catalunya than he was surprised by the outbreak of the Spanish Civil War in July of that year. By chance, Francis Peyton Rous was in Spain at the time and later explained to Duran that «we left Spain not



Protocol corresponding to the F. Duran's research on reciprocal infection of ducks and chicken. The article appaered in 1942 and has become a «classic» text of Virology. (Duran Reynals Papers, Countway Library of Medicine, Boston, USA).

five days before the war broke out. We were unaware of our own good luck! The trip itself was wonderful. The recent course of events made a strong impression on us and we wondered where you were and how things were going» [21].

In July, Duran sent an anguished letter to his former employer, Murphy, asking to be reappointed to the Rockefeller Institute for one year [22]. Soon after he received a cable informing him that his appointment had been reestablished. As a result, Duran left Barcelona on September 27. He returned to Murphy's laboratory and renewed his research on the spreading factor, focusing on snake venom. Murphy recalled Duran's bad luck in a letter to Giovani Favilli: «You may have heard that the very promising beginning made by Reynals in establishing a research institute in Barcelona was completely crushed by the revolution. After some delay we succeeded in getting his reappointment on the staff here and he finally escaped from Spain. He was very much broken up by the experiences he suffered during the four months of terror in Barcelona» [23].

At the same time, he continued experiments on the viral theory of cancer, for example, to see whether viruses could be detected in frogs injected with chemical carcinogens. Duran believed that endemic kidney tumors in *Rana pipiens* were caused by a virus, but only developed in conjunction with some unidentified agent. The notion of a *latent* virus with carcinogenic properties continued to fascinate him.

The viral theory of cancer

When Duran began his research at the Rockefeller Institute in 1926 there were two approaches to the problem of cancer: the orthodox view held that cancer was a disease of cells, rather than organisms, and was generated by an endogenous process in individual cells. The competing view was in a Pasteurian mode: cancer had to be caused by a pathogenic agent which acted like a yeast. The Pasteurian style which Duran's research papers published from the 1920s up to his death was characteristic of the scientific milieu of the Municipal Laboratory of Barcelona and of the generation of scientists trained in circle of Ramon Turró.

Duran was initially drawn to the well-known research on the chicken sarcoma performed by Rous and Murphy before World War I. Rous and Murphy had shown that a filtrate prepared with the sarcoma and free of any cellular matter would continue to cause lesions when injected into other host chickens [24]. Even though they alluded with extreme caution to an unidentified infectious «agent». Duran suspected from the start that a virus was involved.

As we have noted, the greater part of Duran's research before he returned to Barcelona in 1936 was on the spreading factor. When he returned to the United States, however, neither Murphy nor Rous were interested in investing time or energy on the viral theory. Because of Duran's commitment to this theory, both Murphy and Rous thought it would be better for Duran to work elsewhere and they found him a position in the Department of Bacteriology at Yale University, where he started work in the fall of 1938. Directly after his arrival, Duran wrote to Murphy that he had abandoned the term *agent* of the chicken sarcoma and had adopted that of *virus*, «to conform with the expression used by everyone here and in England where so much work is being done on the subject» [25]. Murphy was enraged. «I think you are familiar with the reasons back of my use of terms in regard to the chicken tumor group», he replied. «It has always seemed to me a mistake to dump an agent of unknown nature into a group the nature of which is as varied and uncertain as the virus group». He told Duran that his «action will be taken as a deliberate slap in the face for me», adding that he had already detected Duran's change of mind in 1936 [26]. No doubt because of the strident tone of Murphy's letter, Duran held off on the terminological change and continued using the term «agent» in his 1939 publications. But, starting in 1940, he used terms like «tumor virus», «Rous' virus» or «Rous sarcoma virus». He had declared his independence with respect to Rous and Murphy.

A photograph of Francis Peyton Rous (1879-1970) offered to Duran in June 1936. (Duran Family Collection).

At the International Cancer Congress in September 1939, Murphy asserted, in a veiled allusion to Duran that, even though the chicken sarcoma research was promising, «there seems no justification, in the light of the mass of negative evidence, to discuss seriously a hypothetical universal virus as the cause of cancers» [27].

In the early 1940s, Duran designed an elegant series of experiments to demonstrate the action of the chicken sarcoma virus. First he found that the younger the host animal, the greater the effect of the filtrate, and second, that it caused two different diseases: first, a hemorrhagic disease and, later, a cancerous tumor or sarcoma. That led Duran to speculate than an ordinary virus could, under specified conditions, have carcinogenic effects.

Even though a number of viral cancers had been found in animals, the filtrates derived from tumors had been specific to each species and harmless when injected into a different species. Duran considered this fact to be the greatest impediment to a general viral theory of the etiology of cancer: if each virus was species-specific, there would have to be millions of them.

In 1942, Duran executed a series of highly ingenious experiments where he demonstrated, first, that the chicken sarcoma virus could cause hemorrhagic lesions in ducklings and that when, in growing, these ducklings developed a sarcoma whose filtrate did not cause cancerous tumors when injected into chickens: the chicken sarcoma virus had become a duck sarcoma virus! The ability of these viruses to change their nature became a significant point in the development of a more general theory.[28]

In 1953, Duran proposed a ten-point theory of the viral etiology of cancer [29]: the pathogens were either simple or complex, and of variable size; they were antigenic for heterologous species and frequently for homologous ones; they have a definite morphology revealed by the electron microscope [a new technique that arrived too late in Duran's career to have affected his research]; they are specific to species and tissues; they could be masked; some viruses are able to adapt to different species through a process of variation; all these cancers are conditioned by genetic and hormonal factors; they infect immature hosts, even though the disease is not manifested immediately; they have a well-defined mode of transmission; some cancers destroy cells in young hosts, while they stimulate the same cells in more mature hosts to grow uncontrollably. As he stated in a lecture to the Association of Pathologists of Quebec in April 1955, Duran believed that his theory was based «on the classical principles Microbiology that Pasteur established» [30].

Peyton Rous

One of the most complex and significant aspects of Duran's career was his ambivalent relationship with Peyton Rous. The relationship was not so much ambivalent in personal terms, because Rous –as his private correspondence demonstrates– always referred positively and affectionately to Duran, but rather in scientific terms: Rous' curious ambivalence with regard to his own results of 1912 on the «agent» of the chicken sarcoma strongly influenced his own position on Duran's research. We consider his ambivalence odd because even though the Nobel Committee recognized the «agent» as a virus when it awarded Rous the Nobel Prize for Medicine, he still refused to recognize it as such. When Duran sent Rous five articles for publication in the *Journal of Experimental Medicine*, the journal of the Rockefeller Institute, Rous rejected them all for a series of reasons that he explained to Duran's superior at Yale. This letter is a good example of Rous' habit of praising and criticizing Duran in the same breath:

> «Reynals has the gifts of twenty ordinary workers, but they are matched in almost as great degree by defects. His capacity to persuade himself is extraordinary... The work of the papers now returned is some of it excellent but not all of it good, and his conclusions are sometimes deplorably wild...
>
> I have a stake in Reynals, one of affection as well as of confidence in his real powers... Shouldn't Reynals' papers be water-tight in thought and demonstration, and at least passable in language before they are sent anywhere? [31]»

These five articles, after Duran made adopted some penciled corrections made by Rous, were published, not in Rous' *Journal*, but in the *Yale Journal of Medicine and Biology* [32]. Bearing in mind that at least one of the five –on hemorrhagic disease in chickens– was quickly recognized as a classic of Experimental Virology, we can conclude that Rous' objections were not directed against Duran personally, but rather against an explicit formulation of a viral theory of cancer. We can see this complex relationship more closely by examining annotations that Rous made in the margins of Duran's 1945 grant application to the Childs Foundation. We regard this evidence as particularly revelatory of Rous' stance because the document is a strictly private one, for Rous' eyes only. In the following extracts, we reproduce

F. Duran in his laboratory at Yale in 1957, just before his death. Photograph by Ken Heyman, *Life Magazine*. (Duran Family Collection).

Rous' penciled comments after the relevant phrases in the text of Duran's application:

«FDR: Cancer is a disease of adult and old age.
PR: Only because it's not induced ordinarily until that time. [This is a distortion of Duran's concept of the masked or latent action of viruses. TG/AR]
FDR: Practically all of our work hinges on a principle, which establishes the fundamental importance of the age of infected individuals in the manifold manifestations of viral infections, one of which is cancer.
PR: The generality of course may be due to endogenous agents, some of which may prove transmissible experimentally. But the disease is not a «virus infection.» [Here we see how Rous still resists any conclusions that might be extracted from the evidence that he himself had obtained with the chicken sarcoma virus. TG/AR]
FDR: Many tumors arising in young chicks proved easily transplantable, while only one case for a tumor for an 18 month old chicken.
PR: The old chickens have neutralizing antibodies which act in extracts of the tumors.
FDR: (summarizes the infection of progressively older birds with viruses inducing sarcomas).
PR: That only chickens in middle life should yield tumors transplantable to ducks doesn't sound reasonable. Isn't he generalizing from too few data? [The protocols of this particular series of experiments were viewed, and are still viewed, as especially complete. TG/AR]
FDR: Can one adapt [chicken viruses] to mammals?
PR: A far cry! [Duran in fact achieved such an adaptation in mice. TG/AR]
FDR: (discuses the loss of immunological identity).
PR: Does it really happen?» [33]

In our view, the ambivalent relationship between Rous and Duran can be explained in terms of their differing professional cultures. Rous, an experimental pathologist, was interested in describing and defining lesions, but had no interest in nor feeling for the dynamics of the infection. Duran, by contrast, had been socialized early on in the Pasteurian traditions of Turró's school. Thus did he focus on that process of infection, whose relevance to cancer was difficult for Rous to admit (even though, in reality, he finally did so).

In 1957, Rous was favorably inclined enough to recommend Duran for a grant from the American Cancer Society based on his study of the chicken-duck transference in which he had «again made plain a widening of the scope of virus action» [34]. The application was successful, but did not come to fruition «because of the fatal character of Reynals' illness» [35].

In spite of the deep-seated resistance to the viral theory, Duran's articles were frequently cited in the 1950s and 60s (637 citations between 1955 and 1964, according to the *Science Citation Index*, including 71 citations of his 1940 article on hemorrhagic disease of chickens). Although the current orientation of cancer research has shifted from Virology to Molecular Biology, the research of Duran Reynals was

among the earliest to assert –in effect– the existence of oncogens, even this concept was not part of his conceptual framework. Since his death, many more viral cancers have been discovered in animals, although few in human beings. The first virus that induces cancer in humans was discovered in 1978 by Robert C. Gallo. Moreover, Kaposi's Sarcoma, a cancer associated with AIDS, apparently confirms a process foreseen by Duran. As an experimental system, Duran's program of research on virally-induced cancers has been highly productive.

The case of viral theory of cancer and, in particular, the identification of the chicken sarcoma *agent* as a virus is most interesting from a cognitive perspective and also as a comment on the behavior patterns of scientists [36]. When Peyton Rous received the Nobel Prize in 1966, he had finally overcome his reluctance to consider the agent he had discovered fifty years before a virus. It is clear that understanding of viruses had greatly advanced and they came to be seen as a more highly defined natural entity. The same could be said of the Belgian physiologist Albert Claude, who also had worked with Duran Reynals, when he won the Nobel Prize in 1974. He too had entertained many doubts as to the identification of the sarcoma agent and was not prepared to admit it was a virus until 1947 at the earliest (after Duran's experiments), which led to a confrontation with Murphy.

Duran Reynals died of cancer in New Haven on March 27, 1958. He had fallen ill some eight months before with a rare kind of intestinal cancer which later metastasized to the brain.

There was a strongly heterodox component in the ideas and theories that Duran espoused, even though his prowess as an experimentalist was universally recognized. Insofar as identification with Catalan culture as a citizen of the United States, where he was fully involved in the life of his university community, he never renounced his origins. Up to 1936, he maintained close ties with his colleagues at the Municipal Laboratory and published Catalan versions of his articles in the journal of the Societat de Biologia. After the Civil War, he adopted a personal posture of opposition to the Franco regime, and only returned to the country once before his death, in 1950, when he renewed contacts with his old colleagues, some of whom had suffered reprisals by the authorities. In 1948 he accepted nomination as a corresponding member of the Institut d'Estudis Catalans and kept up both personal and scientific correspondence with residents of Catalunya, in which nostalgia for the land of his youth shows through.

The Catalan scientific community, in turn, has seen in Duran Reynals an example of its ability to overcome historical limitations on research. We can interpret the massive presence of Catalan research scientists, in particular biologists and physicians, in the United States today, as a testimony to that sentiment.

Notes and references

[1] See references to the biographical studies at the end of this paper.

[2] Antoni Roca Rosell, Guillermo Lusa Monforte, «Un altre 98? Ciència i tècnica al tombant de 1900», *Afers*, volume 31, 1998.

[3] See J. M. Sánchez Ron, ed., *La Junta para Ampliación de Estudios e Investigaciones Científicas 80 años después*, 2 vols. (Madrid, CSIC, 1988).

[4] See Josep M. Rovira i Gimeno, «Raimon Duran Reynals o la soledad de un corredor de fondo», *Cuadernos de Arquitectura y Urbanismo*, no. 113 (March 1976), 57-67.

[5] A. Roca Rosell, *Història del Laboratori Municipal de Barcelona. De Ferran a Turró* (Barcelona, Ajuntament de Barcelona, 1988).

[6] A. Roca Rosell, «Científicos catalanes pensionados por la Junta. Algunos aspectos de su papel en el desarrollo científico catalán», in J. M. Sánchez Ron, ed. *La Junta para Ampliación de Estudios e Investigaciones Científicas 80 años después*, 2 vols. (Madrid, CSIC, 1988), II, 349-379.

[7] See, on this score, Thomas F. Glick, «Walter B. Cannon i la fisiologia barcelonina d'entreguerres», *Ciència*, 4, nos. 34-35 (Jan.-Feb. 1984), pp. 40-51.

[8] Francesc Duran Reynals, «Anaphylaxie et gestation», *Comptes Rendus Hebdomadaires de Séances et Mémoires de la Société de Biologie*, 82 (1919), 830-831.

[90 See Marcel Florkin, *A History of Biochemistry* (Amsterdam, Elsevier, 1972), ch. 14: «The Dark Age of Biocolloidology» (pp. 279-284).

[10] Pere Domingo, *Turró, hombre de ciencia mediterráneo* (Barcelona, Pòrtic, 1970).

[11] For the general background, see M. Tuñón de Lara, *La España del siglo XX*. París, Librería Española, 1966); S. G. Payne, *Los militares y la política en la España contemporánea* (París, Ruedo Ibérico, 1968).

[12] J. Sunyer Pi, «José Vidal Munné 1896-1958», *Cifra Médica*, no. 27 (April 1958), 4-6.

[13] Félix D'Herelle, «Sur un microbe invisible antagoniste des bacilles dysentériques», *Comptes Rendus à l'Académie des Sciences*, 165 (1917), 373-375.

[14] Pierre Nicolle, «Eugène Wollman», *Annales de l'Institut Pasteur*, 72 (1946), 855-858.

[15] Francesc Duran Reynals, «Resumen crítico sobre el problema de la lisis bacteriana transmisible (fenómeno de Twort-D'Herelle) y sobre los principios filtrantes y contagiosos en general», *Revista Médica de Barcelona*, 5 (1926), 469-490.

[16] Report to the Junta, París, June 14, 1926, Expediente Duran Reynals, Archivo de la Junta para Ampliación de Estudios; reproduced in Roca and Glick, Francesc Duran Reynals, pp. 174-175.

[17] At the same time, however, he continued to write on clinical aspects of cancer, e.g. his «Introducció a l'estudi del càncer», *Monografies mèdiques* (Barcelona, 1929).

[18] Francesc Duran Reynals, «Les facteurs de diffusion et leur signification», *Annales de l'Institut Pasteur*, 57 (1936), 597-621.

[19] Francesc Duran Reynals, «Hyalorunidase in the Fertilization of Mamalian Ova», *Proceedings of the Society for Experimental Biology and Medicine*, 52 (1943), 119-121.
[20] Francesc Duran Reynals, «Introduction», *The Ground Substance of the Mesenchyme and Hyaluronidase, Annals of the New York Academy of Sciences*, 52 (1950), 946-957.
[21] Rous to Duran, Setember 25, 1936, APS.
[22] Duran to Murphy, July 23, 1936, APS.
[23] Murphy to Favilli, January 19, 1937, APS.
[24] F. B. Rous and J. B. Murphy, «The Nature of the Filterable Agent Causing a Sarcoma of the Fowl», *Journal of the American Medical Association*, 58 (1912), 1938.
[25] Duran to Murphy, November 22, 1938, APS.
[26] Murphy to Duran, 16 September 16, 1938, APS.
[27] James B. Murphy, «The Possible Role of Viruses in the Etiology of Cancer», *Third International Cancer Congress* [Abstracts of papers] (Atlantic City, 1939), p. 177.
[28] Francesc Duran Reynals, «The Reciprocal Infection of Ducks and Chickens with Tumor-Inducing Viruses», *Cancer Research*, 2 (1942), 343-369.
[29] Francesc Duran Reynals, «Virus-Induced Tumors and the Virus Theory of Cancer», in F. Homburger and Fishman, eds., *The Physiopathology of Cancer* (New York, Hoeber, 1953), pp. 298-337.
[30] Francesc Duran Reynals, «Realities and Hypotheses of Viral Infection as a Cause of Cancer», *Revue Canadienne de Biologie*, 14 (1956), 411-428.
[31] Rous to S. Bayne-Jones, March 19, 1940. APS.
[32] The five articles, all published in *Yale Journal of Medicine and Biology*, 13 (1940-41) are «Neutralization of Tumor Viruses by the Blood of Normal Fowl of Different Ages» (pp. 61-76); «A Hemorrhagic Disease Occuring in Chicks Inoculated with the Rous and Fuginami Viruses» (77-98); «Production of Degenerative Inflammatory or Neoplastic Effects in the Newborn Rabbit by the Shope Fibroma Virus» (99-110); «Diminishing Response of the Skin to Frequently Repeated Reinfection with Invasive Bacteria» (217-238); and «The Vaccinial Infection of Fowls of Different Ages in Relation to the Antiviral Power of the Blood» (693-700).
[33] Rous Papers, Childs Memorial Foundation 1945, #8, APS. The proposal is dated June 26, 1945.
[34] Rous to McKeen Cattell, January 14, 1957, APS.
[35] Rous to C. Oberling, December 15, 1958.
[36] See, in this respect, Ilana Löwy, «Variances in meaning in discovery accounts: the case of contemporary biology», *Historical Studies in the Physical and Biological Sciences*, 21 (1990), 87-121.
[37] The reports are reproduced in Antoni Roca and Thomas F. Glick, *Francesc Duran i Reynals* (Barcelona, Ajuntament de Barcelona, 1986), pp. 173-177.
[38] Examples of family correspondence, in *ibid.*, pp. 197-199.

Archival Sources

* Duran Reynals Papers. Countway Library of Medicine (Harvard Medical School). Boston, USA

At the time of his death Duran Reynals' personal and professional papers were donated to Harvard Medical School by his wife. This donation includes correspondence from the time of his arrival in the United States until his death, organized alphabetically; reprints and drafts of articles, experiment protocols; grant applications; passports; manuscript notes; memorabilia; printed obituaries; and letters of condolence received by his widow. His correspondents included José M. Albareda, Jesús M. Bellido, Pere Domingo, Lluís Llimona, Julián Marias, Miquel Pijoan, Gustavo Pittaluga, Peyton Rous, Josep Tarradellas and Josep Trueta.

* Archives of the American Philosophical Society (APS). Philadelphia, USA

The greater part of the papers of persons who worked at the Rockefeller Institute in the 1930s and 40s are here, including those of Peyton Rous and James B. Murphy. Among the Rous Papers are two sections titled JEM [*Journal of Experimental Medicine*] Duran Reynals and JEM Reynals (1938-1940), as well as two labeled Duran Reynals 1 and 2, which cover 1936 through 1958. Another section, The Childs Memorial Foundation 1945 #8, contains a copy of Duran's proposal tot he Foundation dated June 26, 1945, annotated by Rous. The Duran Reynals folders in the papers of Murphy begins with a letter from Murphy to the Junta para Ampliación de Estudios (1928) and ends in December 1938. The Murphy Papers also contain correspondence with Josep and Miquel Pijoan, the latter a medical researcher of Duran's generation then in the United States, who was also studying the spreading factor. The Thomas M. Rivers Papers and Florence R. Sabin Papers both contain correspondence files with Duran Reynals, the former on neoplasties in mice, the second on an article by Sabin on protein colorants.

* Duran Reynals Folder, Archives of the Junta para Ampliación de Estudios. Residencia de Estudiantes, CSIC, Madrid

Duran's fellowship reports and related documents [37].

*Family Papers. Barcelona

The family of Duran Reynals in Barcelona has collected various materials, such as commemorative volumes and articles, unpublished works about Duran Reynals, and correspondence [38].

Biographical Studies

«Hommage à Duran Reynals,» *Biologie Médicale*, 52 (1963), 1-122 (articles by Favilli, Duthie, D. McClean, Kaiser, Gibina, M. L. Duran Reynals, Phyllis Johnson and Caselli).

Thomas F. Glick and Antoni Roca Rosell, «Francesc Duran i

Reynals (1899-1958). La projecció internacional de la recerca biomèdica catalana,» in J. M. Camarasa and A. Roca Rosell, eds., *Ciència i Tècnica als Països Catalans. Una aproximació biogràfica*. Barcelona, Fundació Catalana per a la Recerca, 1995, pp. 1335-1365 (revised abbreviated version of Roca and Glick, 1986.)

A. Roca Rosell and Thomas F. Glick (1986) *Francesc Duran i Reynals (1899-1958). Un investigador català de projecció internacional* (Barcelona, Ajuntament de Barcelona, 1986). (Complementary documents reproduced include 51 letters to colleagues, family members and friends in Barcelona, as well some scientific reports.)

W. M. Stanley, J. Oró, and R. Segura, eds., *Virus y cancer. Homenaje a F. Duran Reynals*. V Congreso Nacional de la Sociedad Española de Bioquímica (Barcelona, 1971). (With biographical articles by Jordi Casals, Pere Domingo, Carles Soler Durall and Ramon Segura. Includes some of Duran's most significant articles.)