



An account on the history of pharmacology in Spain

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ABSTRACT

Here we present an account on the history of pharmacology in Spain. Pharmacology as an independent science in Europe began with the creation of university chairs. Of particular relevance was the appointment in 1872 of Oswald Schmiedeberg as chairman of an Institute of Pharmacology at the University of Strassbourg, Germany. Teófilo Hernando pioneered in Spain the new emerging pharmacology at the beginning of the XX Century. He made a postdoctoral stay in the laboratory of Schmiedeberg, working on digitalis. In 1912 he won the chair of “Materia Médica y Arte de Recetar” at “Universidad Central of Madrid” (today, “Universidad Complutense de Madrid”, UCM). He soon decided to transform such subject to the emerging modern pharmacology, with the teaching of experimental pharmacology in the third course of medical studies and clinical therapeutics (today clinical pharmacology) in the sixth course. This was the status of pharmacology in 1920, supporting the view that Hernando was a pioneer of clinical pharmacology. However, the Spanish Civil War and the II World War interrupted this division of preclinical and clinical pharmacology; only in the 1980’s was clinical pharmacology partially developed in Spain. From a scientific point of view, Hernando directly trained various young pharmacologists that extended the new science to various Spanish universities. Some of his direct disciples were Benigno Lorenzo Velázquez, Francisco García Valdecasas, Rafael Méndez, Tomás Alday, Gabriel Sánchez de la Cuesta, Dámaso Gutiérrez or Ramón Pérez-Cirera. One of the central research subject was the analysis of the effects of digitalis on the cat and frog heart. In the initiation of the 1970 s pharmacologists trained by those Hernando’s students grew throughout various universities and the “Consejo Superior de Investigaciones Científicas” (CSIC). And hence, in 1972 the “Sociedad Española de Farmacología” (SEF) emerged. Later on, in the 1990’s the “Sociedad Española de Farmacología Clínica (SEFC) also emerged. The relationship between the two societies is still weak. Out of the vast scope of the pharmacological sciences, Spanish pharmacologists have made relevant contributions in two areas namely, neuropsychopharmacology and cardiovascular pharmacology. Nonetheless, in other areas such as smooth muscle, gastroenterology, pharmacogenetics and hepatic toxicity, Spanish pharmacologists have also made relevant contributions. A succinct description of such contributions is made. Finally, some hints on perspectives for the further development of preclinical and clinical pharmacology in Spain, are offered.

1. Introduction

Pharmacology is considered to have emerged as a separate science only when the first university chair was established. This occurred in 1847, when Rudolf Buchheim was appointed professor of pharmacology at the University of Dorpat in Stonia, then a part of Russia. His student Oswald Schmiedeberg received his M.D. degree in 1866 with a thesis on the monitoring of chloroform in blood. He succeeded Buchheim in 1869. Although Buchheim is credited with turning descriptive and empirical study of medicines into an experimental science, his reputation has been overshadowed by that of his student, Oswald Schmiedeberg.

In 1872, Schmiedeberg became professor of pharmacology at the University of Strassbourg and received generous government support in the form of a magnificent Institute of Pharmacology. In his 46 years at then German Strassbourg, Schmiedeberg trained most of the pharmacologists who became professors at other German universities and in several other countries. One of his students was Teófilo Hernando, who

introduced pharmacology as an independent science in Spanish universities at the beginning of the XX century.

2. Teófilo Hernando and Spanish pharmacology

Teófilo Hernando (Fig. 1), the son of a rural physician, was born in Torreadrada, province of Segovia, Spain, on April 14th, 1881. He died in Madrid on March 10, 1975, when he was almost 95 years old. He graduated in medicine at Universidad Central, San Carlos Hospital of Madrid in 1907; one of the professors who exerted a major influence on him was Santiago Ramón y Cajal, since Hernando worked in his laboratory with Cajal’s disciples, the great histologists Nicolás Achúcarro and Jorge Francisco Tello. Later on, Hernando recalled this laboratory experience as the most pleasant and touching of his life.

Hernando began his medical career as a doctor of the “Beneficiencia Municipal de Madrid”, as a bath physician, and as an assistant professor of therapeutics and forensic medicine. This introduced Hernando to

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Fig. 1. Teófilo Hernando when he was 80-year-old.

university activities, which oriented him towards academia and science. Ramón y Cajal knew of Hernando's enthusiasm for academic research and teaching; at the time, he was the president of the "Junta de Ampliación de Estudios" (JAE), and he urged Hernando to spend some time at the Institute of Pharmacology in Strasbourg, with Oswald Schmiedeberg. This was possible thanks to a grant from the JAE in 1911. In addition to his stay at the Strasbourg Institute of Pharmacology, he also did other stays in German universities specifically in Berlin with Hefter and in Francfort with Ehrlich. With these stays, Hernando learned the new directions that pharmacology was taking in Europe. Thus, when in 1912 he obtained the chair of "Materia Médica y Arte de Recetar" at the Central University (today, the "Universidad Complutense de Madrid", UCM) he had the knowledge and the courage to develop modern pharmacology in Spain, both from the point of view of medical education and as a science. From an educational point of view, Hernando soon decided to divide the old "Materia Médica y Arte de Recetar" into the subject of Experimental Pharmacology in the third year of medical studies and clinical therapeutics (today Clinical Pharmacology) in the sixth year of medicine.

In 1919, Hernando went to the "Ministerio de Instrucción Pública" to request the creation of a course on Clinical Therapeutics at the "Universidad Central de Madrid"; this new medical subject was approved ("Real Orden de 5 de noviembre, Gaceta del 13 de diciembre de 1919"). Thus, in 1920, for the first time in a Spanish university, Teófilo Hernando taught General and Experimental Pharmacology to the third year medical students and Clinical Therapeutics (later, Clinical Pharmacology) to the last year medical students. In fact, in 1970, Hernando pointed out in a lecture at the Royal Spanish Academy of Medicine that *<<Given the relevance of Clinical Pharmacology, as an educational and scientific matter, it is necessary to develop complete groups of clinical and experimental pharmacologists in the major hospitals in Spain>>*. It is puzzling that in the period 1940–1980, clinical pharmacology disappeared in Spain, to resume its activities only in the last decades of the XX century.

Hernando practiced medicine in the field of gastroenterology. In 1915, with his friend eminent physician Gregorio Marañón, Hernando directed the textbook "Internal Medicine", that provided a didactic information to Spanish and Latin American physicians on the European knowledge of internal medicine during decades, written by Spanish medical doctors.

From a scientific perspective, Hernando trained a remarkable number of students who expanded pharmacology in different universities. Among others, Alday (Universidad de Pamplona); Benigno Lorenzo Velázquez (Universidad Central de Madrid); Rafael Méndez (Universidad de Sevilla, then Harvard University and Loyola University in the USA and later Instituto Chávez de México). Also in Mexico, Pérez Cirera and Francisco Guerra (Guerra later taught at the University of Yale, USA); Planelles (deceased in Moscú); Francisco García Valdecasas (Universidad de Barcelona); Gabriel Sánchez de la Cuesta (Universidad de Sevilla). In turn, these direct disciples of Hernando trained other researchers who introduced pharmacology in all Spanish universities.

Fig. 2 shows a group of direct students ("my pharmacological sons", as Hernando liked to say) and his "pharmacological grandchildren".

The diagram in Fig. 3 shows the origin of pharmacology with Bucheim and Schmiedeberg, Teófilo Hernando, his direct disciples and the following generation of Spanish pharmacologists. A brief description of Hernando's first disciples follows.

Gabriel Sánchez de la Cuesta introduced pharmacology in Andalucía. He graduated in Medicine in 1928 and defended his doctoral thesis on cardiac glycosides in 1933 at the "Universidad Central", a subject that had interested Hernando during his posdoc at Schmiedeberg's laboratory. In 1936 he was appointed to the chair of "Terapéutica Clínica General y Farmacología of the Universidad de Sevilla". With his student, Rodrigo Tallón, Sánchez de la Cuesta studied the lipid spectrum of the blood and the pathogenesis of atherosclerosis, research interests derived from his clinical practice as a cardiologist. One of his more notable disciples was his son, Felipe Sánchez de la Cuesta, who created a solid, relevant and productive School of Pharmacologists at the "Universidad de Málaga", in Andalucía.

Benigno Lorenzo Velázquez studied medicine at "Universidad Central" in Madrid. In 1926 he defended his doctoral thesis under Teófilo Hernando on the pharmacokinetics of adrenaline. Then he made a postdoctoral training with Felix Haffner in Königsberg, Germany, working on the thyroid gland. In 1929 he won a chair of "Terapéutica y Farmacología" at the "Universidad de Zaragoza". In 1941 he moved to the "Universidad Central", to the chair left vacant by his mentor Teófilo Hernando. Velázquez created a broad school of pharmacology with collaborators such as Mariano Mateo Tinao, Perfecto García de Jalón, José María Bayo, Manuel Armijo, Félix Sanz, Javier Elio, Diego Figuera, Luis Aparicio, Alfonso Moreno, Pedro Lorenzo and Pedro Sánchez García, among others. The group carried out studies on histamine release, analgesics and anesthetics, smooth muscle pharmacology, uterine spasmolysis, or respiratory and circulatory pharmacology. In 1930, Velázquez published the textbook of pharmacology "Terapéutica con sus fundamentos de farmacología" with a preface by Teófilo Hernando. "The Velázquez", as it is known by students in Spain and Latin America, is still being edited; its latest editions include a section on clinical pharmacology.

Francisco García Valdecasas studied medicine at the "Universidad Central" and worked in the laboratory of Teófilo Hernando from 1930 to 1932. He worked on adrenergic receptors and sympathetic neurotransmission, defending his doctoral thesis in 1935 and obtaining the Chair of Pharmacology at the "Universidad de Barcelona" in 1940. García-Valdecasas completed his pharmacological training at the University of Göttingen in Germany and several stays at the US Universities of Harvard, Cornell, Pennsylvania, California, and New York. He created a large school of pharmacologists, including José Antonio Salvá, José Laporte, Eduardo Cuenca, Francisco Javier Forn, Sergio Erill, Francisco Jané, Eulalia Planas, Margarita Puig, and Juan Gibert, among



Fig. 2. Teófilo Hernando and various of his disciples in 1971, at Sevilla, Spain.

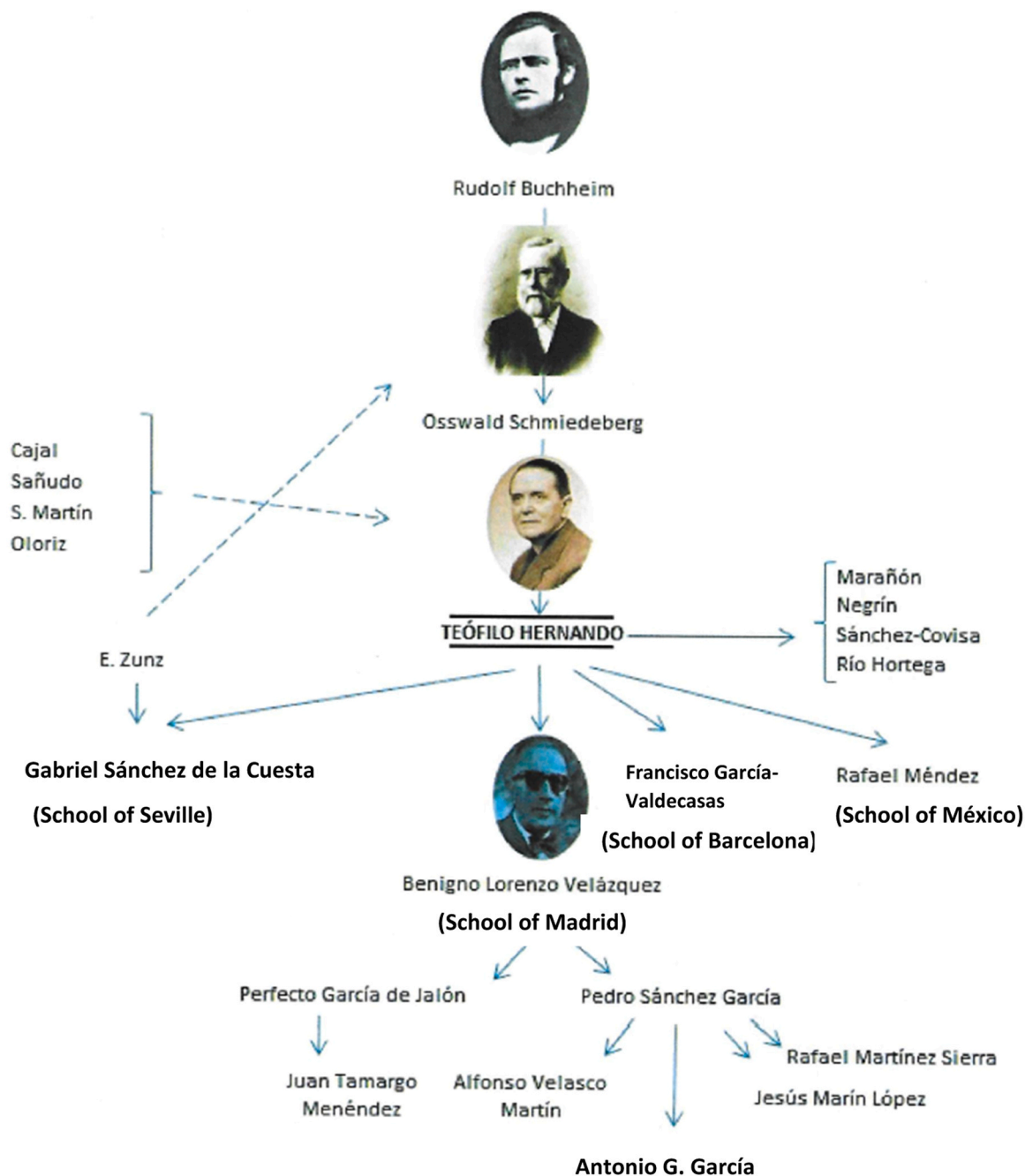


Fig. 3. Scheme showing some of the schools of pharmacologists that directly or indirectly, descended from Teófilo Hernando.

others. Valdecasas focused his research on vascular pharmacology and beta-adrenergic receptors. His collaborator, Eduardo Cuenca, developed a strong line of research in psychopharmacology.

Rafael Méndez studied medicine at the “Universidad Central” and in 1928 he defended his doctoral thesis on ergot alkaloids such as ergotamine, under the supervision of Teófilo Hernando. He made a stay with Joseph Clark in Edimburg to study the antagonism of adrenaline by ergotamine. Subsequently, he worked in Berlin with Trendelenburg and Otto Kraye and obtained the chair of pharmacology at the “Universidad de Sevilla” in 1935. Latter, as a result of the Spanish Civil War and the Second World War, Kraye and Méndez met again at Harvard University, USA. In 1946, after a stay at Loyola University in Chicago, Méndez moved to the Mexican Institute of Cardiology, where he developed a highly relevant research in cardiovascular pharmacology with a solid group of collaborators.

3. The Spanish society of pharmacology

The Spanish Society of Pharmacology (“Sociedad Española de Farmacología”, SEF) was founded in 1972 with the aim of bringing together all university graduates involved in pharmacological or related work or studies, including people with a special interest in this field. Its founding members were based in Barcelona at a time when there were large Schools of Pharmacology led by Professors Francisco García Valdecasas in Barcelona and by Benigno Lorenzo Velázquez in Madrid. The former was the founder of what is now known as the Spanish Society of Pharmacology, originally called the “Asociación Científica de Farmacólogos” (Scientific Association of Pharmacologists).

The first concerns stemmed from the arrival in Barcelona in 1940 of Professor Francisco García Valdecasas, who formed a scientific group in the field of experimental pharmacology. The Barcelona School of

Pharmacology, originally from the field of pharmacy, began to be considered as such. It was headed by Pedro Puig Muset, who proposed to García Valdecasas the idea of creating a pharmacological society within the Laboratory Academy of Medical Sciences of Catalonia and the Balearic Islands. But Valdecasas did not want to accept the presidency because, according to his own testimony –he did not like to hold representative positions. Thus, the pharmacist Puig Muset became the president of the new society. Meanwhile, the teaching of therapeutics in the medical schools was evolving toward more rational and scientific approaches, following Schmiedeberg, who introduced the systematic study of the mechanism of action of drugs.

The pharmaceutical profession also felt the need for a better understanding of the biological evaluation of drugs, which led to the creation of the Professional School of Pharmacologists in Barcelona, directed by García-Valdecasas and within his chair, open to all degrees where drugs were studied. All this was the seed of what was to come. Let us not forget that most of the Spanish pharmaceutical industry came from pharmacies, which initially produced medicines in their back rooms. In Barcelona, these pharmacies were more developed than in the rest of Spain. For this reason, the flourishing and expansion of the pharmaceutical industry - in its present form - had a greater presence in Catalonia.

Therefore, the graduates of the aforementioned School of Pharmacology, coming from different parts of Spain, felt the need to create an association that would be the logical channel to unite so many of those who had been trained in that School and who shared scientific and professional interests. And it was then, in 1972, that Prof. Valdecasas asked a former student of the School, Dr. Manuel Fraile de Blas, to do all the groundwork for the creation of a scientific society. After much deliberation, it was decided that the most appropriate name should be the “Scientific Association of Pharmacologists”, later renamed the “Sociedad Española de Farmacología” (SEF). Once authorised, the first National Congress of the newly created Society was held in 1974 at the Consejo Superior de Investigaciones Científicas (Spanish National Research Council) in Barcelona. It was a resounding success in every respect.

The appointment of the Chairpersons at any given time has been elected at the Congresses held by the Society. Reciprocally, each Chairperson has chosen the venue for the following year. The list of presidents throughout the history of the Spanish Society of Pharmacology is summarized in Table 1.

In its early years, the Society of Pharmacologists obtained authorisation from the Spanish National Research Council (CSIC) to use one of the rooms of the Pharmacology Section, headed by Prof. Valdecasas, as its office. However, the growth of the Society and the development of its more technical aspects made it advisable to create a technical secretariat, which for strategic and budgetary reasons, was transferred to the Professional Association of Biologists of Catalonia and later to its current headquarters in Madrid.

The Society’s journal has received different names, from “Revista de la Asociación Española de Farmacólogos”, to “Revista de Farmacología Clínica y Experimental” and finally to “Actualidad en Farmacología y Terapéutica (AFT)”, as we know it today as the official journal of the Spanish Society of Pharmacology (SEF, as per its acronym in Spanish). It is published jointly with the Fundación Teófilo Hernando (FTH).

Finally, it is worth mentioning that the SEF, under the presidency of M^a Jesús Sanz, instituted the appointment of “Honourable Pharmacologists”. To date, the following professors have been awarded this distinction:

- Jesús Flórez Beledo, Antonio García García, Jesús García Sevilla, M^a Isabel Cadavid, Juan Tamargo Menéndez, Francisco Zaragoza García, Esteban Morcillo Sánchez.

Table 1

Presidents of the Spanish Society of Pharmacology from its foundation to date.

Years	Name and surnames	Practising in
1972 - 1977	Manuel Fraile de Blas	“Laboratorios Sandoz Barcelona”
1978 - 1981	Eduardo Cuenca Fernández	“Universidad de Alcalá”
1982 - 1985	Sergio Erill Sáez	President of “Fundación Esteve” Barcelona
1986 - 1989	Jesús Flórez Beledo	“Universidad de Cantabria”
1990 - 1993	José Serrano Molina	“Universidad de Sevilla”
1993 - 1996	Jesús-Andrés García-Sevilla	“Universidad de las Islas Balears”
1996 - 1997	Juan Tamargo Menéndez	“Universidad Complutense de Madrid, UCM”
1997 - 1999	Esteban Morcillo Sánchez	“Universidad de Valencia”
1999 - 2001	Pedro Sánchez García	“Universidad Autónoma de Madrid, UAM”
2001 - 2005	Felipe Sánchez de la Cuesta y Alarcón	“Universidad de Málaga”
2005 - 2009	Francisco Zaragoza García	“Universidad de Alcalá”
2009 - 2014	Teresa Tejerina Sánchez	“Universidad Complutense de Madrid”
2014 - 2019	María Jesús Sanz Ferrando	“Universidad de Valencia”
5/7/2019 - 2023	Valentín Ceña Callejo	“Universidad de Castilla- La Mancha”
7/09/2023- present	Antonio Rodríguez Artalejo	“Universidad Complutense de Madrid”

4. Development of specific pharmacological areas in Spain

4.1. Cardiovascular pharmacology

Spanish cardiovascular pharmacology began in 1928, when Teófilo Hernando (1881–1976) founded the first Department of Experimental Pharmacology at the Faculty of Medicine of the Universidad Complutense de Madrid. With his students (Dámaso Gutiérrez, Tomás Alday, Gabriel Sánchez de la Cuesta, Ramón Pérez-Cirera and Jiménez-Herrero) he analysed the effects of digitalis on the hearts of frogs and cats. Special mention should be made of Rafael Méndez, who worked in Edinburgh between 1927 and 1932 with Alfred Joseph Clark and J. Yule Bogue, with whom he published “The mechanical and electrical response of the frog’s heart” in the Journal of Physiology in 1930. After the Civil War, Rafael Méndez went into exile in the USA, where he worked with Gordon Moe on the cardiac effects of various digitalis and veratrum derivatives. In 1948 he moved to the National Institute of Cardiology of Mexico and between 1948 and 1961 Rafael, in collaboration with another young Spanish researcher, Carlos Méndez, described that the cardiac electrophysiological effects of digitalis were the result of an increase in vagal tone, inhibition (at low doses) or stimulation (at high doses) of sympathetic tone and a direct cardiac action. Rafael Méndez also analysed the mechanism of action of some antiarrhythmics and various drugs on the coronary circulation and cardiac autonomic regulation.

In the 1960s and early 1970s, there were three groups working on cardiovascular pharmacology in the Faculty of Medicine in Valencia (Juan Esplugues, Arturo Brugger and José Segarra studied the effects of different vasoactive drugs on the coronary circulation), Navarra (Jesús Flórez analysed the antiarrhythmic effects of beta-blockers) and Valladolid (Perfecto García de Jalón). However, only García de Jalón continued in the cardiovascular field. García de Jalón worked in England in the 1940s (with Gladwin Buttle, Marthe Vogt and Wilhelm Feldberg) and in 1945, in collaboration with José María Bayo, described the hypocalcemic Ringer’s solution (“Jalón’s solution”), which is used worldwide for the study of isolated guinea pig uterus preparations and is included in the manuals on “Pharmacological Experiments on Isolated Preparations” (Livingstone, 1970). García de Jalón arrived in Valladolid in 1964 after two years at Syracuse University (New York), where he worked with Gordon Moe and Carlos Méndez on the electrophysiological mechanisms involved in the genesis of cardiac arrhythmias. In Valladolid he organised a laboratory where he studied the

cardiovascular effects of digitalis, adrenergic blockers and antiarrhythmic drugs with his postdoctoral fellow José Serrano (trained by Prof. HF Hardman at the Marquette University School of Medicine), Laura Lastra and some medical students (Francisco Pelayo, Fernando de Andrés, Julio Moratino and Juan Tamargo). In 1971 he was appointed Chairman of the Department of Pharmacology at the Faculty of Medicine of the UCM, where he continued his work in cardiovascular pharmacology. In 1974, together with Félix Sanz, he founded the Journal of Pharmacology and Toxicology, the first Spanish journal of pharmacology. José Serrano moved to the Murcia Medical School, where he worked on cardiac pharmacology with Jesús Hernandez, María Victoria Milanés and María Luisa Laorden.

Juan Tamargo graduated in Medicine and defended his doctoral thesis under the supervision of García de Jalón (University of Valladolid). He completed his postdoctoral training in the USA (with G. Moe and C. Mendez) and at the University of Homburg-Saar, Germany (with Wolfgang Trautwein and Gerrit Isenberg). At the end of the 1970 s, he founded a new cardiovascular pharmacology laboratory at the UCM School of Medicine. He introduced several techniques, including the recording of action potentials and cardiac ionic currents using the patch-clamp technique (with Carmen Valenzuela, trained at the University of Nashville, and Eva Delpón, trained at the University of Colima-Mexico) and the measurement of transmembrane Ca^{2+} and K^+ fluxes in cardiac and vascular preparations (with Teresa Tejerina, trained at the University of Miami, and Santos Barrigón). In the following years, the group led by Juan Tamargo and Eva Delpón analysed the mechanisms of action of antiarrhythmic and cardioactive drugs (calcium channel blockers, local anaesthetics, positive inotropes, antidepressants and inhibitors of the renin-angiotensin-aldosterone system, among others), the mechanisms of drug-induced cardiac side effects (cardiac depression, drug-induced QT prolongation) and the mechanisms underlying the genesis of cardiac arrhythmias. More recently, the Cardiac Electrophysiology Laboratory, led by Eva Delpón and Ricardo Caballero (who trained with Stanley Nattel at the University of Montreal), has incorporated new imaging and molecular biology techniques. In addition to the molecular determinants of the pharmacology of cardiac ion channels, the group focused on the electrical remodelling induced by atrial fibrillation, the interactions between different channel types and the functional analysis of mutations identified in new genes associated with primary arrhythmic syndromes. Numerous students and postdoctoral fellows have been trained in cardiac electrophysiology at the UCM, including Carmen Delgado (Spanish National Research Council), Teresa González (UAM), Oscar Casis (Universidad del País Vasco), Ricardo Gómez (UCM), Lucía Núñez (Universidad de A Coruña), Marta Pérez-Hernández (Spanish National Centre for Cardiovascular Research), Marcos Matamoros (Washington University School of Medicine, St. Louis), among others.

In the late 1970 s, Juan Tamargo also opened a laboratory of vascular smooth muscle pharmacology in which numerous researchers were trained, including Teresa Tejerina, Francisco Pérez-Vizcaíno, Angel Cogolludo (UCM), Juan Duarte (Universidad de Granada) and Eduardo Villamor (U. Maastricht), among others, who currently run their own laboratories of vascular pharmacology. They focus their attention to the regulation of vascular tone by endogenous mediators (NO, thromboxane A_2 , endothelin-1, 5-HT $_2\text{A}$ and PPAR receptors, oxidative stress), drugs (Ca^{2+} channel blockers, K^+ channel blockers/openers, antiarrhythmics, renin-angiotensin inhibitors, sodium nitroprusside) and natural products (flavonoids, polyphenols); the pharmacological modulation of the signaling pathways that regulate the fetal-to-neonatal pulmonary circulation transition and the pathogenesis of pulmonary hypertension; differences between pulmonary and systemic vessels of neonatal animals; the modulation of pulmonary ion channels as potential targets for the treatment of lung diseases; and the role of the intestinal flora and of dietary supplementation with certain probiotics in the development and maintenance of hypertension.

In 1971, at the UAM, the physiologist Salvador Lluch and Bernardino Gómez (a student of García de Jalón who had studied at Harvard)

studied the cerebral circulation in awake animals and brought together a group of young physiologists (Gloria Balfagón, Godofredo Diéguez, Enrique Alborch) and pharmacologists (Jesús Marín, Mercedes Salices). In 1976, **J. Marín** and **M. Salices** formed a pioneering group in vascular pharmacology, which was joined by Carlos Sánchez Ferrer, Leocadio Rodríguez-Mañas, María Soledad Fernández and María Jesús Alonso, all of whom now have their own research groups at different universities in Madrid. After the early death of J. Marín in 2000, the group led by M. Salices analysed the role of endothelial dysfunction, different endogenous (NO, MAP kinases, prostanoids, free radicals, cytokines, endothelin and the renin-angiotensin-aldosterone system) and pharmacological mediators (ACEI/ARAI, ouabain, flavonoids), age and extracellular matrix in different models of arterial hypertension. Currently, this group is led by Ana Briones and focuses its research on the study of pro/anti-inflammatory mechanisms, with particular interest in the role of cyclooxygenase-derived prostanoids (COX-2) and reactive oxygen species involved in functional and structural vascular alterations associated with cardiovascular pathologies, with the aim of identifying new therapeutic strategies to reduce the associated cardiovascular damage. The group of **Carlos Sánchez-Ferrer** and **Concha Peiró** at the UAM focuses on the mechanisms involved in vascular damage, premature ageing and progeric cardiometabolic diseases, especially obesity, type 2 diabetes and/or metabolic syndrome, in an attempt to delay vascular complications.

At the end of the 1980 s, **Pilar D'Ocon** and M^a Dolores Ivorra opened a laboratory of vascular pharmacology at the School of Pharmacy in Valencia, where they analyzed the role of intracellular calcium in vascular contraction, the activity of papaverine-like alkaloids; the role of α_1 -adrenoceptor subtypes, their internalization and intracellular signaling in large and small vessels; the role of NO in modulating the vascular response to hypoxia; and the expression of β_2 -adrenoceptors and GRK2 as biomarkers of human heart failure or chronic pulmonary regurgitation.

María Jesús Sanz leads the vascular immunopharmacology laboratory at the University of Valencia since 1992. Her group focuses on the molecular and cellular mechanisms involved in endothelial dysfunction; the impact of systemic inflammation associated with different diseases (familial hypercholesterolemia, metabolic syndrome, obesity, COPD or menopause) on the development of cardiovascular diseases (CVD) such as atherosclerosis or abdominal aortic aneurysm; the identification of potential biomarkers; and therapeutic interventions to prevent CVD. Finally, **Elisabeth Vila**, from the Faculty of Medicine of the Universidad Autónoma de Barcelona, analyzed the role of endogenous modulators (NO, COX, oxidative stress, ischemia, cytokines, Ca^{2+} handling), ageing and drugs on vascular reactivity and hypertensive vascular remodelling in mesenteric resistance and cerebral arteries.

4.2. Neuropsychopharmacology

Spanish neuropsychopharmacology emerged in the late 60 s and early 70 s of the 20th century from four main and independent groups, led by Eduardo Cuenca (“Universidad de Barcelona”), Joaquín del Río (“Consejo Superior de Investigaciones Científicas”, CSIC Madrid), Jesús Flórez (“Universidad de Navarra”), Antonio G. García (Universidad Autónoma de Madrid). Each of them followed a unique academic and research path, organising different groups at the time when they held chairs of pharmacology in different universities. Later, other groups were established, led by Jesús García-Sevilla (“Universidad del País Vasco” and “Universidad de las Islas Baleares”) and Francisco Artigas (“Consejo Superior de Investigaciones Científicas, Barcelona” (CSIC)).

Eduardo Cuenca graduated in medicine and obtained his doctorate in pharmacology under the supervision of Francisco G. Valdecasas (University of Barcelona). After three years of postdoctoral training in the Chemical Pharmacology Laboratory of Bernard B. Brodie (National Institutes of Health, Bethesda, USA), he returned to Barcelona (1964) where he studied the neurochemical activity of reserpine and

chlorpromazine as antipsychotics and MAO inhibitors and tricyclics as antidepressants. He moved to the Department of Pharmacology at the University of Cádiz, where he established a fruitful link with clinical psychiatry that lasted throughout his academic life, organising a group of young researchers and fellows: Juan Gibert-Rahola, Maribel Serrano, Javier Galiana, Luis Lafuente, Cecilio Álamo, Leonardo Casais, Mario Vallejo, Agustín Arias, Juan Antonio Micó, Rafael Maldonado. He then moved to the University of Alcalá to organise the Pharmacology Department, together with Cecilio Álamo, Agustín Arias and Mario Vallejo. They studied various aspects of the pharmacodynamics and toxicology of opioids and improved the training of young psychiatrists in basic psychopharmacology. Gibert-Rahola and Micó remained in Cádiz, where they continued their research into the treatment of pain and depression, mechanisms of addiction and abstinence syndromes. Maldonado obtained his doctorate in Paris and moved to the Universitat Pompeu Fabra (Barcelona), where he developed his research on pain mechanisms and brain neurotransmitters, mechanisms of tolerance and addiction, and the role of cannabinoids. Overall, Cuenca's group led and maintains a strong interaction with the world of clinical psychiatry.

Joaquín del Río graduated in Chemistry and Pharmacy (UCM). He was initially instructed in the Institute of Medicinal Chemistry (CSIC, Madrid), and received psychopharmacological training in the INSERM (Paris) to get expertise in tests on animal models for the study of psychomimetics, antipsychotics, antidepressants and anxiolytics. He became director of the Institute of Neurosciences Ramón y Cajal (Madrid) until he became chairman of the department of pharmacology at the Universidad de Navarra and investigator at the attached research institute CIMA in Pamplona. His main collaborators were José Ángel Fuentes, José Ramón Naranjo, Javier Garzón, Pilar Sánchez-Blázquez, Rosario Moratalla, María L. de Ceballos, Berta Lasheras, Diana Frechilla y María Javier Ramírez Gil. Garzón and Sánchez-Blázquez engaged in the molecular pharmacology of several subtypes of opioid receptors (μ , σ 1), their involvement in some psychiatric conditions, and the potential role of the endocannabinoid system. Moratalla approached the pharmacology of Parkinson's disease and dyskinesias, and the molecular biology of 5-HT and DA receptors. De Ceballos developed new antipsychotics, studied antidepressant effects, new analgesic peptides, the effects of cannabinoids as neuroprotective agents in Alzheimer's disease, and the role of microglia as a new therapeutic target in the therapy of nervous system diseases. In his last active years, del Río analyzed the neurochemical pathophysiology of Parkinson's disease in the MPTP-treated monkey model, as a basis for new therapeutic approaches, and contributed to the work of Frechilla and Ramírez in the search for new antidepressants.

Jesús Flórez, doctor in Medicine (Universidad de Navarra) and PhD in Physiology and Pharmacology (University of Dartmouth, USA), organized new departments of pharmacology in the medical schools of Navarra, La Laguna and Cantabria, and founded the first Clinical Pharmacology Service in a public hospital in Spain (Hospital Universitario de Valdecilla, 1974). He recruited active collaborators from the three schools: Juan Antonio Armijo, Manuel Feria, África Mediavilla, Ángel Pazos, María Amor Hurlé, Carmen del Arco, Javier Ayesta, Mara Dierssen, Carmen Martínez-Cué, Álvaro Díaz. The main topics of research were: the definition of the site and mechanisms of action of depressant drugs on the ponto-medullary respiratory center, including enkephalins; opiate analgesia; and the role of calcium in the mechanisms of tolerance to and dependence on opiates. In addition, Armijo defined the pharmacokinetics and drug interactions of several antiepileptics in both, humans and animals. Mediavilla conducted the clinical pharmacology of antibiotics in the hospital. Pazos received postdoctoral training in Basel (Dr. José Palacios), where they localized several neurotransmitter receptors and their subtypes in the brain using autoradiography. He contributed to analyze the activity of these receptors in several neurodegenerative pathologies, and to elaborate the neurodegenerative hypothesis of depression. Hurlé's research focused on the role of microRNA-related epigenetic mechanisms in the maladaptive

plasticity of the nociceptive system in chronic pain. She demonstrated a cross-interaction between miR-30c and the anti-inflammatory cytokine TGF- β , leading to dysfunction of the endogenous opioid system and exacerbation of neuropathic pain. Ayesta contributed to the study of the sociological problems of addiction in Spain, particularly smoking. Dierssen and Martínez-Cué developed the brain pathology and behaviour in animal models of developmental disorders, such as Down syndrome, and are looking for chemicals that can target the neural disorders caused by gen anomalies in these conditions..

Antonio G. García graduated in Medicine and obtained his PhD in Pharmacology, under the supervision of Professor Pedro Sánchez García, at the Universidad Central of Madrid, with a thesis on Autonomic Pharmacology. **Professor Sánchez García** founded an internationally renowned Pharmacology Department at UAM. As a medical student, García was introduced to pharmacology by Teófilo Hernando. He then spent three years as a postdoctoral fellow at the State University of New York, Downstate Medical Center, with Sada Kirpekar and Robert F. Furchgott. García subsequently developed his research in neuro-psychopharmacology, working on calcium signalling, the exocytotic release of neurotransmitters, the mechanisms underlying neuronal death in neurodegenerative diseases, and the continued search for drugs with potential neuroprotective effects. He has developed these activities at the Universidad de Valladolid, Universidad de Alicante and particularly at UAM. Most of his disciples work in academia or in the pharmaceutical industry (Fig. 5). He created the Fundación Teófilo Hernando to carry out clinical trials and to support the training of young researchers in the various aspects of drug discovery and development, with various master's degrees and specialized courses. He also founded the Department of Clinical Pharmacology at the University Hospital of La Princesa in Madrid, where pharmacogenetics and personalized medicine have been and are being developed by Francisco Abad and his collaborators. From a pedagogic point of view, Antonio García introduced the Medical Student Congresses to stimulate self-learning and critical thinking in students who will be the future practitioners of medicine. His numerous students (71 doctoral thesis supervised) have developed and are developing competitive neuropharmacological topics in Alzheimer's disease and other neurodegenerative diseases (Manuela G. López, Rafael León, María Cano-Abad, Cristobal de los Ríos, Victoria Maneu, Javier Egea) in the electrophysiology of neuronal calcium channels and neurosecretion (Luis Gandia, Francisco Sala, Jorge Fuentealba, Antonio R. Artalejo, José Carlos Fernández-Morales, Ricardo Borges, Jesús Hernández-Guijo, Almudena Albillos), in pharmacogenetics and personalized medicine (Francisco Abad, Jesús Frías, Pedro Zapater, Jesús Novalbos), among others.

Jesús A. García-Sevilla graduated in Medicine from the University of Barcelona. He spent time in Sweden (1976–78), France (1978–79)



Fig. 4. A course on Fundamental and Clinical Neuropharmacology. Santander, 6 June, 1981.



Fig. 5. Some of the disciples of Antonio G. García in 1997. First row, from left: María Cano, Carlos Herrero, Luis Gandía, Antonio Jesús Pintado, Francisco Abad, Pedro Zapater; second row, from left: Pedro Michelena, Inmaculada Cuchillo, Ana Ruiz, Carmen Montiel, Manuela García López, Antonio G. García, Mercedes Villarroya, Ana María Cárdenas, Jesús Novalbos, Inés Mayorgas, Román Olivares, Francisco Fernández Klett. At present, all of them are professors or researchers in universities, hospitals or pharmaceutical companies.

and the USA (1979–81), where he gained valuable experience in the study of monoaminergic mechanisms in the central nervous system. He was appointed to the Chair of Pharmacology at the University of the Basque Country (1981), where he organised an active neuropsychopharmacology unit, attracting a large group of young researchers who shared his interest in the emerging field of the biological basis of mental illness, pharmacological treatments and the role of neurotransmitter receptors in various psychiatric disorders. To pursue this goal, García-Sevilla worked with clinicians in psychiatry, pioneering what is now known as translational research. During this period, there was a widespread epidemic of opiate abuse, which led García-Sevilla to initiate studies on the mechanisms underlying addiction and abstinence. In 1991, he moved to the “Universidad de las Islas Baleares”, where he continued his research on similar topics. At the same time, he co-directed another research group at the University of Geneva from 1998 to 2003. Many members of the group from the Basque Country went abroad for postdoctoral training, and some have returned to maintain and develop research activities in psychopharmacology, with a focus on depression, schizophrenia and substance abuse. Among the second generation, Luisa Ugedo and Javier Meana stand out. Their current translational activities revolve around molecular pharmacology, functional studies of brain receptors and direct studies using post-mortem human brain samples. Over the last decade, a new generation of researchers has joined the group, broadening the scope of projects and scientific investigations in neuro- and psychopharmacology.

4.3. Other areas of research

At the University of Malaga, **Felipe Sánchez de la Cuesta** created a large group of researchers in preclinical and clinical pharmacology (Fig. 6). One of his main interests was the study of the mechanisms of drugs on platelet aggregation, the thrombotic process and its interaction with the vascular wall; in addition, together with José Pedro de la Cruz and José Antonio González Correa, Felipe studied the oxidative stress that occurs during cerebral thrombotic ischaemia. Located in Andalusia, the main producer of olive oil in Spain, the Malaga group also studied the prophylactic effect of olive oil on thrombotic accidents. Another important line of research concerned the role of platelets in the microangiopathic complications of diabetes. With his collaborators Aurelio Gómez Luque, Inmaculada Bellido, Francisco Martos, Antonio García Ruiz, Elisa Isabel Márquez and José Pavía, Felipe also studied various aspects of receptor pharmacology, particularly muscarinic and



Fig. 6. Some of the members and collaborators of the Department of Pharmacology, Faculty of Medicine, University of Malaga, with the director Felipe Sánchez de la Cuesta in 2006. **First row (left to right):** Elisa Martín Montañez; M^o Isabel Lucena, Juan A. García-Arnes, Antonio Garrido, Felipe Sánchez de la Cuesta, Francisco Hidalgo. **Second row (left to right):** Juan A. López Villodres, Ketevan Pachkoria, Joaquín Sánchez Negrete, Ana Guerrero, María Cabello Porras, Elisa Márquez Romero, Aurelio Gómez Luque, Francisco Martos Crespo, Inmaculada Bellido Estevez, José Pedro de la Cruz Cortes. **Third row (left to right):** Javier Muñoz Marín, Yolanda Borraz, Cinta Hidalgo, José Antonio González Correa, Antonio García Ruiz, José Pavía Molina.

serotonergic receptors. Professor Sánchez de la Cuesta was very interested in the development of clinical pharmacology, and his collaborators, María Isabel Lucena and María del Rosario Cabello, made notable contributions in the field of drug-induced liver damage.

At the University of Granada, a strong group of pharmacologists developed a productive line of research in the pharmacology of pain. The leader was **José Manuel Baeyens**, with various collaborators such as **Enrique Cobos**, who made notable contributions such as the demonstration that sigma receptors exert an additive analgesic effect at the level of opiate receptors. This led to the development of new chemical entities that act on sigma receptors to potentiate the effects of morphine and other opiate analgesics.

The initial development of pharmacology at the University of Valencia was due to **Juan Esplugues Requena**, who graduated in medicine in 1953, obtained his doctorate in 1956 and became Chair of the Department in 1971. He supervised 45 doctoral theses and published 245 articles. Professor Esplugues was a true promoter of experimental pharmacological research, with a vision of the emerging relationship between the university and the pharmaceutical industry. His laboratory was open to the clinical research of outstanding members of the faculty, to the organisation of international meetings and to the beginnings of clinical pharmacology in Valencia. To support young researchers, he created the “Fundación Juan Esplugues”, which attracted several young students to pharmacology. Among the main lines of research developed were pulmonary pharmacology, promoted by Esteban Morcillo and Julio Cortijo, and digestive pharmacology, developed by Juan Vicente Esplugues Mota, as well as inflammatory pharmacology, promoted by **María Jesús Sanz**, which, together with the relevant research carried out in the Faculty of Pharmacy, currently forms one of the most dynamic and scientifically productive departments of the University of Valencia.

5. Clinical pharmacology as a medical specialty in Spain

Clinical Pharmacology is a relatively young discipline, although there have been many contributions in and outside the English-speaking world since the late 19th century. For many, one of the pioneers was Harry Gold (1889–1972) [1], who was also a hospital cardiologist. Gold developed a systematic investigation of the effects of cardiotonics in humans, that can be considered the starting point of Clinical Pharmacology, a term he coined in the late 1920s. This line of research was continued by Walter Modell [2] who in 1944 developed a method for

detecting and measuring diuretic activity in humans. In 1960, he became the editor of the first journal in the field, "The Journal of Clinical Pharmacology and Therapeutics". Another of his students, Louis Lasagna, initiated the first clinical pharmacology program at John Hopkins University in Baltimore in 1954 [3].

The occurrence of various human tragedies caused by drug safety issues, such as the deaths of children in the United States after taking sulfanilamide syrups, aplastic anemia associated with chloramphenicol, or the worldwide tragedy of congenital malformations associated with the use of thalidomide during pregnancy, highlighted the need for a discipline that scientifically assesses the risk-benefit balance of pharmacological therapies in humans [4]. All of these events led many health administrations to establish a safety review of drugs and to recognize the need of training specialists in the use of drugs in humans. This recognition culminated in 1970 in the publication of WHO Technical Report 446 entitled "WHO Clinical Pharmacology: Scope, Organization, Training. WHO recommended the development of Clinical Pharmacology as an integrated discipline within health care systems, with a focus on "improving patient care by promoting more effective and safer use of drugs, increasing knowledge through research, disseminating this knowledge through teaching, and promoting services such as drug information, drug analysis, monitoring of drug abuse, and advice on trial design [5]. In a second report in 1977, the WHO identified the areas in which Clinical Pharmacology activities needed to be developed, including patient care and advisory services, such as care for different patient groups and drug information, teaching of clinical pharmacology and drug research in the fields of pharmacokinetics, pharmacodynamics, drug utilization and clinical trials [6].

The most relevant aspects of the interests and objectives of the discipline as well as its practical development, have been reviewed on several occasions over the last 40 years. In 1986, representatives from 13 European countries established a Working Group on Clinical Pharmacology, which in a number of reports examined the contribution of the discipline to healthcare in European countries [7], analyzed the teaching and organization of Clinical Pharmacology in European medical schools [8] and reviewed the old and current problems of primary care medicine in relation to drug use and continuing education in pharmacology, and the role that our discipline could play in addressing these issues [9].

More recently, the International Union of Basic and Clinical Pharmacology, together with WHO and CIOMS, published a position paper entitled Clinical Pharmacology in Health Care, Teaching and Research, which emphasizes the role of clinical pharmacology in the hospital setting in improving patient care by promoting the safer and more effective use of medicines [10] and contains two important appendices that can serve as a guide for a core curriculum in clinical pharmacology for undergraduate and medical [11].

Therefore, Clinical Pharmacology focuses on clinical activities that require medical knowledge to collaborate with other clinical specialists in making therapeutic decisions for a specific patient. The assessment of drug effects (both efficacy and safety) is focused on the individual, promoting appropriate use based on individual patient characteristics and on a collective level, the general population or patient subgroups, such as the elderly, children, pregnant women, patients with impaired renal or hepatic function, etc. This evaluation leads to activities related to clinical research, pharmacovigilance and pharmacoepidemiology, pharmacoconomics, knowledge of pharmacokinetics and pharmacodynamics, individual factors that may alter the expected response and therapeutic drug monitoring [12].

As mentioned above, Clinical Pharmacology has been recognized as a medical specialty in Spain since 1978 when the Ministry of Health created the National Commission for the Specialty (Royal Decree 2015/78), with the mission of developing specialist training programs, approving and homologating hospital training units, and monitoring compliance with all specialist training requirements [13]. This commission was composed of distinguished pharmacologists, most of whom

were university professors of pharmacology, and representatives of the Ministry of Health, who initially designed a specialist training program of three years. Now, specialization in Clinical Pharmacology is achieved after a 4 years of hospital training, with training in clinical medicine departments (18–24 months) and clinical pharmacology units (24–30 months) [14].

One of the first tangible results of this process was the inclusion in 1978 of two positions for specialists in clinical pharmacology in the newly created training program for internists and residents in the Spanish National Health System. Since then, specialist training positions in Clinical Pharmacology have continued to be offered by the Spanish National Health Service every year. Accredited teaching units for providing specialized medical training in Clinical Pharmacology are located in the centers listed in Table 2.

For several years, Clinical Pharmacology specialists have been mandatory members of drug research ethics committees (currently governed by Royal Decree 1090/2015) [15]. Furthermore, efforts have been made to integrate these specialists into Primary Care teams, successfully achieving this in Cantabria and Catalonia, as well as in local administrations and regulatory agencies such as the Spanish Agency of Medicines and Medical Devices (AEMPS) and the European Medicines Agency.

Table 2

List of clinical pharmacology centres with accredited teaching units for the training of specialists in 2023 in Spain.

City	Clinical Pharmacology Service at	Head
BADALONA	H. UNIVERSITARIO GERMANS TRIAS I PUJOL	Magi Faré Albadalejo
BARCELONA	H. CLÍNIC	Gonzalo Calvo Rojas
BARCELONA	H. DE LA SANTA CREU I SANT PAU	Rosa M ^a Antonijuan Arbos
BARCELONA	H. DEL MAR- PARC DE SALUT MAR	Ana Aldea Perona
BARCELONA	H. UNIVERSITARIO VALL D'HEBRON	Antonia Agustí Escasany
HOSPITALET DE LLOBREGAT	H. UNIVERSITARIO DE BELLVITGE	Pilar Hereu Boher
MADRID	H. CENTRAL DE LA DEFENSA GÓMEZ ULLA	Amelia García Luque
MADRID	H. UNIVERSITARIO CLÍNICO SAN CARLOS	Emilio Vargas Castrillón
MADRID	H. UNIVERSITARIO DE LA PRINCESA	Antonio Portolés Pérez
MADRID	H. UNIVERSITARIO LA PAZ	Francisco Abad Santos
MADRID	H. UNIVERSITARIO PUERTA DE HIERRO -Majadahonda	Antonio Carcas
MÁLAGA	H. UNIVERSITARIO VIRGEN DE LA VICTORIA	Cristina Avendaño Sola
SEVILLA	H. UNIVERSITARIO VIRGEN DEL ROCÍO	M ^a Isabel Lucena González
PUERTO REAL	H. UNIVERSITARIO DE PUERTO REAL	Judith Sanabria-Cabrera
SAN CRISTÓBAL DE LA LAGUNA	H. UNIVERSITARIO DE CANARIAS	Pilar Maiquez Asuero
SANTANDER	H. UNIVERSITARIO MARQUÉS DE VALDECILLA	Carmen M ^a Jiménez Martín
ALICANTE	H. GENERAL UNIVERSITARIO DE ALICANTE	María José Pedrosa Martínez
		Emilio J. Sanz Alvarez
		Mar García Saiz
		Pedro Zapater Hernández
		Ana Peiró Peiró

6. The development of clinical pharmacology in Spanish hospitals and the birth of the Spanish society of clinical pharmacology

The first Clinical Pharmacology Service established in Spain in a public hospital was in 1971 at the Hospital Marqués de Valdecilla in Santander under the direction of Prof. Jesús Flórez, where Dr. Juan Antonio Armijo led a group of specialists and directed a course on drug monitoring that has been a cornerstone in the training of many of the specialists working in Spanish hospitals today. Years later, the group also formed by Drs. África Mediavilla, María Ángeles Cos and Javier Adin, is now led by Dr. Mar García-Saiz, who continues the work in the hospital and in primary health care in the region of Cantabria.

There were also important precedents in the teaching of Clinical Pharmacology at various universities. Professor Teófilo Hernando managed to teach Clinical Therapeutics in the sixth year of medicine in the 1920s. However, it was not until 1970 that the Autonomous University of Barcelona included Clinical Pharmacology in the medical curriculum, thanks to Prof. José Antonio Salvá. The first chair of clinical pharmacology was occupied by Prof. Josep Laporte [16]. In the 1970s, other medical schools, such as Cádiz, Málaga, La Laguna, added Clinical Pharmacology to their medical curriculum, but it was not until 1993 when Clinical Pharmacology was incorporated as an independent undergraduate subject in almost all medical schools in Spain.

In 1983, the first national meeting of clinical pharmacologists was held in Cantabria (https://www.clinicaltherapeutics.com/pb/assets/raw/Health%20Advance/journals/clithe/Spanish_Society_of_Clinical_Pharmacology_CT_SEFC-1403273824863.pdf), leading to the creation of the Spanish Society of Clinical Pharmacology (SEFC). The first meetings served to develop the activities of the specialty and to promote various attempts to establish the still young specialty in different public hospitals in the country. Firstly, the Society was called "Sociedad Española de Farmacología Clínica Hospitalaria". However, with the aim of expanding the possibility of belonging to other non-hospital areas, this initial name was replaced by the current one in 1990 [17]. Since then, annual meetings and congresses have been held, and its statutes, training programs, and events can be consulted on its website (SEFC, <https://se-fc.org/>). The presidents of the SEFC since its creation are shown in Table 3 [18].

An important figure in this early period was Prof. Sergio Erill, who in 1967 was awarded the Merck International Fellow in Clinical Pharmacology scholarship to study in the United States. Upon returning in 1969, he carried out intense research and academic activity in various Spanish universities, in addition to being President of the Spanish Society of Pharmacologists, the Commission of National Clinical Pharmacology (1978–81) and the Commission of National Pharmacovigilance (1987–88), from 2006 to 2010 he held several important positions, like his fellow Patrick du Souich, in the International Union of Basic and Clinical Pharmacology (IUPHAR) [19]. Prof. Erill has trained a great number of students very active in clinical and translational pharmacology.

At that time an important group of clinical pharmacologists were also working in Catalonia, namely Prof Joan Ramón Laporte, Prof Pau Salvá, Prof Francesc Jané and Prof Jordi Camí. It was Professor

Camí who, in 1979, set up the first hospital clinical pharmacology service at the Hospital del Mar. Shortly afterwards, similar services were set up at the Hospital de la Santa Creu i Sant Pau, directed by Francesc Jané, and at the Hospital de Vall d'Hebron, directed by Joan Ramón Laporte, and at the Hospital Germans Trias i Pujol, directed by Pau Salvà [16].

It is important to note that Professor Laporte was the driving force behind the implementation of the voluntary adverse drug reaction reporting program, first in Catalonia in 1982 and then throughout Spain [20]. Members of his team later joined other hospitals in the region where have continued the work and organized their own groups. Dr. Josep María Arnau, with Dr. Pau Ferrer and Dr. Pilar Hereu at the Bellvitge hospital. Dr. Xavier Carné began the development of the clinical pharmacology group at the Clinic Hospital by creating an important clinical research unit at the IDIBAPS, with Drs. Joan Albert Arnáiz and Ferrán Torres, which is now directed by Dr. Gonzalo Calvo. Dr. Joan Costa at the Germans Trias y Pujol Hospital, Dr. Dolores Capellá at the University of Girona, and Eduard Diogene, Inmaculada Fuentes and Antonia Agustí, who is currently in charge of the service at the Vall d'Hebron Hospital.

Professor Francesc Jané together with Dr. Manel Barbanj at the Hospital de la Santa Creu i Sant Pau initiated the creation of one of the first Phase 1 units in the country in 1979 (<https://www.galeriametges.cat/galeria-fitxa.php?icod=EJJD>). This work is now being continued by Dr. Rosa Antoni Joan's group with Dr. Milagros Alonso and Dr. Josep Torrent. At the Hospital del Mar, Jordi Camí started a pioneering group in the study of drugs of abuse, which was continued by Dr. Magí Farré, and a phase 1 unit that is now led by Dr. Ana Aldea. Dr. Magí Farré is currently the head of service at the Germans Trias i Pujol Hospital. Dr. Josep-Eladí Baños, professor at the Universitat Autònoma de Barcelona and the Universitat Pompeu Fabra, is currently rector of the Universidad de Vic-Universidad Central de Cataluña and has promoted innovative educational activities [21].

In Madrid, activities began at Hospital La Paz in 1980, at the start of the National Specialist Training Programme, led by Professors Pedro Sánchez and Antonio García at the Universidad Autónoma de Madrid. At that time, Drs. Jesús Frias, Fernando García-Alonso, Antonio J. Carcas, María Antonia Serrano, Francisco José de Abajo, Belen Garijo, Francisco Abad, Pedro Guerra, Francisco Campoamor, Arturo Soto, Carmen Esteban, Carmen Ibáñez and many others who today work in various hospital centers, universities, the pharmaceutical industry and in the Administration, were trained there. Dr. Jesus Frias, Dr. Antonio Carcas and more recently Dr. Elena Ramírez and Dr. Alberto Borobia make up the Clinical Pharmacology Service of the Hospital La Paz, which is now directed by A. Carcas, where they develop a line of work in pharmacogenetics, toxicology and drug monitoring, pharmacovigilance and co-ordination of the Phase 1 Unit [22]. Later, in the 90s, Clinical Pharmacology Services were set up in two of the hospitals linked to the UAM, in the Hospital de la Princesa Dr. Francisco Abad and Dr. Dolores Ochoa led the Phase I Unit, and since 1995 at the Puerta de Hierro Hospital, Dras. Cristina Avendaño, Belén Ruiz-Antorán, Arantxa Sancho and Concepción Payarés. Also from the La Paz group, Dr. Olga Laosa, and Dr. María de los Angeles Gálvez and Dr. Mónica Aguilar, who carry out research in Clinical Pharmacology at the Hospital de Getafe and at the Hospital Ramon y Cajal in Madrid, respectively.

Table 3

Presidents of the Spanish Society of Clinical Pharmacology from its foundation to date.

Years	Name and surnames	Clinical work
1984 - 1989	Alfonso Moreno Gonzalez	Hospital Clinico S. Carlos, Madrid
1990 - 1995	Joan Ramon Laporte	Hospital Vall d'Hebron, Barcelone
1996 - 2000	Pau Salva Lacombe	Hospital German Trias i Pujol, Badalone, Barcelone
2001 - 2006	África Mediavilla Martínez	Hospital Marques de Valdecilla, Cantabria
2007 - 2012	Antonio Portoles Perez	Hospital Clínico S. Carlos, Madrid
2013 - 2018	Cristina Avendaño Sola	Hospital Puerta de Hierro, Madrid
2019 - present	Antonia Agustí Cassani	Hospital Vall d'Hebron, Barcelone

Another important and pioneering group in clinical pharmacology in Madrid is that promoted by Prof. Alfonso Moreno at the Hospital Clínico de San Carlos, where he has created a group of professionals made up of Drs. Emilio Vargas, Antonio Portolés, Lourdes Cabrera, María del Mar García-Arenillas, Leonor Laredo and Ana Terleira. This group has implemented and coordinated from 2013 to 2020 the ISCIII Platform of Clinical Research Units and Clinical Trials, SCReN (Spanish Clinical Research Network), a network structure to support independent/academic clinical research, which is now coordinated by the Clinical Pharmacology Service of the Hospital La Paz. Professor Alfonso Moreno has been President of the Spanish Society of Clinical Pharmacology and President of the National Commission of the specialty for more than 20 years [17].

In Andalusia, the Hospital Therapeutics Services created by Professors Gabriel Sánchez de la Cuesta and Emilio Muñoz, in Seville and Granada, respectively, were preceded by the development of various Clinical Pharmacology Units.

In Seville, Professors Juan Ramón Castillo and José Antonio Durán were pioneers along with Dr. Jaime Torelló in the setting up of the Regional Pharmacovigilance Center at the Hospital Virgen del Rocío. Dr. Clara Rosso coordinates the clinical trials unit. In Cadiz, Dr. Javier Galiana and Dr. Luis Lafuente started the activities, which are now continued by Dra. Monica Saldaña and Dra. María José Pedrosa, and in Almería by Dra. Carmen Fernández. In Malaga, under the initial direction of Professor Felipe Sánchez de la Cuesta, a pioneering group of clinical pharmacologists working in the fields of cardiovascular diseases, ageing and drug-induced liver injury was consolidated by Drs. Jose Antonio González-Correa, Encarnación Blanco and María Isabel Lucena who coordinates the Clinical Pharmacology Service at the Hospital Virgen de la Victoria that holds the ECRIN (European Clinical Research Infrastructure network) node in Spain. Drs. Macarena Rodríguez-Mendizabal, Antonio Gómez-Outes and Carmen Vergés have been part of the service and are currently working at the AEMPS.

Drs. Jesús Honorato and José Ramón Azanza, who set up a clinical trials unit at the Clínica Universitaria de Navarra, should also be considered pioneers in the field. In Extremadura, at the University of Badajoz there are several independent groups working on pharmacogenetics led by Drs. Julio Benítez, José A. García-Agúndez and Adrián Llerena [23]. There are also renowned pharmacologists in Alicante, Dr. José Horga, Pedro Zapater and Ana Peiró; in Valladolid, Dr. Alfonso Carvajal, Drs. Carmen Ibáñez, Carmen Esteban and Amparo Gil at the Pharmacovigilance Centre of the Community of Madrid; Dr. Carmelo Aguirre in Bilbao, Dr. Carlos Rodríguez in Galicia and Dr. Francisco Campoamor in the Balearic Islands. In the Canary Islands, the service was developed in 1974 by Prof. José Nicolás Boada at the Hospital Universitario de Canarias and later continued by Dr. Mar García-Sáiz, now in Santander, and Dr. Emilio Sanz.

Many other clinical pharmacologists have made important contributions to the development of the AEMPS and to the clinical evaluation of medicines in government and regulatory agencies [24]. Drs. Josep Torrent (first director of the newly created Spanish Medicines Agency in 1999), Fernando Garcia-Alonso and Cristina Avendaño-Solá were executive directors of the AEMPS, Drs. Emilio Vargas and Ramón Palop for the Human Medicines Department and Drs. Mar Antonia Serrano and Carmen Tristán of the Clinical Trials Division. Both Drs. Josep Torrent and Gonzalo Calvo held important regulatory responsibilities at the European Medicines Agency (EMA) and Drs. Ferrán Torres and Aránzazu Sancho at the EACPT and the EMA. Likewise, Dr. Francisco José de Abajo, today at the Hospital Príncipe de Asturias, promoted the initial development of the first database of the Spanish National Health System (BIFAP) aimed at conducting pharmacoepidemiological research [20, 25]. Some others have made relevant contributions at regional governments such as Dra. Caridad Pontes and Dr. Toni Vallano at Gerencia del Medicament in Catalonia. There has also been a significant group of clinical pharmacologists doing pioneering work in the pharmaceutical industry, including Josep Vergés, Belén Garijo, José Antonio Sacristán,

M^a Jose González de Suso, Josep Verges, Román Valiente, Javier Soto-Alvarez, Arturo Soto Matos-Pita, Rubín Lubomirov Histrov, Luis Emilio García-Pérez, Carlos Govantes, Joaquín Delgado, Joan Bigorra, Cristina Campo, Pilar Diego Saíz, Arturo López Gil, Gaspar Amat.

Some other professionals developed their careers at Primary Health Care. Rosa Morros, who leads the IDIAPJGol Unit of Drug Studies in Primary Care in Barcelona is one of them.

The SEFC has approximately 400 members whose main areas of professional activity are clinical practice, pharmacovigilance and pharmacoepidemiology, pharmacogenomics and personalized medicine, research ethics committees, promotion and support of independent clinical trials, government and regulatory activities, pharmaceutical industry and teaching.

The SEFC is member of the Federation of Scientific Medical Associations in Spain (FACME, <https://facme.es/sociedades-federadas/>), the European Association on Clinical Pharmacology and Therapeutics (EACPT, <https://eacpt.org/members/national-societies-affiliated-to-eacpt/>) and the International Union of Basic and Clinical Pharmacology (IUPHAR, <https://iuphar.wppenginepowered.com/membership/>).

7. Conclusions and perspectives

Pharmacology in Spain has reached a reasonable level of development. Of particular impact are two areas namely, neuropsychopharmacology and cardiovascular pharmacology. In the area of clinical pharmacology, medical support is provided to other specialists to follow up patients at hospitals or at primary health centers. Research topics include hepatic drug toxicity, drug monitoring, pharmacogenetics, pharmacovigilance, pharmacoepidemiology and clinical trials.

There are two main platforms for communication among pharmacologists, the “Sociedad Española de Farmacología” (SEF, acronym from Spanish) and the “Sociedad Española de Farmacología Clínica” (SEFC, acronym from Spanish). National meetings of both societies are held annually. Some activities such as special courses are held between meetings. A journal in Spanish (with abstracts in English) is published quarterly by the SEF in collaboration with the “Fundación Teófilo Hernando” (a Foundation involved in clinical trials, drug repositioning, in the field of neuroprotection, and in the training of researchers in drug discovery and development); this is a 21-year-old review journal containing frontier advances in drug therapy, known as “Actualidad en Farmacología y Terapéutica” (AFT). SEFC has a Clinical Research Bioethics Bulletin (ICB). This Bulletin is distributed, through free subscription, to all Institutional Review Boards (Comités de Ética de Investigación y los de Investigación con medicamentos) in the country, partners and interested professionals in clinical research and bioethics (<https://se-fc.org/icb-digital-142-enero/>).

Spain is a large European country with a healthy economic development and in the last 15 years has experienced the most substantial growth in the history of its innovative pharmaceutical industry in investment in research and development (R&D) of medicines. The growth in Research and Development and other challenges in Healthcare of aged population or the life science transformation expected with artificial intelligence, invites to create new scenarios of collaboration between societies. To achieve this goal and to keep the growth of both societies, regional, national and international meetings needs to be held annually facilitating the participation of young specialists in clinical pharmacology, postdocs and younger PhD students with different academic background. A point of greatest importance is the creation of new positions for specialists in clinical pharmacology in hospitals and universities. Other ideas could be (i) the support and strengthen regional pharmacology meetings such as “Farmadrid”(young pharmacologists of “Comunidad de Madrid”) and “Farmacólogos de Andalucía” (young pharmacologists of Andalusia) and to stimulate similar meetings in other regions of Spain; (ii) to attract pharmacologists from pharmaceutical companies to the SEF and SEFC; (iii) to reduce the registration costs of national meetings, thus facilitating the participation of younger PhD

students and postdocs; (vi) to promote contacts with other more powerful clinical societies and hold symposia or joint meetings with them, particularly cardiology, neurology, and psychiatry; (vi) to strengthen the journal AFT and involve both clinical and basic pharmacologists to contribute to its excellence with relevant high-quality review articles, including the teaching of pharmacology; (vii) to organize more focussed courses (online and face-to-face) on advanced therapies and other frontier topics; (viii) to hold meetings with other European societies; and (viii) to get closer to government decisions on drug therapies.

Authors statement

The work has not been published previously, it is not under consideration for publication elsewhere, and it has been reviewed and approved by all authors. If accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

CRediT authorship contribution statement

Zaragoza Francisco: Writing – original draft, Writing – review & editing. **Flórez Beledo Jesús:** Writing – original draft, Writing – review & editing. **Aldea-Perona Ana María:** Writing – original draft, Writing – review & editing. **Frías Iniesta Jesús:** Writing – original draft, Writing – review & editing. **García Antonio G.:** Writing – original draft, Writing – review & editing. **Tamargo Juan:** Writing – original draft, Writing – review & editing.

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