

Feature Article

The Spanish Society of Biochemistry and Molecular Biology, the Development of Biochemistry in Spain, and IUBMB

Vicente Rubio

Spanish Society of Biochemistry and Molecular Biology (SEBBM), Instituto de Biomedicina de Valencia (IBV-CSIC), Jaime Roig 11, Valencia, Spain

FOREWORD

An account such as this includes lots of important actors. To avoid forgetting anybody, I have preferred to forget all: I give only the names for the older ones, although I also mention a few returned or half-turned distinguished expatriates who are leading now a new (for Spain) brand of Spanish research institutes.

This text is purely a personal perspective based on my experience as a SEBBM member since 1973 (although I am a full member from 1980 only). For information before that time, I have resorted to the book “Cuarenta años de la Sociedad Española de Bioquímica y Biología Molecular 1963–2003,” edited by Emilio Muñoz et al. (see ref. 9), as well as other written records (see reference list). I have resorted also to oral stories, such as the recollections of the Madrid FEBS meeting by Julio Rodríguez Villanueva and Carlos Gancedo, both ex-Chairmen of FEBS, and both privileged participants in that event. I have had first-hand accounts of other aspects of Spanish biochemical history from Santiago Grisolia and from Severo Ochoa, Alberto Sols and Francisco Grande Covián, the last three regrettably deceased. Since I did not take written notes, I may have misinterpreted or misremembered something of what they told me. Therefore, any errors that might be found are my entire responsibility.

THE PRE-SPANISH CIVIL WAR YEARS

In a way, the Spanish Nobel Laureate in Physiology or Medicine of 1906, Santiago Ramón y Cajal (1), can take responsibility for the founding of biochemistry in Spain. Although his own research endeavor was cytological and histological rather than biochemical, he led an institution, the Junta de Ampliación de Estudios (2), where physiology turned into biochemistry in the years preceding the Spanish Civil war (1936–1939). It was

in the laboratories set by the Junta de Ampliación de Estudios in the Residencia de Estudiantes in Madrid where another future (1959) Nobel Laureate in Physiology or Medicine, Severo Ochoa, working under the direction of Juan Negrín (a German-trained brilliant Physiology professor, later head of the Government during the Spanish civil war), and powered by the example of the then aging Ramón y Cajal, performed numerous experiments on muscle contraction in which the role of creatine in the contraction process was being explored (3, 4). Young Ochoa also wrote a biochemistry textbook for medical students, and later on became a member of the new Institute of Clinical and Medical Research in the then brand-new Ciudad Universitaria of Madrid. This Institute was the creation of a distinguished clinician, Carlos Jiménez Díaz, foreign-trained also and bringing to Spain the novel ideas of a groundbreaking physiology (which, at that time, included centrally the newly born biochemistry) as the driving force of Medicine. The Spanish civil war shattered all of this (5). Fighting was particularly fierce at the Ciudad Universitaria, destroying all that had been set in the preceding years. After 3 years of conflict Negrín had to emigrate, Ochoa had moved abroad where he would develop a very successful career in Biochemistry, and a bankrupt and destroyed country was led by a government that was not distinguished by placing science and intelligence high in its list of priorities.

AFTER THE WAR, LIFE MAINLY OUTSIDE

In 1939, after the war ended, the Consejo Superior de Investigaciones Científicas (CSIC) was created on the same site where the laboratories of the Junta de Ampliación de Estudios had existed (6). An agrochemist, José María Albareda, was the force behind this endeavor. Some research institutes of the CSIC were involved with biological sciences. In the then few Spanish Universities, Biochemistry, under the name of Biological Chemistry, only existed formally in Pharmacy Schools, although it was taught also in Medical Schools as a part of Physiology. The country was impoverished, the universities were also poor, and brilliant young scientists were nearly

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Address correspondence to: Vicente Rubio, Spanish Society of Biochemistry and Molecular Biology (SEBBM), Instituto de Biomedicina de Valencia, Jaime Roig 11, Valencia-46010, Spain. Tel: +34-963391772. Fax: +34-963690800. E-mail: rubio@ibv.csic.es

always forced to emigrate or could not return. An exception was Angel Santos (7), a professor of Biological Chemistry at the School of Pharmacy in Madrid, who taught, carried out research, and lobbied for biochemistry during those bleak years, being the IUB (now IUBMB) representative of Spain since the incorporation of Spain to IUB in 1955, till 1968. Angel Santos was the mentor of many Spanish biochemists, including Federico Mayor Zaragoza, widely known as UNESCO Director General (1987–1999). By contrast, Francisco Duran-Reynals (8, 9), the father of hyaluronidase and a founding father of cancer virology, was set to return to Spain from the Rockefeller Institute, but the Spanish civil war prevented this. Jordi Folch-Pi (9, 10), the creator of the chloroform–methanol extraction procedure, the discoverer of proteolipids and a father of Neurochemistry, went from Barcelona to Duran-Reynalds laboratory in the Rockefeller in 1936, and remained in the USA for the rest of his highly successful scientific life. In the Medical School of Valencia, the physiologist José García Blanco, trained with Negrín in Madrid and with Knoop in Germany, carried out some modest biochemical work and proposed a then very young Santiago Grisolia to emigrate to Ochoa's laboratory in New York (9, 11). In his 30 years in the USA Grisolia demonstrated biochemically (together with P.P. Cohen and in parallel with Sarah Ratner) the reality of the urea cycle, introduced biochemistry to Kansas, and carried out important work on enzymes and on protein carbamylation. Francisco Grande Covián was another of these pioneer expatriate biochemists (9). He had worked also with Negrín before the war, carried out nutritional studies in Valencia during the war years as part of the effort of the legal Government to feed the population, and emigrated in 1953 to stay more than 20 years in the University of Minnesota where he developed a very successful career in nutritional biochemistry and related areas. Others who left the country at that time to carry out biochemical work (9) were Joan Oró (a founding father of origin of life biochemistry) and Carlos Villar-Palasi (a professor at the University of Virginia with important contributions on glycogen metabolism and on kinases). Pedro Cuatrecasas, one of the first Pharmaceutical biochemists and a father of affinity chromatography, was born in Madrid amid the civil strife, but his family soon fled the country. Marino Martínez-Carrión also developed his entire scientific career abroad, graduating from Berkeley and participating in the development of biophysical biochemistry, first in the Medical College of Virginia and later in Kansas City (Missouri).

ALBERTO SOLS, AND THE BIRTH OF SEB (SEBBM) AND FEBS

Alberto Sols deserves a particular mention (12, 13). An M.D. in 1944, he was on good terms with the regime and spent 3 years (1951–1954) in St. Louis with the Nobel Laureates in Physiology or Medicine (1947) Carl and Gerty Cori (14, 15). The laboratory of the Coris was then a Mecca for enzymology and for carbohydrate biochemistry, and thus, in addition to per-

fecting enzymology, Sols then made very good international contacts with many leading scientists on both sides of the Atlantic. Sols also developed a close relationship with Ochoa and with the Argentinean scientist Luis Leloir, who would be later a Nobel Laureate in Chemistry (1970). Sols returned in 1954 to Madrid and developed his career in the CSIC under the protection of Albareda (at that time in Spain, protection from a big shot was a prerequisite for advance). His endeavors proved very good for Spanish Biochemistry, because he was the right man at the right place and time. Being, in a way, the internationally well known Spanish Biochemist of the time, he helped to open the windows to the external world. After years of stagnation and international isolation, Spain began to return to the international forums in 1953, when a treaty was signed with the USA, which was followed little later by the entry of the country into the UN (1955) and by the launching of the 1st Spanish Development Plan (1963) including the allocation of money for science. The country was in need of international connections, and in the biochemical context, it already had a representative to the recently created IUB (16). Alberto Sols, together with no more than another 34 biochemists/physiologists, helped these connections, in large part by creating SEB (now SEBBM), the Spanish Society of Biochemistry in 1963 (17), the same year that FEBS (the Federation of the European Biochemical Societies) was created (18). In this way, SEB was a founder of FEBS. In addition, SEB became the Spanish Adhering Body to IUB, and, in fact, Sols was the Spanish representative in IUB from 1968 to 1972.

TOWARDS INTERNATIONALIZATION OF SPANISH BIOCHEMISTRY

The creation of SEBBM (I will use from here on the modern term for this society, which includes also molecular biology, as I will use IUBMB rather than IUB) was a turning point in the scientific life of Spain and in the internationalization of Spanish biological science (17). It meant the separation of biochemistry from physiology in Spanish Universities, allowing biochemistry, and later on, molecular biology, to flourish. In 1966, when I entered Medical School in Valencia, it was clear to us that biochemistry was becoming the language of medicine. In my view, SEBBM was highly successful in spreading by way of its members a new creed of passion for understanding and for hard work, and the positivist utopia that the understanding of life was essential for a better life (perhaps a naïve concept; nevertheless, I still firmly believe in it). To us, this creed was very welcomed in those days of revolt against an authoritarian rule because of its reliance on reason rather than on authority.

HELP FROM THE OUTSIDE AND THE GROWTH INSIDE

Since its very beginning, SEBBM and the development of Spanish biochemistry and molecular biology were helped by the Spanish biochemist expatriates. Severo Ochoa (19) and Santiago

Grisolía were promoters of SEBBM from the very start. They, and most other expatriates mentioned above, either trained or provided advice on choosing a laboratory where to train, to numerous young Spaniards who went to the USA (and, to a lesser extent in these years, to Europe) in search of postdoctoral experience. Although some of these postdocs remained in the United States and developed in many cases highly successful careers (9) many others returned and became the now aging, first really numerous generation of internationally-trained Spanish biochemists, microbiologists, and geneticists, those that by working inside have provided the muscle, blood, and the sweat for pushing the wagon of Spanish biochemistry and molecular biology towards its present speed. They are too many to be mentioned here without the risk of forgetting someone.

While this increase in manpower was taking place, a certain degree of modernization was under way within Spain, in part related also to Spanish expatriates. An education minister, Villar-Palasi, the brother of the biochemist expatriate Carlos Villar-Palasi, called a committee of experts that included Severo Ochoa and Santiago Grisolía, to provide advice on how to modernize the Spanish Universities. This led in the late 60s to an important reshuffling and expansion of the Spanish University system, with creation of many new universities including two excellence-focused universities (called Autonomous Universities), in Madrid and Barcelona. This made room, not without trouble, for the young trainees returning from abroad, and led to development in the late 60s and 70s of new centers of science production outside Madrid and Barcelona. The influence of Ochoa (19) and the funds derived from the treaty of collaboration with the USA were put to good use in the creation of the Centro de Biología Molecular (CBM; now called Centro de Biología Molecular Severo Ochoa, CBMSO), a center of the CSIC and the Autonomous University of Madrid that was conceived as state-of-the-art. The CBMSO, opened in 1975, hosted Severo Ochoa later in his life, and set the standard for future centers in Spain. In other parts of the country, in addition to the universities, other Institutes were being opened in the 70s, generally as part of CSIC or as joint ventures with it. These included the Instituto de Biología Fundamental of Barcelona, the Instituto de Bioquímica Vegetal of Seville, and the Instituto de Investigaciones Citológicas (IIC) of Valencia. Shortly after the return of democracy, the IIC of Valencia was to be led by the Spanish biochemist expatriate, Santiago Grisolía. In Zaragoza, a private research institute belonging to a baby formula laboratory, Ulta, was directed by another Spanish expatriate, Francisco Grande-Covián. The heading by expatriates of new research centers is a constant of Spanish scientific life that continues in good shape, sometimes with mixed feelings of both the imported brains and the locals, although generally the outcome appears highly positive (20). In recent years, the Centro Nacional de Investigaciones Oncológicas (CNIO) and the Centro Nacional de Investigaciones Cardiovasculares (CNIC) were created in Madrid and are led by Mariano Barbacid (previously at Bristol Myers Squibb) and by Valentín Fuster (Mount Sinai).

In Barcelona, the Centres de Regulació Genòmica (CRG) and de Medicina Regenerativa (CMR) were also created recently and are directed, respectively, by Miguel Beato (Marburg, Germany) and Juan Carlos Ispizua (Salk Institute), and the Institute for Research in Biomedicine (IRB) was opened and had Joan Massagué (Sloan Kettering) as Associate Director.

THE VI FEBS MEETING

The year 1969 was a turning point for Spanish biochemistry in the internationalization process and also the point of reaching adulthood. It was the year when Spain became member of EMBO (although not of EMBL, a decision that was postponed until 1987), and also the year in which the VI FEBS Meeting was organized in Madrid (21). This meeting added a pinch of political drama to the generally peaceful life of FEBS. The meeting was planned for early April under the honorary presidency of Ochoa, but, in January, the State of Exception, a sort of curfew with loss of basic rights, was established by the government as a response of the regime to the student's uproar. Some European scientists called for a boycott of the Madrid Meeting. Ochoa on one side of the Atlantic, and the FEBS authorities and the local organizing committee on the other, had to work very hard to prevent the failure of the meeting, which finally took place in an improved political context, since the State of Exception was abolished before the Meeting began. The presence of 2,000 delegates, including several Nobel laureates and many highly distinguished biochemists attests to the meeting's success. A poster was painted by Dalí and perhaps ranks highest in artistic quality among those used for FEBS meetings. The fact that Dalí and Ochoa were friends from the pre-civil war years (22) made of Dalí a great fan of biochemistry (23). He also painted memorable posters for the Urea Cycle Meeting organized in Valencia by Grisolía in May 1975 (24), and for the meeting celebrating, in Barcelona, the 70th anniversary of Ochoa (see ref. 22). In the case of the VI FEBS meeting, a stamp was also printed by the Spanish Postal System to commemorate the meeting. Only many years later, in 1996, was another FEBS meeting (the 24th) to take place in Spain, in Barcelona. No IUBMB Congress has ever been held in Spain; it is scheduled for 2012, in Seville.

FRESH AIR FOR SPAIN AND THE NORMALIZATION OF SPANISH SCIENCE

With the death of Franco in November 1975, a rapid process of institutional normalization and modernization of Spain took place. This included a democratic Constitution and the advent of democratic Governments. The CSIC got a new set of more open rules (1977), and, after a failed attempt led by the Minister for Research and Universities, Federico Mayor (a biochemist trained with the Nobel Laureate Sir Hans Krebs), the University System was reformed again (1983), this time under the rule of the Socialist Party. This reform and the passing of the Law for

Science (1986) fostered rapid scientific growth. The entry of Spain into NATO (1981/1986), and particularly into the European Union (1986) completed the process of normalization of the international links with Spain. During these years of Socialist Party rule, Spain established the workings of its science system, based on the competitive funding of science and of peer review orchestrated by a neutral evaluation agency (ANEP), with funds provided by a 4-year National Plan, and with an Inter-ministerial Committee administering and overseeing the process. A number of Spanish biochemists including prominently the late Roberto Fernández de Caleyá, were among the group of scientists that drew the basic lines of the system. The entry into the EU greatly spurred research thanks largely to the skills of Spanish negotiators that introduced the Structural Funds (FEDER) and the idea of positive discrimination for science initiatives that included groups from the countries being accepted into the EU (Portugal, Spain and Greece at the time). Never again, as in the immediate years after incorporation into the EU, has Spain had such a large mass of Spanish scientists leading or participating in European initiatives. This had a great impact in setting strong links between Spanish and European groups and in rendering Spanish scientists very accustomed to the day-to-day uses of international science. On the other hand, Structural funds have pumped money into the science system and into the building of new scientific institutes and the incorporation of scientific infrastructures. This has allowed to close the gap between the meager science funding of the pre-EU era, and the more up-to-date funding of nowadays. With the entry of Eastern European countries in the EU, Spain is losing its privileged position as a receiver of Structural funds, but, nevertheless, it would not be expected that the country were to revert to lower science budgets, although growth might slow down.

TODAY'S SPANISH BIOCHEMISTRY AND MOLECULAR BIOLOGY IN PERSPECTIVE

When the state of Spanish Biochemistry, Molecular Biology and allied disciplines of today is compared with the state prevailing 30 years ago, there are reasons for being proud. After coming to a standstill in the late 80s and early 90s, funds for science have steadily increased in Spain, and the public contribution is nowadays ~1% of the GNP, with the present government having tried hard (although not fully succeeding) to keep its word to increase research funds by 25% yearly (25). Science, and particularly biomedical and molecular disciplines, are in the limelight of Spanish life (26). Press records of biological and biomedical advances are numerous and quite accurate. Spanish biochemists and molecular biologists are visible in international journals and in scientific forums such as congresses and meetings. New Statutes for the CSIC were approved in 1993 and 2000, and this research institution, of which about 50% is biological-biomedical, has grown steadily, being now the center of a change of status to adapt it to the challenges of 21st century research. The University has modified again its rules in 2007, in

part to facilitate the recruitment of scientists. The Ramón y Cajal and Juan de la Cierva programs have allowed recruitment of many senior and junior postdocs. The Ministry of Health has taken up biomedical research as the centerpiece of its performance, and has opened physical (CNIO and CNIC) and virtual centers for biomedical research (seven Centros de Investigación Biomédica en Red, or, in short, CIBERS; and even more Networks, called RETICS), allowing the contracting of a large number of scientists. In addition, the Health Ministry has funded three Spanish centers of regenerative medicine and has passed a law regulating biomedical research, creating the bases for structured research within the Health System. Large hospitals have organized research foundations, and a host of young researchers has been incorporated into them, perhaps with mixed results, but, nevertheless, increasing the level of science performance of medical institutions. Several regions, including Catalonia and Madrid, have acquired the status of Bioregions. Many classical centers for research have expanded a lot and sport new, well furnished buildings, whereas numerous new institutes and research centers dedicated to biomedical subjects have been created all over the country by the central or by the local governments.

And yet, there are many challenges and reasons for strong concern. Although players in the game, we are not yet in the front line. The science system in Spain is still quite closed to foreign talent (27–29). There is no statute regulating specifically the activity of the public research worker. The bureaucratic machine for hiring people and for using funds can suffocate Spanish science if it is not soon abolished or replaced by more sensible and specific control systems (30). Publication and patent record is reasonable but not high. There is too little pharmaceutical and biotechnology-based industry, and thus scientists have the universities and the public system as the only niche for work. In most cases, the universities are not science-driven, and their recruitment of personnel always includes tenure. In fact, staff professors and scientists in the public system (including the Universities and the CSIC) are civil servants, a status that some think should be abolished (20). There are few charities devoted to science, and those that exist follow a policy of marginal science support rather than creating stable, self managed, research centers and funds for specific purposes. Private universities are not real players in science. Concerning the international status of our scientists, relatively few Spanish scientists win international awards or lead EU grants. With the growth of Asian countries, we are at risk of falling again into scientific (and economic) irrelevance. This is at odds with claims from all parties involved, including SEBBM, that we should build a knowledge-based society and economic system. All these concerns are serious but can be considered minor by comparison with the leap that Spanish science, and in particular Spanish biochemistry and molecular biology, has made since the days of Alberto Sols. This leap has been largely possible through the effort of the Spaniards, but it has included as key support the interaction with international bodies such as FEBS

and IUBMB. Spanish biochemists would be happy and ready to return this help by serving in these international bodies. The full support of SEBBM, now a society of over 3,500 members, in the organization of the IUBMB Congress of 2012 in Seville will be a proof of the commitment of Spain with IUBMB and with world biochemistry and molecular biology.

REFERENCES

- Ramón y Cajal, S. (1989) *Recollections of My Life*. MIT Press, Cambridge.
- Before the CSIC: the JAE. <http://www.csic.es/historia.do?lengua=en>.
- Ochoa, S. (1980) The pursuit of a hobby. *Annu. Rev. Biochem.* **49**, 1–30.
- Santesmases, M. J. (2001) Severo Ochoa (1905–1993): the changing world of biochemistry. *Trends Biochem. Sci.* **26**, 140–142.
- Preston, P. (2007) *The Spanish Civil War. Reaction, Revolution, and Revenge*. W. W. Norton, New York.
- Rideal, E. K. (1950) The Spanish Higher Council for Scientific Research. *Nature* **165**, 790–791.
- Mayor Zaragoza, F. (2005) Homage to Angel Santos Ruiz. *An. R. Acad. Nac. Med. (Madr.)* **122**, 506–514.
- Gardner, W. U. (1958) Francisco Duran-Reynals, 1899–1958. *Cancer Res.* **18**, 1352–1353.
- Pellicer, A. (2004) Contribuciones de los científicos españoles en Estados Unidos a la bioquímica. In *Cuarenta años de la Sociedad Española de Bioquímica y Biología Molecular 1963–2003* (Muñoz, E., Santesmases, M. J., Romero, A., and Ávila, J., eds), pp. 227–248, Sociedad Estatal de Conmemoraciones Culturales, SA, Madrid.
- Lees, M. B. (1998) A History of proteolipids: a personal memoir. *Neurochem. Res.* **23**, 261–271.
- Aupí, V. (1998) Santiago Grisolia. Apuntes para la historia biológica del hombre. Universidad Politécnica de Valencia.
- Gancedo, C. and Aragón, J. J. The presence of Alberto Sols in modern biochemical research. Available at <http://www.fundacionareces.es/albertosols.htm>.
- Santesmases, M. J. (1998) Alberto Sols. Instituto de Cultura Juan Gil Albert, Diputación de Alicante-Ayuntamiento de Sax, Alicante.
- Cori, C.F. (1969) The call of science. *Annu. Rev. Biochem.* **38**, 1–20.
- Kalkar, H. M. (1958) Gerty T. Cori, biochemist. *Science* **128**, 16–17.
- Kamminga, H. (1999) Internationalizing biochemistry: the 1949 congress in context. *Trends Biochem. Sci.* **24**, 404–408.
- Santesmases, M. J., and Muñoz, E. (1997) Scientific organizations in Spain (1950–1970): social isolation and international legitimation of biochemists and molecular biologists on the periphery. *Soc. Stud. Sci.* **27**, 187–219.
- Feldman, H. (ed.) (2004) *Forty Years of FEBS. 1964 to 2003. A Memoir*. Blackwell Publishing, Oxford.
- Santesmases, M. J. (2000) Severo Ochoa and the biomedical sciences in Spain under Franco, 1959–1975. *Isis* **91**, 706–734.
- Barbacid, M. (2007) Returning home. *Cell* **129**, 641–644.
- The editor (1969) FEBS in Spain. *Nature* **221**, 702–703.
- Dalí, S. (1976) My homage to Severo Ochoa. In *Reflections on biochemistry. In honor of Severo Ochoa* (Kornberg, A., Horecker, B. L., Cornudella, L., and Oró, J., eds.) Pergamon Press, Oxford, New York.
- Guardiola, E. and Baños, J. E. (2003) Dalí and the double helix. *Nature* **423**, 917.
- Grisolia, S., Báguena, R., and Mayor, F. (eds) (1976) *The Urea Cycle*. Wiley, New York.
- Schiermeier, Q. (2004) Spain aims at premier league. *Nature* **431**, 488–489.
- The editor (2004) Ending the pain in Spain. *Nature* **428**, 1.
- Pickin S. (2001) Spain is a closed culture to foreign researchers. *Nature* **410**, 627.
- van Raaij, M. (2004) New law does little to ease research pain in Spain. *Nature* **428**, 365.
- Lombardía, M. O. (2004) Spain: politicians need to challenge the status quo. *Nature* **428**, 365.
- The editor (2007) Independence day? *Nature* **446**, 347–348.