

FRANCESC DURAN I REYNALS

DURAN-REYNALS SPREADING FACTOR

The eponym

Duran-Reynals spreading factor. Hyaluronidase, an enzyme in the family of hydrolases that acts on hyaluronic acid. It plays a physiologically significant role in fertilisation: sperm contains a notable amount of this enzyme, which promotes the spermatozoa's progression through the cervical canal and penetration into the ovum. Certain pathogenic gram-positive bacteria produce extracellular hyaluronidase that seems to contribute to infection through its histolytic action on host tissue¹. It is also known as Duran-Reynals permeability factor¹⁻³, Duran Reynals diffusion factor, Duran Reynals factor, Reynals factor, T factor⁴, and invasin¹.



Francesc Duran i Reynals
(1899-1958)

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Francesc Duran i Reynals was born in Barcelona on 5 December 1899. The youngest son of Manuel Duran i Duran, a writer and illustrator, and Agnès Reynals i Maillol, he was orphaned in 1906 and, along with his four brothers, was raised by three of his mother's sisters and one of their daughters. All his brothers flourished within the early 20th century cultural movement *Noucentisme*: Eudald (1891-1917) was a renowned novelist who died at early age; Raimon (1895-1966), a notable architect; Estanislau (1894-1950), a lawyer involved with *Acció Catalana* (a Catalan nationalist party), who was prohibited from practicing law under Franco's dictatorship; and Manuel (1896-1946), who devoted his life to private industry. Francesc, however, chose a completely different career: scientific research.

Francesc Duran i Reynals studied medicine in Barcelona (1916-1925). From his first year at university, he frequented the *Laboratori Microbiològic Municipal* headed by Ramon Turró. In 1919 he presented



Four of the five
Duran
i Reynals brothers,
from left to right:
Manuel, Raimon,
Francesc, and
Estanislau⁹. c. 1920s

his first research results at a session of the *Societat de Biologia de Barcelona*^{4,5}, a branch of the *Institut d'Estudis Catalans*, from a study on anaphylaxis and pregnancy in which he aimed to show that, once a mother induced anaphylactic sensitivity in her baby, desensitisation occurred in the mother⁶. The results were also published by the *Société de Biologie de Paris*⁷ –a brilliant start to his career in research. Until 1925, he devoted part of his investigative work to this subject along with other investigators at the *Laboratori Microbiològic Municipal* (P. Domingo, M. Dalmau, and P. González, among others), beginning his study into bacteriophages in that period.

For six months in 1922-1923, he was mobilised and sent as a military health worker to Melilla to help with the repatriation of Spanish prisoners after the Disaster of Annual (1921), a Spanish military defeat during the Rif War at Annual, in northeastern Morocco. This experience marked him for life.

In 1925 he obtained a grant from the *Junta para Ampliación de Estudios* (JAE) to work at *Institut Pasteur* with Professors A. Besredka and E. Wollman, both Russian scientists, on evaluating the organic reactions of animals subjected to experimental infection and techniques for studying bacteriophages⁸ (shortly beforehand, he had, in all likelihood, been the first person in Barcelona to obtain bacteriophage viruses). In June 1926, Duran wrote a report to the JAE^{4,5} justifying the need to change location and attend the Rockefeller Institute in New York:

"Very recent research studies, especially those conducted by Professor Alexis Carrel of New York's Rockefeller Institute, have shown unsuspected relationships between the problem of cancer (in the novel aspect with which it is viewed after Peyton Rous's work) and the problem of bacteriophagy.

In the critical review of the question published in *Revista Médica de Barcelona*, which I attach, I attempt to establish the analogies clearly.

Furthermore, for the last month approximately I have been studying experimentally the Rous sarcoma virus in chickens, collaborating with Mlle Harde at the Pasteur Institute, within the means here possible and will continue to do so until the end of my grant.

My plan is, specifically, to apply to the problem of infectious sarcoma all the questions that a full study of the problem of bacteriophages has suggested”.

In 1910, Peyton Rous had discovered sarcoma affecting chickens, which he demonstrated was transmissible. This suggested that the sarcoma might be caused by a virus, supporting an infectious theory of cancer.

Using his grant extension, he travelled to New York’s Rockefeller Institute, where he worked from 1926 until 1938, when he joined Yale University. His studies on the relationship between viruses and cancer multiplied and soon brought him worldwide fame⁹.

Duran-Reynals diffusion factor

In New York, Duran began to work with J. B. Murphy on the Rous chicken sarcoma and, in 1927-1928, while working on receptivity of viruses in different tissues and organs, he discovered that the addition of testicular extracts to the saline solution in which the infectious material was suspended had a spectacular effect on the viruses’ infectious power. This is how Duran himself described this discovery¹⁰:

“The spreading factors were discovered in 1928 during a study of the effect of testicular extracts on vaccinia infection. The finding came, both unexpectedly and expectedly, as the experimental answer to a question formulated (1) on the basis of the general principle of the indispensable dependence of viruses on cell’s life, and (2) on the basis

of previous studies on bacteriophages and sarcoma agents: how would a typical virus behave when brought in contact with cells or extracts from either susceptible or refractory tissues? The inoculation of the test mixtures containing testicular products revealed their enhancing effect through spreading of the virus".

The exact date of the discovery of the factor (which Duran called "T factor" because he first found it in testicular tissue) is unknown. The first report was in the June 1928 issue of *Comptes Rendus de la Société de Biologie de Paris*¹¹. That summer he worked on this subject at the Barcelona's *Laboratori Microbiològic Municipal* with Jaume Sunyer Pi and, by the end of the year,

First publication of what would be known as "Duran-Reynals spreading factor"¹¹ (1928)





Francesc Duran i Reynals at
Yale University School of
Medicine in 1945

Comptes Rendus published the results of a series of five experiments demonstrating that when the testicular extract was injected together with staphylococci into rabbits, it apparently always increased the infectious power of the microorganisms^{4,5}. Duran studied the effect of the factor on a large number of substances. The studies he carried out using Indian ink suggested another effect of the T factor: an increase in host cells' permeability to exogenous factors. And finding large amounts of the factor in neoplastic tissues made him think that its action could clarify the mechanism by which cancer cells infiltrate normal tissue. It also pointed to the significance of the role of connective tissue in this process.

Years later, Josep Trueta became interested in the role of the T factor in the opposite phenomenon, the de-permeabilisation of tissue in bacterial invasion. E. S. Duthie would identify the T factor (already known as Reynals factor) with the enzyme hyaluronidase. Moreover, Duran continued studying neoplastic processes in mammals ("filterable chicken sarcomas", and sarcomas in dogs and rabbits).

In 1932, Duran thought about going back to Barcelona. The possibility of founding a research institute for biomedical research (the *Institut Miquel Servet per a l'Estudi del Càncer i d'altres Malalties d'Etiologia Desconeguda*), a broad and ambitious project, brought him home. Problems obtaining funding and the outbreak of the Spanish Civil War prompted him to request his reincorporation into the Rockefeller Institute and to leave Barcelona on 27 September 1936. From then on, he returned for only a few days in 1950, on his way to Paris. Three years before, in 1947, he had accepted an appointment as a corresponding member of the *Institut d'Estudis Catalans*⁵.

In the United States, he continued his studies on the viral theory of cancer: he was still fascinated by the notion of a latent virus with carcinogenic properties. In autumn 1938, Duran re-joined the Department of Bacteriology at Yale University, where he continued his experiments. During the 1940s, he carried out a number of studies to show the viral action of chicken sarcoma. In 1953, the results of his studies led him to propound a ten-point theory of the viral aetiology of cancer. The ideas predominant at that time resulted in manifest hostility toward the viral theory among scientists. Even so, Duran's articles were often cited during the 1950s and 1960s. In fact, as has been widely recognised, Duran i Reynals researches were among the first to reveal the existence of oncogenes, and the research programme on virus-induced cancer he initiated proved highly productive.

His work was extensive, and various biographical studies of Duran i Reynals have been published^{4,5}. In 1971, the V Biochemistry Congress, held in Barcelona, saw the publication of the book *Virus y cáncer. Homenaje a F. Duran Reynals*¹² (Virus and cancer: Homage to F. Duran Reynals), containing several biographical studies and an extensive bibliography on Duran, as well as reproducing some of his articles. A year earlier, Josep Pla had devoted a chapter of his series *Homenots*¹³ (Great men) to him. Coinciding with the centenary of his birth, *Annals de*

Medicina published an article on the current state of his contributions to science¹⁴.

In 1957, Francesc Duran i Reynals attended the 48th Annual Meeting of the American Association for Cancer Research (AACR) in Chicago, where he defended his fundamental contribution to the viral aetiology of cancer. He died shortly afterward, on 27 March 1958, in New Haven, Connecticut. Eight months earlier, he had fallen ill with a cancer of the small intestine that would soon metastasise to his brain.

Francesc Duran i Reynals' personal papers, known as the "Duran papers", have been deposited in the Countway Library of Medicine at Harvard University.

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