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State of competition: conceptual shoehorning behind priority on calcitonin precursor biosynthesis

Abstract

Until the 1950s, the first results in the studies of calcitonin-thyrocalcitonin were ignored in the accepted research scheme. However, it was José Fernández Nonídez from the Spanish School of Histology, died in Augusta (Georgia, USA) in 1947, whose expertise in the parafollicular cells of the mammalian thyroid had led him to an advanced understanding of this separate endocrine organ, which secretes calcitonin. The antecedent of the secretion was present in the cytoplasm of these cells, which Nonídez explained in a paper published in 1932.

In 1973, a Spanish group from the Instituto Gregorio Marañón (Madrid) leading the research into the ectopic production of calcitonin identified the precursor responsible for its biosynthesis.

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Nonetheless, given the informal power in connection with the communication between the scientists, this significative contribution was absolutely discarded in terms of acknowledgment within their social circle. The services responsible for dissemination of scientific knowledge considered that priority should be given to another group of young scientists dedicated to pro-calcitonin evidence.

The nature and extent of informal communication are highlighted in countries with different measures to guarantee the autonomy and independence of their state powers. Irrespectively of political circumstances, the paper is focused on the competition between two different approaches in science particularly important for progress in medicine: the perspective presented by experimental studies in basic sciences (in animals) and the models developed in clinical sciences.

Keywords: *anatomy, thyroid, endocrinology, Madrid, calcitonin, thyrocalcitonin, pro-calcitonin*, *Instituto Gregorio Marañón*, *Jose Fernández Nonídez*, *conceptual shoehorning, thought collective*

Stan rywalizacji: priorytetowe znaczenie biosyntezy prekursora kalcytoniny i zniekształcenia pojęciowe

Abstrakt

Do lat 50. XX w. nie uwzględniano w przyjętym schemacie badawczym pierwszych dowodów przemawiających za istnieniem kalcytoniny-tyrokalcytoniny. Jednakże, znajomość przez José Fernándeza Nonídeza (z hiszpańskiej szkoły histologii, który zmarł w Augusta (Georgia, USA) w 1947 r.) komórek pęcherzykowych tarczycy ssaków doprowadziła go do zaawansowanego rozumienia tarczycy jako odrębnego narządu endokrynnego, wydzielającego kalcytoninę. W artykule opublikowanym w 1932 r. Nonídez wyjaśnił, że prekursor wydzielania znajdował się w cytoplazmie komórek tarczycy.

W 1973 r. hiszpańska grupa z Instituto Gregorio Marañón (Madryt), prowadząca badania nad ektopowym wydzielaniem kalcytoniny, zidentyfikowała prekursora odpowiedzialnego za

biosyntezę kalcytoniny. Niemniej jednak, biorąc pod uwagę nieformalną władzę związaną z komunikacją między naukowcami, znaczący wkład Nonídeza został absolutnie odrzucony i nie zdobył uznania w tej grupie społecznej. Upowszechnianie usług wiedzy naukowej spowodowało, że przyznano priorytet odkrycia grupie młodych naukowców zajmujących się badaniami pro-kalcytoniny.

Podkreślono charakter i zakres nieformalnej komunikacji w krajach, które wykorzystują różne środki dla zagwarantowania autonomii i niezależności uprawnień państwowych.

Niezależnie od uwarunkowań politycznych artykuł koncentruje się na konkurencji między dwoma różnymi podejściami w nauce, szczególnie ważnymi dla postępu w medycynie: perspektywą przedstawioną w badaniach eksperymentalnych w naukach podstawowych (u zwierząt) i modelach opracowanych w naukach klinicznych.

Słowa kluczowe: *anatomia*, *tarczyca*, *endokrynologia*, *Madryt*, *kalcytonina*, *tyrokalcytonina*, *pro-kalcytonina*, *Instituto Gregorio Marañón*, *Jose Fernández Nonídez*, *zniekształcenia pojęciowe*, *kolektywy myślowe*

1. Introduction

Despite Ortega y Gasset's words that "perhaps, science and government are the two most contradictory human activities" (Ortega 1969),[1] when reading the history of Spain in the 20th century as marked by a relationship between "new science" and government, a historian (as well as a sociologist) should examine the generational singularity, the particular features of biographies. The facts are plausible, as Baltazar Gracián used to say, as far as they are fully described and justified (Gracián 1685).[2] This

[1] "Rather, it can be learned from history that intellectuals are one thing in politics: obstacles. Perhaps, science and government are the two most contradictory human activities. The intellectual who knows what his destiny implies, instead of asking the politician to make him a member of the Parliament, he should ask him to read his books. If he is successful, he would have shaped public policy as far as his influence could reach." This text was originally published in the Madrid newspaper El Sol on July 10, 1922 (Ortega y Gasset 1969).

[2] "In matters that concern judgment, it is dangerous [novelty], because it runs upon paradoxes; in knacks of subtlety it is laudable: and if novelty and invention jump well together, they are plausible" (Gracian 1685, maxime 283).

trust can and should be analyzed in a broader and even openly political domain, like in history when it focuses on competition as an underlying theme to bridge contexts of discovery and justification (Allchin 1994).

The case of disagreement among researchers on the precursor of calcitonin, a hormone that maintains the constant level of calcium in the blood, provides an example. The available historical information on this case indicates a pattern where relevant facts are omitted, emphasis is misplaced, and qualifications are abandoned. This dominance of conceptual shoehorning reflects a deliberate distortion or a conscious manipulation of historical facts and could be used to help students learn how to do science (Allchin 2003; 2004).[3] In the early fascist period in Spain, a well-known example of these errors of historical shoehorns resulted in obsolete scientific theories like reticular theory in neurobiology regaining attention when the Cajal Institute was re-founded by CSIC (the Spanish Research Council) (Jabonero *et al.* 1951). At the time of Cajal's posthumous publication (1934), a paucity of new evidence in support of the synaptic discontinuity led to a political requirement being made with regard to the neural theory. The neuron theory with its insistence on the anatomical discontinuity of all neurons and theories based on chemical mediation across hypothetical gaps was said to require a major revision. Eminent neurohistologists in Nazi Germany (Philipp Stöhr (Bonn), Karl August Reiser (Bonn)), and a number of contributors (Jabonero *et al.* 1951; Jabonero 1952) from the histologist in Spain, Jabonero, discussed the idea of a terminal reticulum in the autonomic nervous system. Nonídez, who went into exile as a teacher of anatomy at Cornell University in Ithaca, New York (Pinar 2001), presented a sober, midway account of the struggle (Nonídez 1944).

We are dealing in this communication with a chronicle where only one key is used to open two different locks. These two different locks

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[3] It is the argument of this contribution that the history of biomedical experiments on calcitonin is an important example to indicate a purely political affair behind scientific competition. Following Fleck, all knowledge expresses the forces that makes it intelligible; "instead of what separates, it will point to that which will be common to all, and which brings them closer together" (Fleck 1947/1936). Collectively, the structure of the relevant thought is stylized and such stylized solution is called truth (Fleck 1935/1979). This proposed Fleckian framework provides a way of considering the historical shoehorn as a finding way to explore the potential for distortions studied here.

are the breath of the Spanish exile molding science in Franco's Spain, and the disappointed absence of competitiveness faced by those scientists when confronted with the march of invention abroad. The key to open these two doors is the purely political problem of control of scientific work on the international scene to abolish aggression. Always with an emphasis on the fact that in a particular context a combination of careful measurements and sensitive and specific experiments makes the discovery possible (Gervais, Weber 2015),[4] the determination of the problem for the study attracted our attention because of its precarious intellectual discussion, previously retained in the context of the history of biology.[5] Consistently drawn on competition as an underlying theme, the rapid development of the C cells research, as indicated by the publication rate, compels to its study.[6]

2. Scope determination

In a certain sense, this research question has taken us aside, as an interaction between two worlds. Clinical practice in Spanish endocrinology gained in importance with the exile of the scientific community. And one of the key elements of the history of experiments on procalcitonin (PCT) is its use in basic and clinical research as a biomarker

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[4] High levels of procalcitonin are observed in cancer patients (making the neuroendocrine cells of the lungs a probable site of its production), burnt patients with severe lung injuries brought about by the inhalation of toxic gases, and pediatric patients with a signaling increased level in bacterial and not in viral infections (e.g. young patients with meningitis). A few months before the Gulf War in 1991, a group of French army physicians while healing burnt patients revealed the relationship between procalcitonin and sepsis (Bohuon 2000). Positive results of the procalcitonin test in infections associated with a severe systemic response resulted in an increase in research into the prognostic value of the measurement of its release into the blood (by the spleen, the liver, the testes, or the brain).

[5] As the founder of the Seville department of genetics, Enrique Cerdá Olmedo, has asked for concrete relevance or benefits of biotechnologies for different sets of audiences (Ávila *et al.* 2003).

[6] Pearse showed that calcitonin was localized in the parafollicular cells (Bussolati 2014); these cells are now commonly called the C cells, but they have also been called the cells of Nonídez (Goormaghtigh, Thomas 1934), and light cells of the thyroid (this last name was introduced in preference to parafollicular cell because it did not imply any restriction of the cells to any particular topographical site).

(Bohoun 2000).[7] So the models to understand the production of science through the computational methods that characterize the science of science had a pending thorough study on the relative efficacy of the alternative portfolios in the basic vs clinical competition for the space between theory and praxis. The procalcitonin case could be an interesting historical reference, by tying its discovery to the framework of the latter (Markoš, Švorcová 2009), by a scientist and a medical professional distinguished in the defense of democracy in Spain and forgotten in the US, who first understood the relevance of C cells in the thyroid gland.[8]

A kind of symbiosis between the two worlds, the process of which led to the discovery of a large precursor to calcitonin – this is a real live-science history which comes out of journals, but journals are tough to master (Price 1981). Because of this it can be discussed as a political history of a research community through the microanalytic strategies relevant to invisible colleges (Ogurtsov 2001). This is a strategy that focuses attention on the power of personal and informal contacts to shape scientific careers, and generally is identified with the history of society as a course of interpersonal ways of communication, forms, entities, institutions and practices.

3. Models for the study of thyroid in different basic and clinical contexts

What passed unperceived and no attempt at a remedial action was made, was divide between the first period of discoveries on thyroid (1930–1938), which is characterized by the activity (at Cornell University) of José Fernández Nonídez from Spain (Pinar 2001), and the research to find the precursor of calcitonin that embraced new biotechnologies (in the seventies). Simply put, what was involved was the continuity of those who supported Spanish science, formally around the journal

[7] The existence of this biologically active pro-hormone (PCT) was established chromatographically for the first time in 1975 (Moya *et al.* 1975), unequivocally associated with sepsis and microbial infections, a fast detection of PCT levels directly at the patient's bed would result in significant help in treatment.

[8] In 1932, to bring about the triumph in the academic world of a just and democratic freedom, Nonídez fought with all his might from the pages of the journal *Science* (a periodical publication of the American Association for the Advancement of Science, AAAS (Nonídez 1932b)).

Fig. 1. The clinical researcher José Luis Rodríguez Candela (1908–1985) at CSIC and Professor José Fernández Nonídez (1892–1947) at Cornell University. (Source: historical pictures in the General Archive of the University of Navarre and in the National Natural Science Museum (CSIC) Archive.)

published by the Spanish republicans *Ciencia* (López Sánchez 2014).[9] When it is said that in these days action was for the scientists a part of their everyday professional life, and to run away from it was as inconceivable for them as to close their laboratories (Rodríguez Quiroga 1996), Cajal's conviction on the importance of will, at the basis both of political and scientific affairs (Ramón y Cajal 1951), made the skills of the scientist close to the main characteristic of a politician, never losing faith in the usefulness of their actual tasks. So when in 1947 in Paris, the physiologist Juan Negrín talked about the Marshall Plan aid for Spain,

[9] Spanish medical and scientific culture did fit within a journal published in México D.F., between 1940 (March 1) and 1975 (December 15). *Ciencia. Revista hispano-americana de Ciencias puras y aplicadas* was digitized after a 2009 congress "The Republican Scientific Exile" organized by the López Piñero History of Science and Medicine Institute. Its 29 volumes are available from the Universitat de València and the Residencia de Estudiantes – see: http://cienciaexil.uv.es/volumenes.htm and http://www.edaddeplata.org/tierrafirme_jae/revistaciencia/index.html.

and Nonídez died in the USA, the profoundness of Spanish exile was a central element shaping research directions concerning endocrinology in Spain, which occurred differently in Britain or Austria (Medvei 1982).

I offer below a brief inquiry within this large compass, my purpose being to exhibit a concrete case of a generation facing an original aspiration to work simultaneously in science and politics, and the professional roles of biological researchers in the 1970s, under the historical parameters of molecular endocrinological research. After the Francoist war, to add to the coincidence between the courageous scientific minds and the courageous political minds follows the access of fascist scientists to international politics (Price 1945). And, following the Korean War and the conditional determination of the great powers to build an international organization against war, the Spanish Diabetes Society was founded in 1955 by José Luis Rodríguez-Candela. Rodríguez-Candela was an official in the post of adjunct professor of physiology (at the Madrid University Medicine School), left by the exile S. Ochoa, who had a major interest in the mechanisms of action of hormones, in particular running calcitonin research in the early seventies.

One has to mention the fact that, at that time in Spain, all research into endocrine glands was done in the service of clinical medicine. And as the war is not lost if it is not given up, the development of the research worked in the opposite direction to the firm beliefs of Juan Negrín, who had sharply criticized clinicians' excesses (Medvei 1982). The real problem was not the sharing of information, or the control of scientific work, but the purely political problem of exile. Vain theories and even errors of the over-zealous clinicians slipped under the radar. At the core of these deficiencies was the abolishment of the political unity. That can only exist if the great scientists stand together. Without the generous solidarity and sense of universality (intentions to re-establish democracy in Spain) on the part of the Republican exile, the institutionalization of endocrinology followed a model which had been handed down in a limited quantity of printed materials.

Because the procalcitonin literature in 1974–1975 was concerned with the intellectual unity of an overarching network of co-authorships during the "sixties" period of the Spanish biochemistry, it is argued here that this discovery mobilized a research effort which was not duly recognized. The problems specified by the discovery of the biosynthesis of the precursor of calcitonin are very difficult to consider away from

the historical molds which the research faced in this field. The starting point here, as explained by Studer, is that the history becomes a properly sociological tool for disaggregating and interpreting scientific growth (Studer 1977); because in 1975 procalcitonin (PCT) was identified as one of the precursors to calcitonin (CT) in animals, prior to being discovered in humans and was quickly vitally relevant as an integrative factor in endocrinology. Beyond its seemingly modest content, procalcitonin is a very interesting and original marker, and its brief history continues to assume an integrative role for those biomedical researchers interested in calcitonin – itself an excellent marker for medullary thyroid cancer (Bohuon 2000) – who are looking for a historical interpretation for diabetes, and an endocrine-related cancer.

4. Cells producing calcitonin

This contribution analyses the emergence of C cells research in Spain throughout the comparative histories of José Fernández Nonídez (1892–1947) and José Luis Rodríguez Candela (1908–1985). Significantly, J. F. Nonídez formulated the problem very carefully, and put the name of parafollicular cells (also called C cells) to the thyroid gland cells where calcitonin is secreted (Nonídez 1932a). The economic and political powers, which made Nonídez due funding and institutional support possible, paid special attention to the different experimental cultures (Mendelism genetics) which emerged on the basis of his effort while he was in Spain. Rodríguez-Candela was awarded the title of Doctor in Medicine from the University of Madrid (1932) with a distinction "cum laude", given by a jury including Juan Negrín, for his doctoral thesis on experimental diabetes. After the war he was transferred to the CSIC, where he spent most of his career dealing with the director's duties at the Institute of Metabolism and Nutrition; his most cited publication concerned the discovery of the calcitonin precursor in 1975.

Histology, with the silver nitrate method of Cajal (Ferreiro, Ferreiro 1984), brought the parafollicular (C) cells of the thyroid gland into consideration (Fig. 2). Together with Baber's first evidence, Nonídez's professional work endeavored to demonstrate the relevance of C cells, and made him their chief proponent. Baber noticed spaces between these cells; for Nonídez the spaces resulted from the release of a fluid secretion produced through dissolution of the granules in their

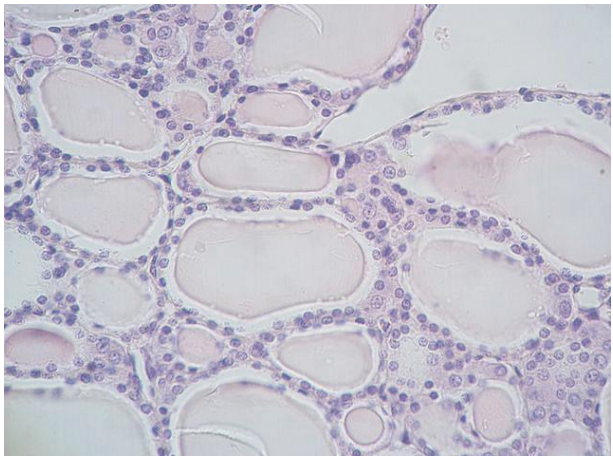

Fig. 2. Parafollicular cells in the wall of a follicle of the thyroid of a dog. Cajal method (Bussolati 2014; source: *Wikipedia*).

cytoplasm. Baber (1876, 1881) first described the cells (termed by Nonídez "parafollicular" cells (1932)) under the name of "parenchymatous" cells, in the thyroid of the dog. The findings of Baber were confirmed by Huerthle (1894), who termed them "grosse" or "protoplasmareichen Zellen". From the observations of Takagi (1922) their nature is undoubtedly secretory. The cells were seen to contain numerous granules in their cytoplasm, which produce the internal secretory activity that maintains the constant content of calcium in the blood. In a sense, Nonídez's approach emphasizes the context to understand the significance of competition.[10] We focused on the ways to discriminate priority

[10] As discussed by Harold Copp, in the first Gordon Conference on Teeth and Bones (1954), the medical problem how to determine with precision the physiological basis of the level of ionic calcium to be maintained was of critical importance. Copp reported on his discovery of calcitonin in 1962 (Copp 1962). In an explicit historical article he introduced his researchers to a small shark ("dogfish", *Squalus suckleyi*), thus providing support on the current view that calcitonin is produced in the thyroid of mammals and the ultimo-branchial glands of low vertebrates (Copp 1967; Copp *et al.* 1967).

However, Anthony G.E. Pearse (1916–2003) was convinced that calcitonin as a second thyroid hormone had to have its origin in a second type of cells. And after having assumed that the parafollicular cell (as a second endocrine-like cell type) might be the source of calcitonin, he proved it by immunocytochemical studies using anticalcitonin antisera. By the discovery of calcitonin, Pearse formulated his APUD

in the case of procalcitonin, and the justification became linked to the development of J. Fernández Nonídez's ideas (Allchin 1994). Disclosed by a technique (the reduced silver nitrate method), more specific than the staining methods used by the early investigators, Nonídez's interpretation of the origin and the purpose of the parafollicular cells received a definite support (Nonídez 1932a; 1933). With the loss of time during the Francoist war, an account of the historical anomalies affecting the studies by J. F. Nonídez can be explained in part. The senior members of the scientific society retained his "rights" even in 1938, in particular to those experiments that had led to the location of the cardio-aortic chemo-receptors in the-aortic glomus tissue. There is no better example of this than Corneille Heymans's 1938 Nobel Lecture, where the Belgian Nobel laureate explicitly presents Nonídez's analysis (Heymans 1938). In 1939, Nonídez's writing for the Spanish journal published in Mexico, D.F. *Ciencia: Revista hispano-americana de Ciencias puras y aplicadas*, underlined the important participation of the Spanish histological school in the research on the anatomical base of the cardiovascular reflexes (Fig. 3). This was a study on the receptor areas which initiate the reflex cardiac acceleration that tributes Cajal "to whom we owe an irreproachable neurological technique" (Nonídez 1940). In this spirit, the ingenious experiments formulated in the study of the problem (especially by Heymans and his collaborators) made him admit that they constituted one of the most brilliant pages of the physiological experimentation. In the case of Heymans, Nonídez says that the Nobel was awarded to him "last year" (1938), i.e. as soon as he proved his solidarity with the scientists compelled to leave Spain. He did so by publishing this article related to his specialty, and written at Cornell University, when the first volume of *Ciencia* was published in México D.F. in 1940 (Giral 1994).

The visibility of Cajal's first preoccupation regarding the spread of histology to the entire biology (Marañón 1958) concerned the

(Amine Precursor Uptake and Decarboxylation) hypothesis on the common origin in the embryonic neural crest for the cells producing peptide hormones. Despite the fact that the hypothesis lost his basis following extensive embryological investigations on the endocrinological cells – showing that pancreatic islet cells were not derived from the neural crest – Pearse's view has inspired today endocrine histology and pathology (by defining the diffuse neuroendocrine system, and multiple endocrine carcinomas) (Bussolati 2014).

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Fig. 3. With "The anatomical basis of reflex blood pressure regulation", Nonídez expanded upon his newly published in 1940s paper for the new republican journal *Ciencia: Revista hispano-americana de Ciencias puras y aplicadas*, a Spanish version of his most recent research on the Bainbridge's reflex. (Source: © 2018, Fundación Residencia de Estudiantes.)

experimental diabetes results achieved by the early Spanish biomedical research (Blázquez 2002). As seen in Fig. 4, the question of the scientific domination of one or another aspect (basic vs. clinical) mirrored the effects of calcium that are manifested in pancreatitis. The date distribution indicates that the academic response to the discovery of C cells, calcitonin and procalcitonin was symmetrical (Fig. 4). In spite of the fact that, in Cornell and Madrid respectively, Nonídez and Rodríguez Candela started their research in 1930 and 1932, but lasted until 1933 and 1975.

The suggestive idea of a conceptual shoehorn is conform with the spirit of a comparative method, in the frame of historical and sociological investigations. Once the political unity has been broken, the mind of a collective body is split in different communities. If supposedly they are rival academies, distortions and complicated factors are to be

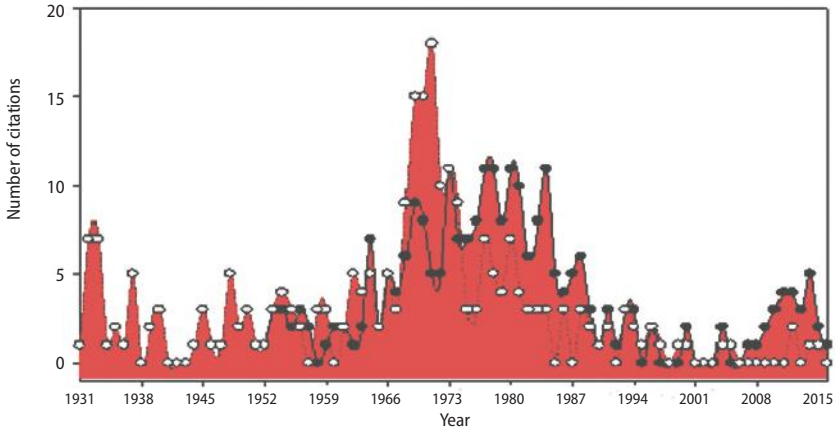

Fig. 4. Citation dates of the research literature using Nonídez's (1930–1933) (white dots) and Rodríguez Candela's (1932–1975) (black dots) ideas on calcium and PCT. (Source: Compilation based on the data mentioned above.)

detected on the base of statistics and at international level. It is easy to see (Fig. 4) that the starting points of the reflections of the two physicians were quite distinct. In 1930, while engaged in research into the anti--rachitic factor in avian rickets at the Medical College of Cornell University (N.Y.), Nonídez had first formulated his ideas (on dogs) on the existence of a parathyroid tissue located in thymus (a hypothesis that he was able to link with the existence of the parafollicular cells (Nonídez 1932a)).[11] From the early 1950s, it was Candela's turn to emerge with his experimental research into diabetes mellitus with tangible results. Going so far as to raise – in terms of citations – the properly sociological question of the captive Spain by Franco with the internal vision of endocrinology based primarily on clinical experiences. Indeed, as problems became redefined with the accumulation of knowledge Nonídez's work stands as a historically important discovery relevant to all areas of

[11] The anatomical connection between this tissue and the follicular cells made Nonídez certain that para-follicular cells had to exist. Again a fair amount of conceptual shoehorning clearly made the distance between Nonídez's discovery and the histological discovery in a clinical case that served to the characterization of calcitonin as a relevant ectopic hormone (the first demonstrated case of truly ectopic calcitonin production by a tumor was in a patient with a small cell carcinoma of the bronchus (Silva *et al.* 1973)).

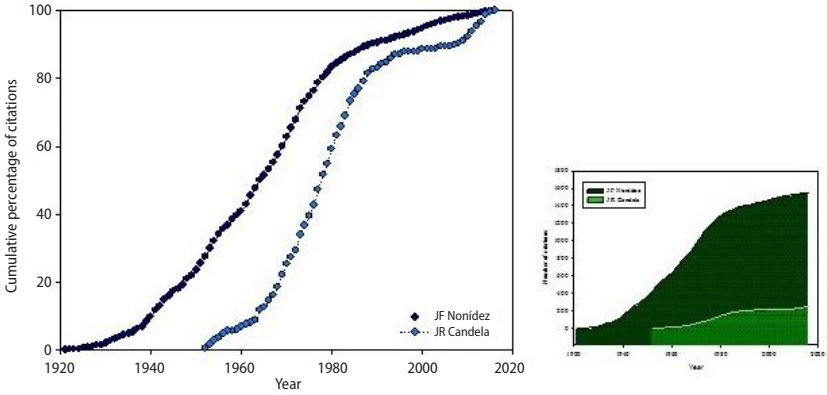

Fig. 5. In a line plot, the symbols (blue and cyan circles) show the cumulative percentage of the total citations received by Nonídez (1552) and Rodríguez Candela (248); for comparison, the citations of both physicians (dark vs. light green) are shown in the area plot on the right. (Source: Compilation based on the data mentioned above.)

biology and medicine and a basic research result. Thoroughly absorbed by a specialty that he had not founded, Rodríguez-Candela (former worker at the Cajal Institute (1934)) obtained outstanding experimental results regarding diabetes achieved as a promoter of biomedical research (Blázquez 2002).

A version of this approach is a point presented in Fig. 5. In accordance with the three fields where Nonídez gave his views from the USA (agricultural breeding research, C cells, anatomy of the cardiac reflex), the ideas raised by his articles are imbued with a "prophetic" quality eventually recognized along a span of 96 years. The realistic descriptions of diabetes mellitus by Rodríguez Candela accounted for the growth of biomedical science with a number of works as was called for by the Francoist authorities (Marañón 1958).

5. Professional science survival in top ranking research posts

Of the two Spanish scholars which reported the "parenchymatous cells" as a separate cellular entity (Nonídez) and the existence of the precursor of calcitonin (Candela), one did it in the first part of his career (1932), but the other did report on a precursor derived from chicken ultimobranchial glands as a measure of last resort (1975).

Consequently, the temporal discordance between the suggested existence of a precursor for calcitonin and of a second epithelial component of the thyroid might be the basis of a survival model of science and politics, when drawing on the endocrinological studies of the Spaniards. The discovery of the second epithelial of the thyroid gland had a strong focus on basic principles (and not on mere descriptive anatomy), but the range of conditions which the Spanish milieu offered in biomedical sciences had a very close relationship with the structure of the medical profession itself. In effect, only to a very limited extent was the laboratory tradition maintained in the biomedical sciences, and that could be explained because – in its organization – it followed the French model of the Centre National de la Recherche Scientifique (CNRS).

It appears that Nonídez pursued his (three) lines of research (1915––1929, 1930–1933, 1934–1947) throughout 32 years, in three temporal sequences that can be recognized from Fig. 6. In the 15 early years (1915–1929), working with agricultural breeding research; between 1930–1933 historiographically privileging a second thyroid epithelial as the site suited for the study of C cells, and over the last 15 years (1934––1947), forging crucial links at the base of the cardiovascular reflex.

By the 1950s, the work of Rodriguez-Candela evidenced that pancreas secretes glucagon. In fact, he investigated if glucagon could be considered an insulin antagonist, which itself made him become a part of

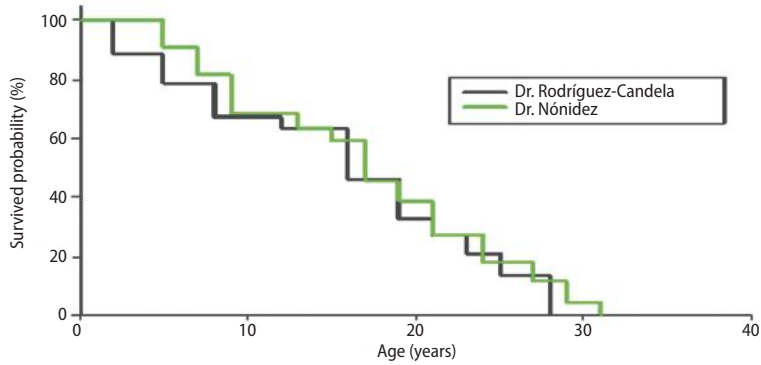

Fig. 6. Kaplan-Meier curves representing the distribution of the age intervals covered by the scholarship of the two authors during their life-time: Nonídez (1915–1929, 1930–1933, 1934–1947) (green line) and Rodríguez Candela (1932–1975) (black line). (Source: Compilation based on the data mentioned above.)

the CIBA colloquia. With this political progression, he took the direction that would lead him to get his work published in the *Perspective in Biology*, where Cori and Ochoa served on the editorial board at the time.

Candela devoted a major part of his research program to proving the physiologic effects of insulin (*in vivo* and *in vitro*). In full accord with observed facts, he subjected duck, rabbit and rat pancreas to a variety of metabolic procedures to determine insulin secretion, reasoning that the biochemical action of the hormone was concomitant with the secretion of ATP. Over a lifetime of work, he accumulated experience that beta-cells contain nucleotides that amplify the insulin secretory response. In connection with his work on insulin secretion by intracardiac glucose Candela's evidence that ATP-induced stimulation of insulin secretion remains a result of interest. In his clinical studies, Candela asserted that in pancreatic islets, when stimulated from exogenic ATP (by intravenous administration), the endocrine pancreas release insulin from beta-cells (Rodríguez-Candela *et al.* 1963). This experiment (extracellular ATP pancreatic beta-cell physiology) led to the launch of a new area of research known today as "Purinergic Signaling".

Rodriguez-Candela scientific program was an answer to the question of the "insulin secretion metabolism". His most remarkable research interests can be translated into three local institutional initiatives,[12] which can be sequenced in the following way (see Fig. 6): his first years, under Enríquez de Salamanca's (the physician of the royal household)

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[12] On 9 December 1943, the daily newspaper *ABC* announced Mr. Rodríguez-Candela's study tour in the United States. According to the same source, during those years he published communications of true importance and his travel was motivated by a desire for a further study, by dealing with nutritional and alimentary problems.

In February 1944, Candela began with one study comparing alloxanic and pancreoprivic diabetes at the Metabolism Department, headed by Professor L. Bauman, College of Physicians and Surgeons, Columbia University, and with the collaboration of Professors W. Palmer and A. Whipple, heads of the departments of medicine and surgery of the Columbia University. In April and September of that year he presented his results and communicated them at New York's Mount Sinai Hospital and at the College of Physicians and Surgeons of Columbia University.

In the Department, headed by José Luis Rodríguez Candela, where he worked with peptide hormones at the Instituto Nacional de Ciencias Médicas, and from the University where he was Professor of Pathology, the Cultural Relations Attaché at the US Embassy in Madrid was invited to Valladolid in March 1945.

direction at the Instituto Nacional de Ciencias Médicas (1942–1955); between 1956 and 1959 at the head of the Instituto de Metabolismo y Nutrición; and during the last 15 years at the top management of the Instituto Gregorio Marañón (1960–1975).

6. Canonical pathway for calcitonin and its precursor

The circulation of ideas between Nonídez and Rodríguez-Candela was motivated by their desire to communicate. But other social forces resulted in their concepts reaching recipients for whom they were not intended. To explain why, the collective of experiences involved in this circulation is described in terms of citation credit received (always related, in principle, to the creative capability of transformation of original concepts, which is one of the style-determining factors of thought). We derived the publication and the citation timelines for each of their research domains (Fig. 7).

At the center of the circle, the unveiling of C cells as an important source of calcitonin secretion. Anatomico-physiological data on the internal secretory activity of a second epithelial component of the thyroid gland modified the curriculum in endocrinology and the methods of diagnosis and treatment of endocrinological disorders. Also through pharmacological screening of the ATP effect on insulin secretion from rat pancreas, scientific work dealt first of all with problems of the pathogenesis, the clinical picture, and the treatment of diabetes mellitus. Also, the clinical management of medullar thyroid cancer patients is behind the biochemical interests in the secreted product of thyroid C cells, calcitonin, and the identification of its precursor.

Central to Nonídez's activities during 1930–1933 was a passionate description of the "parafollicular" argyrophilic cells. Immersed in that work from 1928, when he first provided advances on his work around the vascular innervation of the thyroid gland in the New York annual meeting of the Association for Research in Nervous and Mental Diseases, Nonídez provided the essential theoretical foundation for the study of parafollicular cells in the thyroid.

These cells have been promptly recognized and appreciated by comparative neurology as a valuable research tool. One year after Nonídez had associated Baber and Huerthle cells with his discovery (1933), researchers focused on experimental designs to examine the histological

structure of the human thyroid gland. N. Goormaghtigh, the director of pathology at the University of Ghent, wrote: "We have come to the conclusion that the parafollicular cells (Nonídez) of small mammals are homologous to the small satellite follicles of the human thyroid" (Goormaghtigh, Thomas 1934, p. 727).

While Candela and his students successfully introduced the ATP mechanism of insulin release in the space between medical science and clinical practice in 1963, they also gradually constructed an argument for the phenomenon of heterogeneity of calcitonin (present in multiple heterogeneous forms in medullar thyroid carcinoma patients), which in 1975 became the research program that demonstrated that calcitonin is biosynthesized as part of a larger prohormone, procalcitonin.

These two scenes help to characterize a debate in science in 1975, bearing a striking resemblance to the political world in 1945: a qualitative change in the control of scientific work resulted in both cases in the situation where fascist scientists in Franco's Spain had no political unity. On Christmas 1945, Candela communicated for the first time in the medical press his experiments in which the pancreas is removed from an alloxan diabetic dog (Rodríguez-Candela 1945), and supported the hypothesis that the pancreas affects ketone body production through the elaboration of a hormone other than insulin. It was thus then when his first more prestigious experiment was born, whose methods would result in him being present on the pages of *Endocrinology*, the journal of the Endocrine Society (Washington, DC, USA), discussing subnormal activity of the complement one month before the death of Nonídez, on August 25, 1947 (Rodríguez-Candela *et al.* 1947).

Already in those days, the significance of the "parafollicular cells" in thyroid disease followed a unity of purpose that augured well for the future and that was immersed in the work Nonídez himself encouraged others to join in. In summary it can be said that in the summer of the year 1947, at the crossroads of C cells tissue and diabetes, the development of influence strategies and coverage of scientific competition meets the approach advocated by this analysis. We derived the citation timeline for each of the research domain.

So long as the sum of knowledge was similar between Candela and Nonídez, large percentages of citations were published for each research domain where they were credited. The maximum was 35% of the citations in the category anatomy and morphology; the minimum

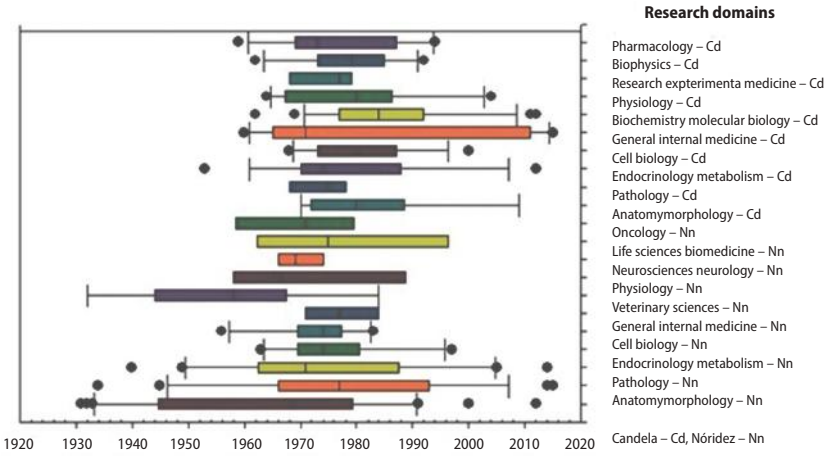

Fig. 7. Citation dates of Candela's and Nonídez's papers in the 15 research domains corresponding to the C cells researches (496 citations). As a source of technical illustrative material for an introduction to the basics of competition at the frontiers of their studies, a detailed analysis was performed on the 496 citations. The data were obtained for 5 articles published by Nonídez between 1931 and 1933, and for 53 articles published by Candela between 1947 and 1975. Box-plot representation: The horizontal line inside the box represents the median; the lower and upper borders of the box represent the 25th and 75th percentiles respectively; the whiskers correspond to the extension of 1.5 times of the box width from both ends of the box, and the circles represent values outside that interval. (Source: Compilation based on the data mentioned above.)

was 7% in the category oncology, both obtained by Nonídez. 24%, and 25% of the citations dealing with endocrinology and metabolism, were credited to Nonídez and Candela respectively. The median citation dates for the different research domains (see Fig. 7) differed significantly ($p<0.001$).

Interwar work on C cells by Nonídez formed an integral part of his consistent basic research career. Clinical work in Franco's Spain systematically advantaged Candela, particularly because he was at the head of medical investigation. On a practical level, their impact was similar concerning endocrinology. And as far as solid cancer with amyloidosis of the stroma arises from C cells, their influence existed on several levels; but in the total picture of contrasting controllability of life and fate, including political fate, it was certainly Nonídez's inheritance that was much more interesting and fruitful. Bearing in mind such a dominion in the medical research on the part of the professor of anatomy at

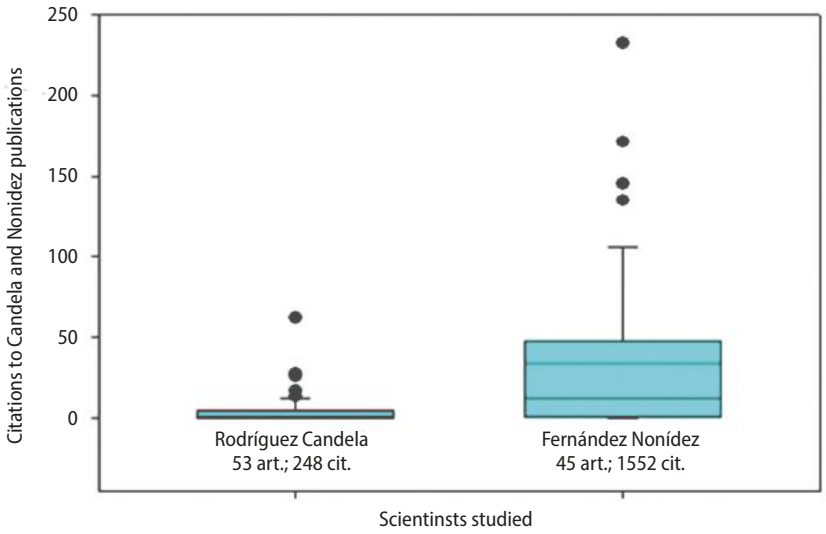

Fig. 8. Population sizes used in the citation studies on Rodríguez Candela and Fernández Nonídez (98 articles). The study population was composed of the 1800 citations received by 98 articles authored by Rodríguez Candela (53 art.; 248 cit.) and Fernández Nonídez (45 art.; 1552 cit.). The largest citations sample was 1552, obtained by Nonídez. The sum of citations is 1800 because the two citation studies analyzed the whole population of articles. Box-plot representation: as in Figure 7. (Source: Compilation based on the data mentioned above.)

Cornell, Fig. 8 reveals the depth of Nonídez's commitment to his chosen research themes, in connection with Candela's professional and intellectual echoes in the international press.

7. Conclusion

Nonídez came to terms with the errors of conceptual shoehorning reflecting on academic freedom by stressing how, as Fleck puts it, "we look with our own eyes but we see with the eyes of the collective". He was dissociated from the principles or interests of any religious faith, political school or political party and asserted the freedom and inviolability of science and the right of every teacher to an independent pursuit of knowledge without interference from any authority. But, on a practical level, the war of ideas in Spain coincided and fused with a common stock of knowledge in which self-interest and moral obligations are important.

In a way that makes sense of the certainty that para-follicular cells had to exist, Nonídez chemical methods and physiological procedures, in

their historical singularity, provided the idea from which the finding of the precursor of calcitonin was constructed 40 years later (with the intervention of the clinician Candela). Keeping in mind that the theory that the C cells excrete the hormone actively into the blood stream was initially discarded, it is through its originality, in greater or smaller increments that Nonídez contribution was acknowledged. We have transferred that standard to the state of affairs of procalcitonin, by considering where the 'oxygen' the discoverers breathed was ultimately located. A test for competition in the absence of unity was designed. Dedicated to research in the medical sciences and animal biology, the presented findings have indicated that in the tradition of scientific research in Spain biomedical sciences maintained some degree of continuity.

While endocrine metabolism is primarily the area of competition between both parties, the impact of the discovery of C cells reflected and contributed to a theoretical conflict, the investigation of which was indeed a key element for the implementation of control policies in the hospital and in the general population; it spanned from medullar thyroid carcinoma (MTC) to the 1991 Gulf War burn patients. A large number of such investigations, reflecting the broader need of showing the presence of calcitonin on the basis of its clinical behavior, extended the common cytochemical, structural and functional characteristics that had been codified for the endocrine C cells to pathology.

Besides, the exile as an influential psychological factor made the Republican community appeared as active, competent, successful, its scientists having a journal ready for use at the moment of return, once the victory by the forces of freedom in World War II had been obtained. But these difficulties to translate results of animal experiments (Nonídez) to the human being (Candela) reveal collective moral (political) problems. At the end of the 1950s, the common use of new technology (electron microscopes) enabled building consensus around the specific characteristics of cytoplasmic granules. And in Spain, in the absence of a public debate, it was after the unconditional surrender of the last Axis power, in the year 1947, when Candela became a protagonist of this line of research (he published for the first time in an international journal in the same year, aged 39 in August 1947); the same year, at the age of 55, Nonídez died.

Biochemical and pharmacological phenomena associated with clinical studies were devoted to assessing real-time diagnostic tools and an

immense amount of applied research work by Spanish hospitals. We are talking then of an inheritance that is to be estimated in terms of those students who were trained by Candela and learned medicine research by working with him in the hospital. The Higher Council of Scientific Research (CSIC) appeared to be a fruitful place for "bright boys" who had little financial support and who needed to earn some money in order to continue their academic career. Involving the traditions which surround biochemistry research and the structure of the medical profession itself, doctors have always had a very close relation with their patients, the result of this is that Candela had a "positive" image that attracted students to the center of a circle where insulin secretion, pancreatic islets, ATP release and prohormones like PCT combined enough mystery to motivate research with very careful clinical study making the discovery possible.

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