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Early bases of modern Embryology in Spain: Microscopical Anatomy and the introduction of Cell Theory and Histology in their scientific and social European context[#]

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ABSTRACT We present a survey of the introduction and evolution of microscopy techniques in Spain, and the concepts and lines of research developed around this instrument, particularly in the field of Biomedical research. We cover in our article the long period from the XVII Century to the arrival of the great figure of Santiago Ramón y Cajal (1853-1934). We particularly want to mention many of the previously neglected pioneers who certainly paved the route for his discoveries and, we believe that without them, he would never have arrived to his important position in the annals of Biology and Medicine. The historical, scientific and social framework of that period also helped the approach to important biological concepts such as the *cell* and *tissue*, which are previous and essential ideas for a correct understanding of *Development.*

KEY WORDS: *Cell Theory in Spain, Spanish School of Histology, Spanish Embryology, History of Medicine, History of Biology*

For centuries, the more dynamic part of Spanish society tried repeated attempts to break its isolation and become part of the more advanced and progressive scientific and technological movements in Europe. We present here the ups and downs of this process exemplified in one of the key advances of the scientific methodology for modern Embryology and other biomedical sciences: *Microscopy*. Its impact in our understanding of how living systems are organized, developed and function cannot be sufficiently emphasized.

We will briefly review the first of these attempts at the last quarter of the XVII century and the following one, essays that collapsed at the beginning of the XIX century to finally concentrate on how the situation slowly improved, closing the distances at the end of that century. One important aspect of this process is that, at the same time, the more advanced European nations also modified their scientific organization, exponentially increasing the number of scientists and the economic resources involved in the process. New countries, in the modern scientific world, such as the United States of America and Japan, also joined the race.

The work of Santiago Ramón y Cajal (1852-1934) in solving most of the questions of the microscopic structure and organization of the Nervous System gives us possibly the climax of this last phase with everlasting impact on the country, but it is not the only case. In fact, his enormous impact on the Spanish society, a community that has not overcome an inferiority complex, forgetting or ignoring many of the important contributions to science and culture produced in the Iberian peninsula, led to the idea that Cajal and his work was a product of mere "*chance*" (López-Piñero, 2006). As we will recapitulate, in the same way that "*spontaneous generation*" mechanism of biological reproduction has been re-

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Note (†) Roberto Marco-Cuellar, prestigious Spanish biochemist, brilliant teacher and even better friend, died after a severe and sudden illness on 27 June 2008. This collaboration article is the fruit of a shared old and lasting interest in the History of Science to understand our present times. It is also, unfortunately, his last scientific publication. *Requiescat in pace.*

Note # This article is dedicated with fondness, friendship and admiration to José María López-Piñero and the late Luis García-Ballester (1939-2000), former professors of History of Medicine at the Universities of Valencia and Granada, Spain. They were our mentors at the beginning of our scientific carrers and they seeded in us a deep passion to know the historical evolution of Cell and Developmental Biology.

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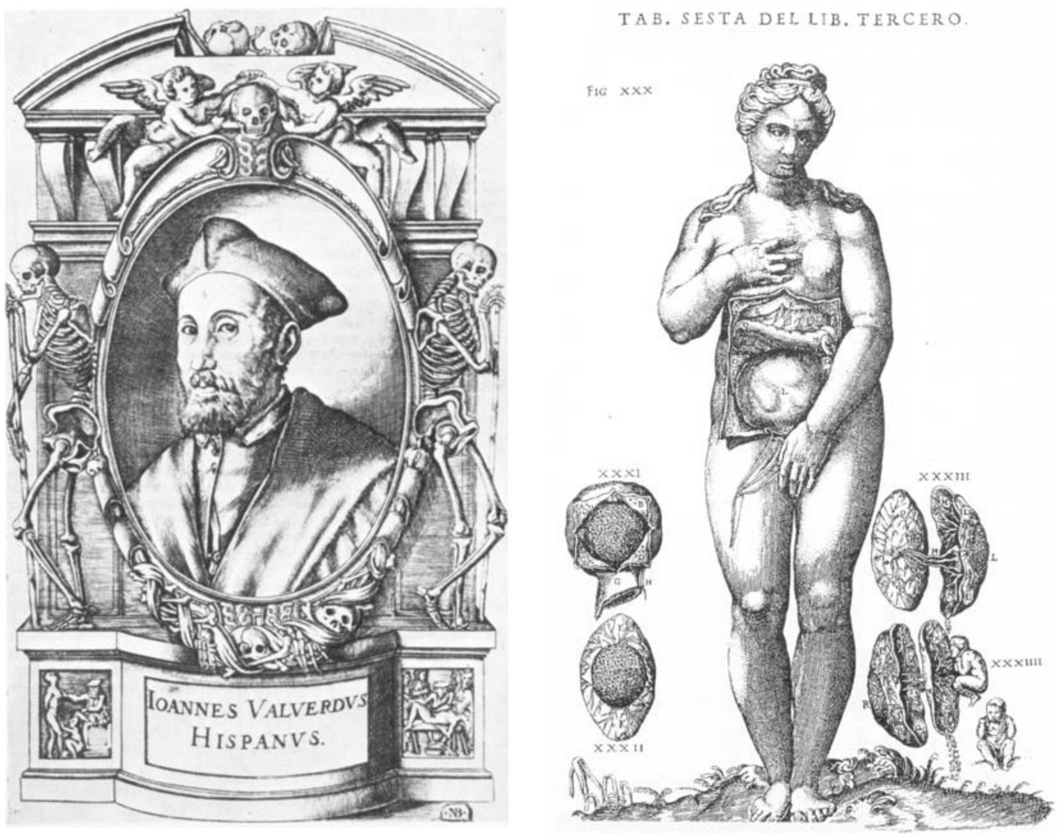

Fig. 1. Portrait of the Spanish anatomist Juan Valverde de Amusco (ca. 1525-1588) and reproduction of one of the illustrations of Gaspar Becerra for his great treaty of Human Anatomy entitled *"Historia de la Composición del Cuerpo Humano"* (1556). *It is interesting to note that the human discoidal type of placenta drawn in the text of Valverde corrects previous errors of interpretation by Leonardo Da Vinci (1452-1519) in his anatomical drawings and Andreas Vesalius (1514-1564) in the first edition of* De Humani Corporis Fabrica *(1543). Both authors depict, as human, the cotyledons of the ruminant placenta or the carnivore zonary placenta respectively. This is also the first illustration of a woman (in the* Venus of Medici *position) in a European anatomical treaty. This work of Juan Valverde was a popular textbook for medical students in Europe during the XVI century, reaching several editions in four languages Spanish, Italian, Latin and Dutch.*

jected long time ago, it is neither applicable to Sociology or, in our case, to the concept of the *"unexpected"* popping-up of a scientist of Cajal´s caliber in XIX century Spain. On the contrary, at the beginning of the 1900s, Spain was in the way of becoming incorporated to the group of leading nations in Science. Unfortunately, because of the 1936-1939 Spanish Civil War consequences, after the institutional crack, material destruction of the country and terrible social effects caused by a cruel socialist revolution under communist guidance, with strong anarchist support (the so-called *Frente Popular* regime) and the posterior military triumph of highly conservative and immobilizing forces, many of the persons that were involved in that pursuit disappearing inside the country or into exile, put us back once more at the starting line of the course. Similar stories can be told in the case of other scientific disciplines, such as Natural Sciences, Mathematics, Chemistry, Physics, etc (Sánchez-Ron, 1988). A situation that today is fortunately surpassed.

Prolegomena, the XVII-XVIII centuries: first attempt to bring Spain to the level of the advanced scientific and technological countries

As has been thoroughly studied (for example, see Clark, 2006), the medieval Universities had become trapped in their own antiquated organization and goals. Thus, the University system was only a minor force in producing the birth and maturation of Western Science. The remarkable capability of adaptation shown by Universities in the XIX and XX centuries does not extend to modern times. Researchers and scientists had to look now for external sources of money (personal jobs, patrons, etc). Few were actually employed by Universities that remained anchored in the methods and disputes of the medieval University. New institutions and research organizations sprang all over the scientific Europe outside of he old Universities, which in many cases were the refuge of the more traditional and conservative forces. Thus, the Military Colleges of Surgeons revitalizing Medicine, as well as the Economic and Learned Societies and the Army and Naval Forces renovated Mathematics, Physics, Chemistry and Geography mainly in France, England, Netherlands, Prussia, Austria, Sweden and Spain.

The case of the Netherlands is emblematic for our story. The Low Countries, encompassing all the current *Benelux* countries, and also a large part of Northern and Eastern present day France, were inherited from his grandmother Mary of Burgundy by the Emperor Charles V (Carlos I of Spain), who was actually born in Ghent, making all these territories part of the Spanish Crown from 1516. The Low Countries were at that time a land of merchants (Cook, 2007), more particularly during the *Dutch Golden Age* in the XVII Century (the Protestant United Provinces forming the *Union of Utrecht* proclaimed their independence in 1581, being its sovereignty finally recognized by the Catholic Spain in 1645) but they were one of the first and major sites where the modern scientific revolution took roots. A new University founded then in Leyden, known as a bastion of liberty (Pawerlecz, 2005), attracted scholars from the rest of the country and from all over Europe. The Netherlands was the place where the first microscopes were made (probably in Middelburg, c. 1590-1610) during the Spanish domination, although the name of the exact inventor is discussed. Later, Cornelius Drebbel (1572–1633), from Alkmaar, associated two convex lenses to manufacture a compound microscope in

1619, but, previously, another Dutch lens grinder, Hans Lipperhey (1570–1619), of German origin but settled in Middelburg from 1602, have applied for a patent in 1608 and Jacob Metius, from Alkmaar, and Zacharias Jansen, from Middelburg, also claimed to be the inventors of the microscope. In any case, one of these devices was brought to Italy, so, in this case, the information traveled in opposite direction, from the Netherlands to the Italian peninsula, where Galileo Galilei (1596-1650) and other scholars developed their own telescopes and microscopes and members of the *Academia dei Lincei* of Roma coined the word *microscope* in the first monograph devoted to the biological use of this instrument (*Melissographia*, a microscopical description of the anatomy of the honey bee, in 1624). However, the more important Italian name in early microscopical research was Marcello Malpighi, (1628–1692), very likely the initiator and one of the major contributors to the histological constitution of the animal tissues (Harris, 1999). In the case of plants, some of the English scholars linked to the Royal Society, such as Nehemiah Grew (1628-1711) competed with Malpighi on the description of their microscopical anatomy. Important references in this respect are the extensive observations from a Dutch amateur biological microscopist, Anthony van Leeuwenhoek (1632-1723) who used single lens microscopes allowing higher magnifications than the available compound microscopes (from 1663 on) and the monograph of Robert Hooke´s *Micrographia,* published by the *Royal Society* (1664). Jan Swammerdam (1637-1680) and colleagues of the Low Countries were also among the firsts to explore their biological applications. Regarding the early reproduction biology theories (called then as *theoria generationis*), Marcello Malpighi and Jan Swammerdam were *ovists* and Anthony van Leeuwenhoek and Nicholas Hartsoeker (1656-1725) *animalculists*. In other words, all of XVII microscopists interpreted the animal development in the sphere of *preformationism.*

During the last part of the XVII Century, an increasingly active movement of renovation in Spain led by a group of learned men, known as *Novatores* (innovators), initiated a recovery from the stagnation and decline that affected the country, especially in Castile and other areas stricken by the Moorish expulsion (López-Piñero, 1969). This recovery was actively pursued in the XVIII Century, supported by the change in the Spanish royal dynasty from the Habsburg to the Bourbon families, after the *Succession War* (1702-1713). It is interesting to note that close to the *Novatores* group, we can find one of the earliest Spanish microscopist. His name was Crisóstomo Martínez (1638-1694), an anatomist and engraving expert who was commissioned in 1685 by the city of Valencia and its University Medical School to travel to Paris in order to complete an anatomical atlas initiated in his hometown in 1680. The government of Carlos II, the infirm last Habsburg King, gave him a substantial fellowship. In Paris, in 1689, he studied the structure and functions of the bone and the ligament and muscular insertions as well as the vascularization of the bone and the bone marrow for two years, preparing an *Atlas of Osteology*. Crisóstomo Martínez could culminate this scientific labor in Paris at the *Académie des Sciences*, a recognized center of excellence in Baroque Anatomy, to access the latest technological advances in engraving. By methodically dissecting a variety of dry, boiled and fresh bones, he made his careful and detailed observations using the microscope. He systematically applied different kinds of optical lenses to understand the fine structure of bone. At first, low magnification was used to study the gross structure, and then lenses at increasing magnification were employed to tease out the finer structures he had identified within his low-resolution lenses. With this simple microscope and an optical resolution of 0.7 μm, he was able to observe the trabecular bone structure and its details. With extraordinary care and dissecting skills, he traced the pathways of branching arteries, the capillary plexus (which he named “adipose vessels”) and the emerging veins. The work remained unfinished and was partially published in Paris in 1689, in Frankfurt and Leipzig in 1692 and reprinted in Paris by the *Academie Royale de Peinture* in 1740 and 1780 for the teaching of artistic anatomy. The nineteen Plates included in the Atlas show that Martínez was, in addition to an expert artist, a knowledgeable anatomist and microscopist. His beautiful drawings on the bone microscopical structure show as novelties, among other things, the vascular channels, today known as the unjust eponyms of Clopton Havers (1657-1702) and Alfred W. Volkman (1800-1877) who publish his discoveries in 1691 and 1873, respectively*.* Besides, Crisóstomo Martínez was the first to give notice the trabecular bone structure and the ossification process of the human fetus. In terms of the worldwide importance of the Dutch microscopists at that time, it is curious that Martínez´s death occurred in the Spanish Flemish territories four years later (López-Piñero 1964, 2008; Terrada-Ferrandis 1969; López-Piñero *et al.,* 1979).

At the turn of the XVII Century, other Spanish scientists such as Juan Bautista Corachán (1661-1741) and Tomás Vicente Tosca (1651- 1723) were informed of the microscopical descriptions of Malpighi and of the English and Dutch microscopist under the still dominant *Fibrilar Theory* as ultimate morphological element of composition of animal body (Bunge 1943; Marco-Cuellar, 1965; López-Piñero 2008). An old theory originated from the XVI century French and Italian anatomists and incorporated in Spain very early in the monumental seven volumes treaty of Juan Valverde de Amusco (ca1525-ca1588) (Fig. 1) entitled “*Historia*

Fig. 2. Auto portrait of the Spanish microscopist Crisóstomo Martínez (1638-1694).

de la Composición del Cuerpo Humano" (History of the Human Body Composition) of 1556 (Terrada-Ferrandis 1969). During the XVII and XVIII centuries the *Fibrilar theory* was more elaborated with new microscopic and empiric data to lay the foundation of the concept of *"tissue".* On the other hand, the new *epigenetic* view on the biological development by Caspar F. Wolff (1734-1794) in his *Theoria Generationis* (1759) and his concepts *of globuli, soledescibilitas* (solidification capacity) *and vis essentialis* (essential force) will be the main intellectual support for the building of the *"Cell Theory"* in the XIX century. As we will see later, the introduction of all this new ideas in Spain will be delayed for different political, war and social circumstances (Aréchaga 1973, 1974, 1977b; Aréchaga *et al.,* 1976).

However, the trend initiated in the final years of the XVII Century in Spain, was continued, not without opposition of the conservative forces (university, religious and political), during the next Century. We will only give a few examples of the vigor of the movement:

1) During the XVIII Century, the work of Crisóstomo Martínez (Figs. 2 and 3) and colleagues was followed even though the problems that limited the application of the Microscope, its multiple types of aberrations, made many authors skeptical about the information that could be gathered with its help. An example of this attitude was the royal physician Andres Piquer (1711-1772), but there were also scientists who continued to use the microscope such as Sebastian M. Guerrero Herreros Morales, anatomist in Seville (*Medicina Unisal o Academias Médicas, Chirúrgicas, Chymicas y Pharmacéuticas, 1774)* Jaime Bonells and Ignacio Lacaba (1745-1814) in Barcelona, publishers of an important *Curso Completo de Anatomía del Cuerpo Humano (Complete Course on the Anatomy of the Human Body)* in four volumes (1796-1800), and especially, the naturalist Franciscan José Torrubia (1700-1768), who systematically applied the microscope to the study of the fossils, and the botanist Antonio J. Cavanilles (1743-1804) who was an expert microscopist as well (Terrada-Ferrandis, 1969).

2) The renovation of the Scientific Institutions and the medical education and practice by establishing the modern *Royal Colleges of Surgery*, linked to the Spanish Navy (*Real Armada*) and the Army (*Reales Exércitos*) because the need of advanced trained war surgeons (Aréchaga, 1975). These were establish in Cádiz for the Navy (1748) and in Barcelona (1764) and in Madrid (1787) for the Army, in a way similar to the ones that were being founded for the same reasons in Prussia (Berlin, 1714) France (Rochefort 1722, Paris 1731), the United Kingdom (Edinburgh 1695, London 1800) and Sweden (Stockholm, 1810, the actual *Karolinska Institutet*) many of them persist today transformed into University Medical

A B

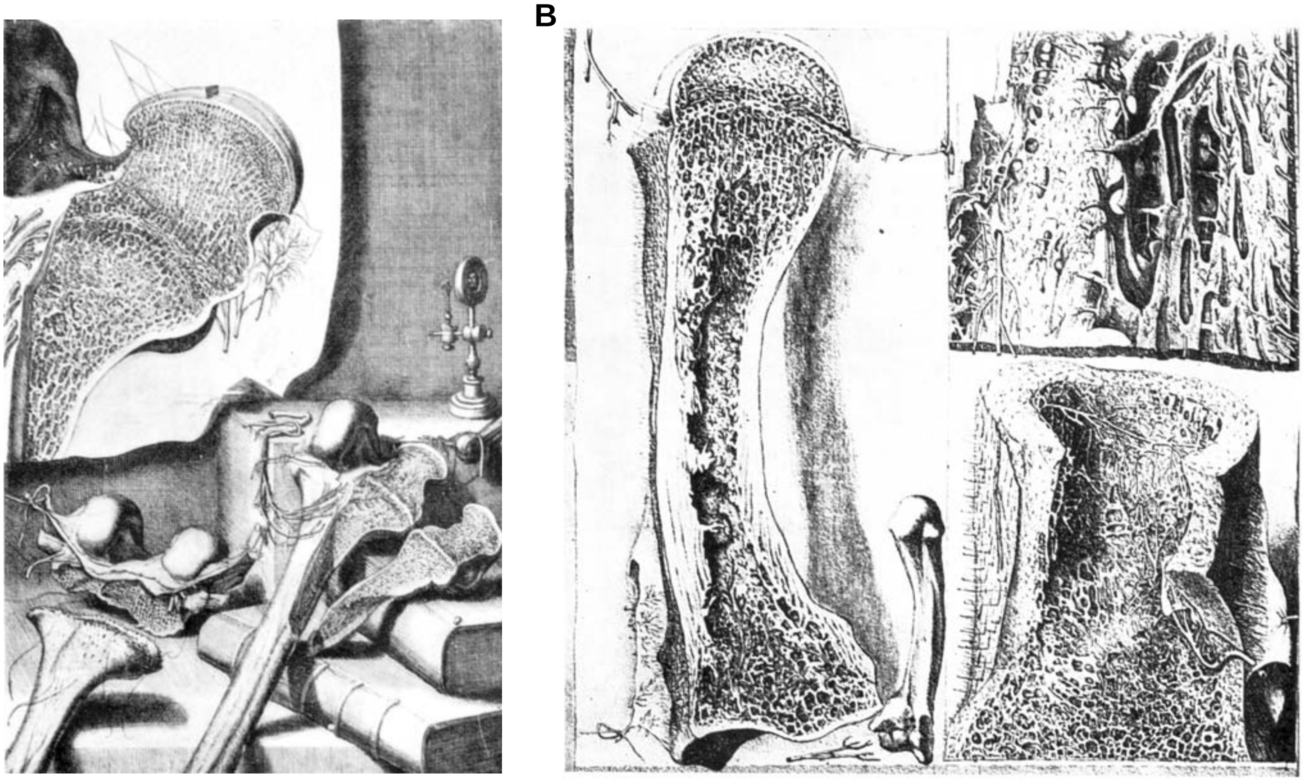

Fig. 3. Two drawings from the *Atlas of Osteology* (h. 1680-1689) of Crisóstomo Martínez on bone vascularization. (A) *Superb study of bone vascularization in a posterior view of the femur distal extremity in a young adult. To the right, the external condile is sectioned showing the growing cartilage. To the left, the joint capsule is partially preserved and the epiphysis separated from the diaphysis after desiccation, which eliminated the conjunction cartilage. In the top part of the picture, he shows at higher magnification the bone trabecular structure and the particular vascularization of the red medulla, and of the growing cartilage too. In the upper right, the microscope used by Martínez is also drawn.* **(B)** *Longitudinal section of the fifth metatarsal, probably belonging to the same corpse. The periostium is partially detached to show its own vascularization and the vascularization of the growing cartilage is enhanced. At higher magnification is shown the bone trabecular structure and the vascular channels, a discovery which was erroneously ascribed to Clompton Havers (* Osteologia Nova, *1691) and Alfred W. Volkman (* Uber die näheren Bestandtheile der menschlichen Knochen, *1873), when we had to name them more properly as* "Martínez channels".

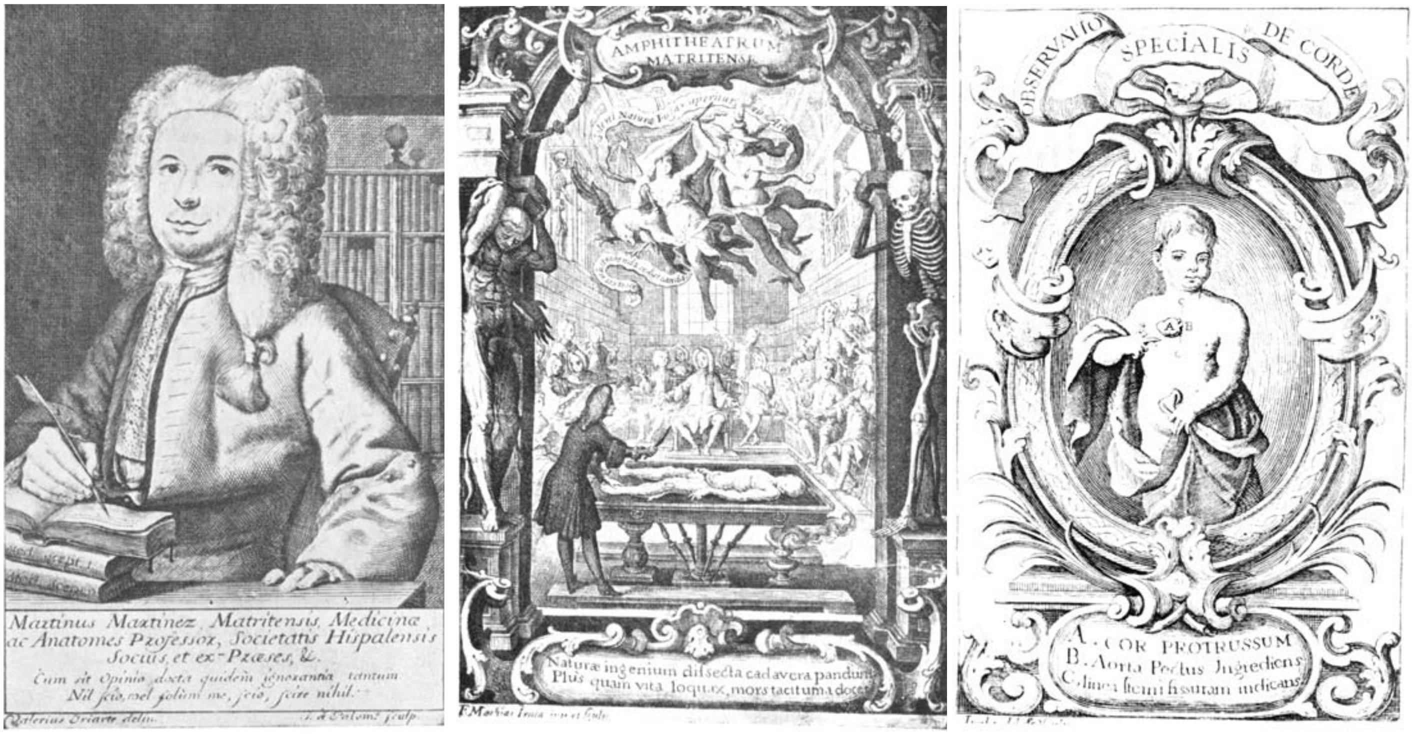

Fig. 4. Portrait of Martín Martínez (1684-1736), *(centre) representation of the Amphitheater of Anatomy of Madrid from his Treaty of Anatomy (* Anatomía completa del hombre, con todos los hallazgos, nuevas doctrinas, observaciones raras y muchas advertencias necesarias, *1728) and (right) teratological observation of a case of* ectopia cordis *in his monograph entitled* Observatio rara de corde in monstruoso infantulo *(1706).*

Schools or Medical Academies. Antonio Gimbernat (1834-1816), Spanish military surgeon disciple of John Hunter in London, represented in, was the most well-known and prominent scientist from these Royal Colleges (Aréchaga, 1977a). Other new medical institutions of that time in Spain, mainly in Madrid and Seville, were the *Royal Academies of Medicine* and the *Anatomical Amphytheaters of the Hospitals* being Martin Martínez (1684-1736), author of the *Anatomía Completa del Hombre* (Complete Anatomy of the Man) of 1728, and Juan de Dios López (1711-1773), author del *Compendio Anatómico y Fisiológico* (Anatomical and Physiological Compendium) of 1750-52, the more representative anatomists of these institutions (Ara, 1930; Sánchez-Granjel, 1963) (Figs. 4, 5 and 6). In the same way were founded or renovated in Madrid the *House of Geography* (1657), the *Botanical Gardens* (where the military surgeon, José Quer y Martínez, followed by Miguel Barnades Mainader and later Casimiro Gómez Ortega, and A. J. Cavanilles worked introducing Linneus's ideas on botanical classification in Spain), the *Astronomical Observatory*, etc. One quite significant and almost forgotten step in this direction was the decision by Charles III following the French model to build a large *Natural History Museum* in the neoclassic building that now holds the Royal Art Gallery, the *Prado Museum*. As a consequence, the botanical garden in Madrid was moved in 1781 to its current near-by location.

3) The organization and participation in many Scientific Expeditions to carried out in the Spanish colonies (which started as early as the XVI century during the reign of Felipe II; at that time, Spain also founded the first universities of America and Asia in Santo Domingo and Manila, respectively). Although the criteria change, it has been possible to count up to 58 scientific expeditions from 1735-1807. Among them, the Spanish-French Geodesic Mission to Perú (1735-1742) with Jorge Juan and Antonio de Ulloa to measure the length of a degree of longitude at the Equator, leading to the metric system, Ruiz-Pavón botanical expedition to Perú (1777-1788), Celestino Mutis botanical expedition to New Granada, present Colombia (1783-1810), Malespina comprehensive exploration expedition (1789-1794), the Royal Scientific Expedition to New Spain (Mexico, 1788-1797) led by Marín de Sessé y Lacasta and José Mariano Moziño. Many of these expeditions suffered from the problems in the metropolis once they were completed, hindering the completion and publication of the work. More lucky, Felix de Azara, who was not sent with expedition status, but assigned as military engineer to settle the Paraguay border between Spanish and Portuguese possessions (1781-1801), published several books in French on his studies on the natural and political history of Paraguay and La Plata region (Argentina and Uruguay) under the auspices of his brother Nicolás, Spanish Ambassador in France until his death in 1803. Not the less significant, the Francisco Javier de Balmis (1753-1819) expedition around the world (1803-06), the first sanitary expedition of the world. Very soon after the discovery of Edward Jenner (published in 1798), Spanish military surgeons headed by Balmis, with a group of orphan children to maintain the virus during the long trip, disseminated the smallpox vaccine for America and Asia. They started from the Canary Islands, and after traveled to many Spanish colonies, mainly Venezuela, Cuba, Colombia, Ecuador, Peru, Mexico, other North American territories and the Philippines, finishing in China.

4) The development of Chemistry and its applications to Artillery and Mining, already one of the classical strengths of the Spanish

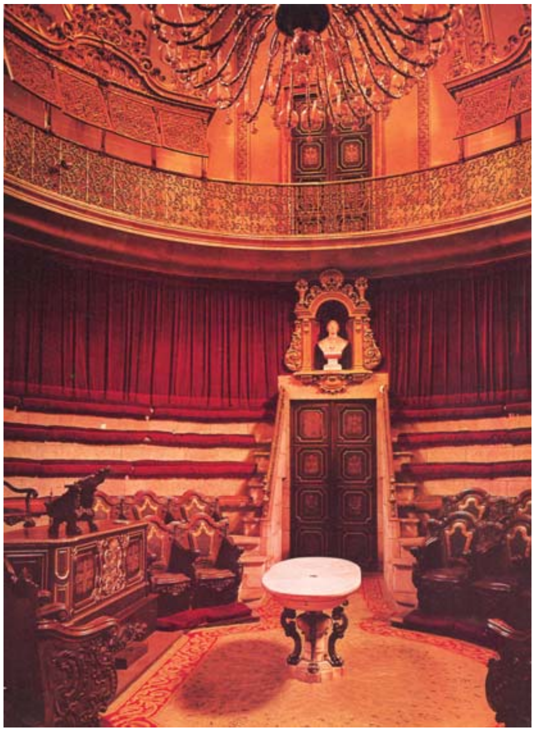

Fig. 5. The Spanish anatomist and military surgeon Antonio Gimbernat y Arbós (1734-1816) and the Anatomical Amphitheater of the Royal College of Surgeons of the Army (1764) of Barcelona, *in which he taught Army surgeons. Gimbernat is international well known as an anatomist because of his discovery of the* ligamentum lacunare *(also named after his eponym* Ligamentum of Gimbernat*). He was pupil of the English surgeon William Hunter in London and founder of the* Real Colegio de Cirugía de San Carlos *(1787), later the Madrid Medical School. Portrait from José Teixidor (* Museum of Modern Art, *Barcelona) and present Auditorium of the* Royal Academy of Medicine of Catalonia *(Barcelona).*

Technology. Special interest deserves the foundation, by King Charles III, of the *Sociedad Bascongada de Amigos del País* (Basque Society of Friends of the Country) in 1765, which was the first of the many Economic and Scientific Societies founded all across Spain, based on the interest in experimental sciences, industry and commerce. The high quality of scientific modern chemistry reached by a few individuals, such as Munibe (1751-1774), Ibañez (1749-1809), J. J. Elhuyar (1754-1796) and F. Elhuyar (1755-1833), Antonio de Ulloa (1716-1795), del Rio (1765-1849), Martí y Franques (1750-1832), Aréjula (1755-1830), Carbonell y Bravo (1758-1837) and Porcel y Aguirre. Probably the most brilliant contribution of Chemistry of this time refers to the discovery, by Spaniards, of the three new chemical elements (Pt, W and V). This was achieved by the combination of factors: The involvement of foreign chemists (Bowles, De la Planche, Proust and Chavaneau, spent many years working in Spanish institutions and laboratories) the chemical training acquired by their protagonists in other countries (France, Germany and Sweden, especially) as well as from the growing impact of the quickly developing modern chemistry in France which led to the chemical revolution, based essentially on the explanation of the process of combustion, the setting of a new systematic and rational nomenclature of chemistry (introduced in Spain by the military surgeon Juan M. de Aréjula in 1788; see Gago and Carrillo, 1979), the establishment of quantitative analytical procedures, the development of the chemistry of gases and the growing interest for practical and industrial Chemistry.

Fig. 6. Wax sculpture of a pregnant woman at natural size *constructed under the supervision of Antonio Gimbernat for the former* Real Colegio de Cirugía de San Carlos *in Madrid.* Anatomical Museum *of the Faculty of Medicine of the Complutense University of Madrid.*

In summary, this epoch was a period of splendid scientific progress in Spain which abruptly ended because of the consequences of the *French Revolution* of 1789 and the *Convention War* (1793-1795), followed by a series of calamitous alliances, first with the French Directory (*Second Treaty of San Ildefonso,* 1796) and, after, with Napoleon (*Third Treaty of San Ildefonso,* 1800 and *Treaty of Fontainebleau,* 1807). These events pushed Spain, among other sad facts, to a war with the brother Kingdom of Portugal (*Guerra de las Naranjas,* 1801), the naval disasters of Capes San Vicente (1797) and Trafalgar (1805) against the British and, finally, to admit the crossing of its territory by the French Army to attack Portugal (1807), a fact which would trigger the subsequent Spanish *Independence War* (1808-1814) against the French invaders.

Development of biological Microscopy in nationalistic Europe during the XIX Century

Important changes, both at the social and political level, were taking place in Europe at the time. Starting in the last third of the

XVIII Century and continuing during the entire XIX Century, not only then*Industrial Revolution*, but the breakdown of the institutions and systems into different national oriented sociopolitical trends. They took over as much as the unifying role of universal links weakened, links such as those provided by religious orders (for example, the Jesuits), a single language (latin), the up and downs of the hegemonic political powers and the breakdown of the *Old Regime* in Europe, etc. With different rhythms, the changes affected the organization of the learning Institutions and particularly the emergence of an independent, organized, way of conducting research, more or less linked to the University system that had remained trapped in an obsolete organization and had to be renewed almost everywhere. It is against this background that we have to consider the development of the new histological and cytological ideas in Europe. It is important to point out several factors that are critical for understanding this development.

The prominence of the nationalistic approaches converted the subject in a dispute on the priorities held by each country or nationality; this trend took over the original disputes about priority of the individual scientists in making a particular discovery or by introducing a new instrumental or theoretical tool in research. The control of publications was linked to this problem. For example, it was clearly relevant in the field of Microscopy during the XVII Century, when publication in the *Proceedings of the Royal Society* became popular among microscopists from over all Europe. The probably mischievous assertion of Mathias Schleiden in 1843 that N. Grew in his capacity as secretary of the Royal Society had held back Malpighi´s contribution to ensure his own priority proves the importance of the scientific journals and their capability of controlling Science mostly with national points of views, a trend that was initiated in the XIX Century, becoming a key factor in the process and still operating in current science (we must keep in mind, for instance, the actual control of science of Anglo-Saxons countries with journal like *Nature* or *Science*).

The confusion about names and concepts is also a factor. For example, *"cell"* had been and continued to be used with completely different meanings since the initiation of microscopical studies in the XVII Century. It has not to be equated with what we understand now as cells. As we will briefly describe, it took almost the whole XIX Century to complete the microscopical description of living systems, to understand and agree on the properties of what we know now as "*cells"*. This process went together with equivalent advances in complementary disciplines, including our understanding of the biochemical constituents of the cells and extra-cellular compartments, etc. In addition, important advances in related fields came about in the XIX Century (Physiology, Comparative Anatomy, Evolution, Genetics, etc).

The slow increase in knowledge was also accompanied by the advances in building better (free of aberration) and more powerful microscopes in the XIX Century, as well as by the agreement on the way living tissues had to be treated to maintain the original structures (fixation) and to visualize them (tissue processing and staining). They took also most of the century to be brought to a satisfactory state, in a similar way that it took time to scientists to agree how electron microscopy in the XX Century could be used. The combination of *flint* and *crown* glasses to remove the chromatic aberration problem was proposed around 1735 by Chester More Hall and finally patented by John Dolland, an instrument maker in the 1750s. George Adams, Jr. (*Essays on the Microscope*, 1884) introduced several practical improvements and built several microscopes that were used all over Europe. Pistor and Schiek in Berlin also produced microscopes from 1819 on. In 1824, Giambattista Amici (1786-1863), an Italian microscopist and instrument maker, after reading the report given by A. J. Fresnel (1788-1827) at the Royal Academy of Sciences in Paris on the achromatic microscope developed by A. F. Gilles (1784-1845), called Selligue*,* improved the instrument. Charles Chevalier (1804-1859), an optician in Paris, was one of the first to use multiple lenses screwed together to achieve higher magnifying power, but the chromatic aberration, which had plagued the users of microscopes since their beginnings, was still a problem with lens combinations. In 1830, Chevalier with the help of the already mentioned French microscope maker Selligue, started to make microscopes after a design shown to him in 1827 by Amici. In fact, Amici introduced further improvements in the field beyond the work of Selligue and Chevalier because he demonstrated that in order to obtain a high-resolution power the objective had to be composed by different parts whose aberrations were not totally eliminated if taken separately, but calculated to neutralize reciprocally when combined. J. M. Petzval, professor of Mathematics at the University of Vienna in the late 1830s designed a lens, aiming for a flat field and an aperture wide enough for the fast shutter speeds needed for portraiture, and motivated by the monetary prize offered for such a lens in a competition. The lengthy calculations involved in lens design motivated Petzval to enlist the help of artillery gunners, which in those days was one of the few professions to practice computing. It took Petzval, for eight gunners, six months to complete the job, producing two variations of lens. The f 3.6 lens had at front a conventional telescope objective, an f 5 cemented doublet; and at the rear an air spaced doublet, for the separated elements were needed to control spherical aberration and coma. J. F. Voightländer made the first such lens for Petzval in 1840, a 150 mm f 3.6, delivered mounted on a camera, a major improvement which was about 20 times faster than the lens by Charles Chevalier commonly used at the time. His disciple, Simon Plöβl (1794-1868) from 1830 on, produced microscopes with achromatic objectives of the highest quality in Vienna, a technical improvement that was disseminated in Europe, including England. The spherical aberration problem had been also solved by J. J, Lister in 1830. A clever arrangement of weaker lenses would yield higher magnification without adding up the spherical aberrations, so in the end the aspheric lens (array) was created. First implemented for telescopes, almost 20 years passed until aspheric lenses for microscopes were manufactured. Amici is universally acknowledged too with the merit of having applied the immersion method with success for the first time, as Ernst Abbe also remembered in 1879 (*Ueber Stephenson's System der homogenen Immersion bei Mikroskop-Objektiven*), and 1847 is generally recognized as the date of this fundamental evolution in microscopic optics. The first technical sheet which has been conserved until today of a water-immersion microscope is the one of professor Donders of Utrecht built in the second half of 1849. In 1877, Ernst Abbé, who was working for Carl Zeiss, showed that there is an ultimate limit for the resolution given by the angular aperture: the resolution is the limit, and it is given by the wavelength of light divided by twice the numeric aperture. The numeric aperture is in its turn related to the distance of the focal spot from the lens and the lenses width. Otto Schott formulated glass lenses that color-corrected objectives and produced the first "apochromatic" objectives in 1886. Few major improvements were made after the last half of the 19th Century, but microscopes remained expensive gadgets for a very restricted community of scientists. By that time, topnotch microscopes were being manufactured by *Powell & Lealand* and *R & J Beck* in England and by *Charles A Spencer* in the United States. At the end of the 19th Century, *Zeiss* and *Leitz* in Germany and *Chevalier*, *Oberhauser, Verick* and *Nachet* in France were the main microscope builders.

As we said before, during the XVIII century, the scientific views on the elementary microscopical constitution of animal systems remained primitive, and the fiber (Haller, Baglivi, etc), or the cylinder (Fontana) were proposed to be their key element in contrast to the description in plants of vesicular, globular (solid) or cellular (empty or fluid full) components (Aréchaga 1974, 1976b; Marco-Cuellar 1973; Terrada-Ferrandis 1969). As stated by Harris (1999), in fact, by the end of the eighteenth century almost all botanists accepted that plants where largely composed by cells, but what where these cells, what did they contain, do they communicate and how are they formed? On the other hand, claims that both plants and animals share the same cellular/ globular structures were not credible (Studnicka, 1932). As we enter the XIX Century, the whole issue was increasingly distorted by the nationalistic dispute between countries, especially between France and Germany. Following the previous description on the development of research structures, Germany eventually took the lead, but the situation was more balanced at the beginning of the XIX Century when the initial descriptions of the basic united structure of the animal and plant tissues was becoming possible by the introduction of better preservation techniques and more powerful and less aberration prone microscopes. During a long time, until the second part of the XIX Century main questions to be solved were how many types of basic components there were in living beings and how did they originate: can the anatomical components, the cells, arise *de novo* in the middle of the original *blastema*?

Nevertheless, the more important initial contribution to Histology at the turn of the Century was the work done by the prematurely deceased F. Xavier Bichat (1771-1802). Bichat, under the influence of the Montpellier school of *vitalism*, was convinced that the living organisms were completely separated from the inorganic world. In Nature there were for him, and the men of his generation, two types of objects (organic and inorganic), two types of properties (vital and non-vital), two types of sciences (physical and physiological). Bichat´s research objective was to align the second group with the information available for the first. Following the procedures used by the chemists, he adopted every possible method to try to establish the elementary composition of the living beings dissecting, boiling, cooking, macerating, treating with acids and alkalis, etc, until reproducible elements could be detected. He was skeptical though about the use of the compound microscope. In this way, he characterized the properties of a large set of different tissues, 21 of them, following the trends in Physics (of Newton) and, particularly, in Chemistry (of Lavoisier) where a large series of elements were being discovered and described during the years preceding and following the turn of the century. Bichat also was convinced that in a diseased organ only some of its tissues might be affected. He defended the view that these tissues would be made up of elementary components, *"anatomic elements",* that should be identified and characterized. An initial large group of anatomic elements were identified by his followers, many of them using the best microscopes (for instance, six of them: amorphous material, granules, nuclei, cells, fibers and tubes). The French scientists after Bichat, for example, H. Milne-Edwards (1800-1885), R. J. Dutrochet (1776-1847), F. V. Raspail (1794-1878), among others, continued his work but using an increasingly mechanistic approach. Some times, they were confused by preparation artifacts. Milne-Edwards, using a large *Adams* achromatic microscope, claimed in 1824 to have seen all the anatomic elements to be formed by an irregular but linear concatenation of uniform *"globules"*. The fully materialistic Dutrochet, inventor of the first osmometer, although using improving techniques that allowed him to isolate plant cells of different sizes and to observe ganglion cells with their nuclei in gastropod brains, continued to accept Milne-Edwards view of animal tissues as aggregations of membrane bound globules or vesicles. His studies on cell physiological processes, called by him "*endosmosis"* and *"exosmosis"*, showed semi-permeable membranes controlling the metabolism by the inflow and outflow of substances in these uniform vesicles. Raspail, an intransigent republican, revised his *Nouveau system of Chimie Organique* when he was in prison (1833). He was also mainly concerned with the cell´s chemistry and introduced many technical advances, such as being probably the first to obtain frozen sections, developing a novel range of chemicals to identify individual cellular components. Paraphrasing the astronomer S. P. Laplace (1749-1827), he wrote *"Donné-moi une vésicule organique et je vous rendrai le monde organisé"* (1833) and *"A cell is therefore a kind of laboratory within which all tissues organize and grow"* (1843). Equipped with an excellent microscope made by *Deleuil* in Paris, he did not accept many aspects of Milne-Edwards model, such as the uniformity of size of the tissue components. He saw red cells in the blood, as many other early microscopists had seen, but also cells in the epidermis and dermis. As indicated by Harris (1999) an important example of the deceptiveness in the use of words is the Latin aphorism included by Dutrochet as epigraph in an early work of 1825: *Omnis cellula e cellula* (see below). Finally, the Belgian B. C. Dumortier (1797-1878), in a paper published in French in 1832 and presented by Cuvier at the Paris Academie of Science in 1829, was probably the first to describe cell division in the fungus *Conferva aurea*. Although not directly involved in Histology, a very important figure is the Spanish chemist and toxicologist Mateo J. B. Orfila (1787-1853) professor in Paris at the School of Medicine, who supported many of the next generation of scientists interested in the microscopic constitution of living tissues, such as the German Hermann Lebert (1813-1878) working in Paris and Charles Ph. Robin (1821-1885). Robin, strongly influenced by the positivist movement in France, became the more influential figure in that field. Initially, following the research program of identifying the elementary constituents of the tissues, that he believed to be molecular, the microscopic elements were a combination of them. Robin set forth in detail his own ideas on biology in two books: *Du microscope* (1849) and *Tableau d'anatomie* (1851). In this view of General Anatomy, Robin went beyond the work of F. Xavier Bichat, asserting that the anatomical element itself, independent of the tissue of which it is a part, ought to be the subject of both morphological and physiological research. At the same time, Robin asserted that life did not depend on a rigid structure but on a “state of organization”; in fact, on “a particular molecular state.” The notion of the *blastema*, central to Theodor Schwann’s cell theory, fully corresponded to Robin’s ideas, but he was never able to adopt the cell theory in its newest phase, as formulated by Rudolf Virchow. Thus, Robin never accepted the view that that the cell could be the single fundamental component of organized beings. Beyond the fixed anatomical elements, there must be, he thought, a molecular organization that explained the morphology. In his opinion, therefore, microscopic investigations were only a stage of biological research and must be substituted by chemical analysis. In collaboration with a chemist, F. Verdeil, Robin studied the chemical compounds of which the organism is composed. Despite its display of useful information, the resulting *Traité de chimie antomique et physiologique, normale et pathologique* (1852-1853) showed that research oriented in this direction led at that time to a dead end and that, given the contemporary state of chemical knowledge, the superiority of a morphological approach was undeniable. The next generation of French microscopists, for example, Mathias Duval (1844-1904), first at Strassburg and successor of Robin at the Paris Medical School, Louis Ranvier (1835-1922) disciple and associated with the influential French physiologist Claude Bernard, at the College de France, Eduard-Gerard Balbiani (1823-1899), co-founder with Ranvier of the first French Journal entirely devoted to microscopical studies, were key players in the final stages of the development of Histology in Europe overcoming some of the barriers imposed by the national and political conflicts at the time (see below).

At the beginning of the XVIII Century German scientists were in one way or another under the influence of the idealistic *Naturphilophie* and were convinced that Nature will be found to be organized on single or just a few principles, such as the one that finally led to the so-called *Cell Theory* in Germany. Leaving aside important contributions made earlier (for example Heusinger´s System of *Histologie Eisenach*, 1822), it is interesting to point out that in a standard textbook (*Allgemeine Anatomie der menschlichen Körpers* of Braunschweig, 1830), H. E. Weber accepted a similar description of 6 types of elements. A similar classification appeared in Meyen´s *Phytotomie* (Berlin, 1830). As already indicated the main problem in advancing Histology and Microscopical Anatomy was not in the resolution of the microscopes, but on the methodology of the preparation of tissues for microscopy, especially of animal ones. For example, J. E. Purkinje (1787-1869) and his disciple G.G. Valentin (1810-1883) invented the *microtome* in the 1830s, perfected later for serial sectioning (an essential method for descriptive Embryology) by Wilhem His in 1866. Purkinje also introduced the *daguerreotype* and Remak hardening agents to obtain satisfactory microscopical observations of animal tissues in 1855. Arnold´s Lehrbuch of *Physiologie* (1836) has hardly moved forward. The transition came from works carried out in two groups, in the Johannes Müller (1801-1858) laboratory of Berlin and in Purkinje´s chair and Institute of Physiologie in Breslau, the first of its kind founded in Germany. They were in the mainstream of the German intellectual ambitions (Harris, 1999). Using a hand lens, Purkinje described in 1825 the germinal vesicle inside the hen’s egg, although at least until 1834 when a Polish student of him, Adolf Bernhardt, described a similar structure inside a mammalian ovum, he did not think that it could be related to the cell nucleus that he saw in many other animal cells. Nuclei can be identified in Bauer’s drawings published between 1830-1838 and R. Brown in 1833 gave the name of nucleus to the structures he described in certain plant cells. In 1832, Purkinje acquired a new achromatic microscope made by *Simon Plöss* in Vienna and began a systematic study of the microanatomy of animal tissues. His former student and collaborator G. G. Valentin, who later move to Bern, Switzerland in 1836, to avoid the discrimination against Jews in the German Universities (see below) described the nucleus in animal cells in 1836 and the nucleolus in 1839, although initially there was some confusion about which one was which. J. Müller, initially a full professor in Bonn, forced in someway his nomination to a chair in Berlin after C. A. Rudolphi (1771-1832) died. He received a *Plöss* microscope around the same time than Purkinje and started a similar research program. However, there were no laboratories for experimental work in the Anatomical Institute of Berlin and the distinguished Muller’s School founded there was for many years obliged to work in cramped rooms within the main university building. He was not able to win a new Institute for himself. In spite of these limitations, the work of his students, initially in microscopical research (J. Henle, Th. Schwann, A. von Koelliker, R. Remak, R. Virchow) and later in Physiology (E. DuBois-Reymond, H. Helmholtz) or even in Evolution (E. Haeckel) includes some of the more distinguished German scientists of the XIX Century.

Although many researchers interested in the history of the *Cell Theory* are less than convinced that Th. Schwann and particularly M.J. Schleiden deserve the almost generalized attribution to them of this concept, it is a fact that this is the almost universally accepted view. Although as pointed out by J. R. Baker in his seminal articles (1948, 1950, 1952a, 1952b, 1955), Schleiden´s choosing the endosperm of a plant seed to study was a very bad choice since this is a structure that is first a syncitium before it is cellularized, it is fair to say with Harris (1999) that no part of the scheme proposed by Mathias J. Schleiden (1804-1881) turned out to be correct. The not too pleasant for reading *Beitrage zur Phytogenesis* (1838), when he was a professor in Jena, influenced Schwann and tried to remove any claims for priority of other scientists in particular, the French ones. His personal influence on Theodor Schwann (1810-1882), to whom he met in Berlin visiting his small laboratory, was probably Schleiden´s more important contribution to Anatomical Microscopy. Under the theoretical principles of the *Naturphilosophie,* that had also greatly influenced Johannes Müller approaches, Schwann followed Schleiden ideas for the identification of the laws governing the development of the elementary morphological units of animals and plants. The concept that biological form should come about by a kind of crystallization process was a familiar idea to natural scientists (for example, for G. Proschaska in 1810). But, in Schwann’s work on fermentation (1837), where he defends himself against Valentin’s claims of priority of the *Cell Theory*, indicates that he did not had any doubts that spontaneous generation did not occur. Nevertheless, he adopted M. Schleiden’s ideas on cell generation by crystallization of the *blastema,* that was a form of spontaneous generation *(generatio aequivoca)* and, for this reason, T. Schwann was opposed from the very beginning to the posterior Remak´s aforism “*omnis cellula in cellula”*. However, Schwann´s monograph *(Mikroskopische Untersuchungen über die Ueberinstimmung in der Struktur und dem Wachstum der Thiere un Pflanzen,* 1839) deserves its fame since it was one of the main books were the histological observations were brought together unified by a single theme, even though it was finally proven to be wrong. Due to the insufficiency of resources for getting an appointment in Germany and his profound Catholic personality, Schwann moved to Louvain and later to Liege Universities in Belgium from 1839 until his death in 1884, where he continued working on Physiology and producing some results, but not a single additional contribution to the *Cell Theory* or Animal Microscopy!

In the following years, a series of important reviews of Schwann´s contribution appeared and many German textbooks (Gerber 1841, Bruns 1841, Henle 1841, Kölliker 1852, Gerlach 1854 and Leydig 1859) adopted his views, at least temporarily, without mentioning other contributions such as those coming from the Purkinje Institute in Breslau, then still a part of Prussia. In this way, Unger, in 1844, produced a series of papers where he described how new cells are formed by the cell division in the meristem of plants. F. Cohn's work on microorganisms was also important to enlarge the view on the living cells. Nevertheless, the main evidences against Schwann views were the observations of Robert Remak (1815-1865), another student of Johannes Müller, and J. L. Schönlein (1793–1864). Starting in1841 on the multiplication by binary fission of chick embryonic red cells, muscle cells (1844), the vertebrate notochord (1845) among other similar observations, Remak defended in 1852 that binary fission was the only form of cell multiplication in animal bodies, but even Rudolph Virchow (1821-1902) was not of this opinion until 1854. Working on early amphibian embryos during the 1840s, Bergmann, von Siebold, Bagge and Rathke led to the proposal that cleavage was a form of cell division, a concept that was not completely accepted. It took almost 6 years, from 1840 till 1846, for K. Reichert (another student of Johannes Müller) to modify his position of support of Schwann's ideas on the cleavage of the hen and frogs embryos. As stated by Harris (1999), the demonstration that the *egg was itself a cell and that it begat daughter cells by fission* was a decisive step for arriving to the definitive *Cell Theory* and for the later building of the Genetics as an independent science. Robert Remak was also a Jew who refused to become a Christian to facilitate his appointment to a German University. In fact, he had many problems and never obtained a permanent position in Germany (but, must not be forgotten that this was still the rule in XIX Century Europe; for example, no Jews were elected to a tutorial fellowship in Oxford and Cambridge until 1882). He earned his living in Schönlein´s Klinik in Berlin, working and collaborating with numerous physicians and professors. Even though he was a kind of protégé of the influential Alexander von Humboldt, but his *Habilitation* was delayed more than 10 years; he was only appointed Extraordinarius Professor in 1859, only six years before his death. His extensive microscopical, physiological and clinical work was of such an importance that one is struck by the fact that he is almost forgotten now. He made also key embryological observations, creating the neologisms ectoderm, endoderm and mesoderm for the three germinal layers in 1842 and advanced the description of the nervous cells and their axons where he first noted the cytoskeletal fibrillar structure of the cytoplasm (1843, 1844).

As mentioned in a preceding paragraph, Remak rejected, from almost the very beginning, Schleiden and Schwann´s theory of how cells originate. He was convinced, as early as in 1852, that his findings were relevant to Pathology and Physiology and the extension of these ideas to understand malignant tumors growth was crucial. Remak was also opposed to J. Müller´s ideas to explain the genesis of tumor cells; his ideas were similar to those defended in Paris by the French School (for instance, by Ch. Robin, that used the apparent emergence of different anatomical elements to describe the tumor cells as tissue-specific). In addition, they moved in parallel to R. Virchow´s concepts on *"Cellularpathologie"*. It was a heavy blow to Remak when Virchow was made an *Ordinarius Profesor* on Pathological Anatomy and Therapie in Berlin in 1856. Remak moved then to work on Galvanotherapie, subject that he very actively practiced until his death in 1865. Rudolf Virchow, universally recognized as the main founder and champion of the definitive Cell and of Cell Pathology theories, was student of J. Müller and during that years a friend of Robert Remak. Remak knew about his work and as mentioned above, remained critical of his views and supportive of Schwann´s theory until he changed abruptly his position in 1855, when he published in his still existing Journal (*Archiv für Pathologische Anatomie und Physiologie, und für klinische Medizin*; today known as *Virchows Archive*) a paper entitled *"Cellular Pathologie"* in which he adopted virtually without modifications the position of Remak on this subject. Virchow had been appointed full professor in Würzburg in 1849, where another famous microscopist and student of J. Müller and Jakob Henle, Albert von Kölliker, was *Ordinarius Profesor* since 1847. After the 1855 paper, Virchow published his famous book *"Die Cellularpathologie in ihrer Begründung und in ihrer Auswirkung auf die physiologische und pathologische Gewebelehre,"* (Berlin, 1858 and subsequent editions). Together with the new studies on bacteria and viruses, Virchow´s books during these years are certainly the basis of the new scientific medicine. We have already mentioned that the Latin aphorism universally attributed to Virchow *(Omnis cellula e cellula)* had been used by Dutrochet in 1825. Actually, Virchow wrote initially *"Omnis cellula a cellula"*, changing it to the Dutrochet version after that in the publication of Franz von Leydig (1821-1908) *"Lehrbuch of Histologie"* (Frankfurt, 1857) amended it. What cannot be denied is that Virchow´s meaning was completely different from the one that Dutrochet had in mind. Virchow assembled in his book many observations, own and from other scientists, united by the concept of the generation of tissues driven by binary division of cells. Although some additional pieces of the puzzle remained to be filled (see below), the present *Cell Theory*, the real one, was in its way to establish itself as the new paradigm of Biology that we currently support.

The description of properties of cell division: the role of the nucleus and the chromosomes had to be completed. The Germans Henle (1841), Nägeli (1842), Reichert (1847), Hofmeister (1848), Remak (1852), Schültze (1861), Schneider (1873) and the Russians Kowalevski (1871), Russow (1872) and Tschistiakoff (1875), all gave information that led to the influential Eduard Strassburger book, *Zellbildung und Zelltheilung* (Jena, 1875) and to Otto Bütschli´s 1876 long paper in which the descriptions advanced to a point close to be almost definitive. Strassburger´s position was still of a transitional nature. With many important observations, he, for example, still defended that the nuclei in the endosperm were formed *de novo* as proposed by Schleiden. The work of the already mentioned French researcher Edouard-Gerard Balbiani, appointed as an Embryology professor at the

College de France in 1854, indicates that the flux of ideas coming out from Germany were returning there, after revitalizing the rest of Europe. Although in a series of papers published in 1861, Balbiani draw metaphases and prophases, he misinterpreted what he saw. It was only in 1876 when he described all the mitotic phases in the ovary of a grasshopper. Walter Flemming´s work (1879 and 1880), the work of the French Hermann Fol in Geneva, published in Paris (1877 and 1878) and especially, the contributions in French of the Belgian pupil of Theodor Schwann in Louvain, and later professor of Zoology in Liege, Edouard van Beneden (1846-1910), who, in 1883, after the study of *Ascaris megalocephala* eggs*,* completed the present view of cell division discovering the reductional mitosis or *Meiosis* (Hamoir, 1992). A work successfully continued by his collaborator H. Winiwarter on the development of mammalian ovary (1901). The *Cell Theory* was then almost complete, waiting only the works of the Spanish histologist Santiago Ramón y Cajal (1853-1934) and the development of the electron microscopy and the biochemical and genetic advances in the XX Century to fit everything in place, as we know it today.

We have not insisted on the evolution of microscopic ideas in France and in Britain. Besides being a subject that may require further investigation in a framework similar to that presented here, it is true that the situation in France had a big impact in how these ideas were disseminated in Spain. As the last contributions show, the German hegemony although maintained until the beginning of the XX Century, gave place progressively to a more balanced situation with additional participation of scientists from other countries. The nervous system was the last bastion of a non-typical cellular structure that was actually overcome by Cajal's work at the turn of the XIX Century.

Introduction of the concept of tissue and initial development of a cellular based Histology in Romantic Spain

As we mentioned above, the successful process of scientific renovation in Spain collapsed during the transition between the XVIII and the XIX centuries. Several reasons were the cause of it: 1) the leading classes including the Kings and the members of their governments, supporters of the European alignment of Spain were mere conservative, enlightened (*ilustrados)*. They were worried by the consequences of the French Revolution of 1789, although this effect should not be exaggerated. If we take for example, the case of the Spanish scientific expeditions, many of them were actually undertaken after 1779. 2) On the other hand, this reaction probably became operative during the Napoleonic invasion and the subsequent *War of Independence* (1808-1814); in fact, many of the protagonists in the effort to modernize Spain were *Francophiles (afrancesados)*, known for their sympathies and admiration for the new and modern scientific and social ideas of invaders. As consequence, they had to immigrate to France at the end of the war or suffered a deep margination inside their country. The war itself left Spain bare and destroyed 3) the final failure and/or destruction of the scientific laboratories (i.e. in Vergara, Segovia, Valencia and Madrid) and research institutions described above, in some cases linked to the war. The destruction of the *Royal Astronomical Observatory*, transformed in barracks for the French Napoleonic Army; its excellent Herschel telescope and its archives burned to heat the troops is an obvious example. 4) The loss of the majority of the Spanish colonies in America and its deep economics consequences. 5) A large fraction of the country population including the young, despotic and revered King Ferdinand VII (called *El Deseado,* The Wished, by its subjects), the Church and the religious leaders, as well as the core of the less educated people were against any measures that could align Spain with the more progressive Europe (*long live the chains!* was one of the main shouts to be heard in the streets of Spain after the restoration of the Bourbon royal family in 1814). 6) The opinion and help of the similar conservative governments, mainly in France, but also in other European countries, at the beginning of the XIX Century. For example, the new intervention in Spain of a French Army in 1824, under the support of the European *Saint Alliance* (Austria, Prussia and Russia) to restore the absolute mandate of the Spanish King Fernando VII after the short period (1820-1823) during which the liberal Spanish army had forced him to accept the liberal Constitution voted in Cadiz in 1812 and other reforms.

After the so-called *"Ominous decade"* (1823-1833) under the absolute rule of Fernando VII, the situation of the country was pushed back again more than a century; all supporters of liberalism had been exiled or strongly repressed, many Universities and newspapers were closed, etc. Fortunately, as it turned out, the large, more conservative, fraction of the country aligned itself behind Carlos María Isidro, King Ferdinand´s brother, who was a defender of the more conservative positions in political and religious terms. The only born child in Ferdinand last marriage was a three years old girl, Isabel, who accordingly with the Borbonic rule was not to be considered a candidate in the succession line of the throne. Eventually at the end, Fernando VII decided to abolish this policy and after his death, Isabel with the help of a large part of the Army and the liberal party (divided into two branches: *moderates* and *progressives*) was proclaimed Queen of Spain under the regency of her mother Maria Cristina. The *First Carlist Civil War* (1833-1840) was immediately unleashed. One of the main political tasks for the country was to agree on a Constitution that could be supported by the majority of the people, but that was also compatible with the changes that were occurring in Europe and in the rest of the world. This is the starting point of Spain in the XIX Century where we want now to consider how the new histological and microscopic concepts of the structure and function of living organisms were introduced in Spain.

Under the Regency of the Queen Maria Cristina (1833-1842) after the King Fernando VII dead, through the action of her governments (Moderate and Progressive), a long period of reforms was initiated, many of them tame and incomplete, where the liberals (politicians and military) could finally try to implement their ideas, following those already incorporated in the Cadiz Constitution of 1812. The Universities were reopened immediately, but they were subjected to many changes. In fact, they followed the French System as devised by Napoleon as basic model because the influence of the German development took longer to be imported and it had mostly a marginal influence. The reform and development of the educational system in Spain was one of the main objectives of the liberal movement. Peset and Peset (1974) put as the starting point of the new High Education System (including the Universities) in the Contemporary Spain with the laws passed at the end of the 1840s: *"The old University* *has passed away; the one that we know has began"* they wrote. The Universities lost their incomes and endowments, as well as their dependency from a far away Church but became now under the close control of the government (similar to the Napoleonic Imperial University) who took care of their funding. Everything was legislated and regimented including the teaching programs and the textbooks. The professors became public servants and bureaucrats. The French system of concourses, of gaining the positions, centralized in Madrid was adopted, etc. This University, at least initially, had no place for research; the laboratories founded in the XVIII Century, most of them not linked to Universities, had disappeared long ago. The more active professors in the Spanish University (a small percentage of the total number of 276 in 1847, 301 in 1862 and 342 in 1878) were actively engaged in the objective of expanding the new scientific ideas among the students using oral lectures, translations and manuals. Theology was no longer the main subject (it disappeared in 1868), but initially Philosophy took its place. Medicine and Pharmacy were the main Science Schools. Practical laboratories were almost inexistent, although this slowly changed during the second part of the XIX Century. A separated system of Polytechnic Schools for Engineers and Architects and Military Academies remained in place. The legislation related to University was completed in 1857 (*Ley de Instrucción Pública* of the Minister Claudio Moyano). In it, finally, Schools of Sciences made its place among the rest of Faculties, overcoming the period in which they were included as part of the School of Philosophy! The University that came about, although in turmoil during the years that led to the 1868 Revolution *(La Gloriosa)* which dethrone Isabel II, the daughter of King Fernando VII, and the subsequent period of great political instability so-called "*sexenio revolucionario"* (1868-1874), including the short reign of Amadeo I of Savoy, the First Spanish Republic and the *Third Carlist Civil War*, was remained basically as proposed by the previous Moyano's legislation into the long and stable Restoration Period (from1874 till well into the XX Century).

In this difficult political and social context (see López-Piñero *et al.,* 1964) one has to consider what happened in relation to the incorporation of the new ideas on the structure of the living organisms in the Spanish scientific community, even if we are allowed to use this notion, i.e, scientific community, in a very extended and weak meaning. The starting point was very low, almost minimal. Thus, during the main collapse of the Spanish Science (1808-1832) very little happened or was attempted that could be considered as providing a real starting point for the future events (Aréchaga, 1973, 1977b). A few translations of French authors were the works of F. Xavier Bichat, first the *General Anatomy* (translated by Ramón Truxillo), which appeared in Madrid from 1807 till 1814 (a second edition in 1844) and, after, the *Treaty on Membranes* in 1926, followed by some additional books on *General Anatomy*: the one written by A.L.J Bayle and H. Hollard (translated by Cayetano Balseyro in 1828) and by P.A. Béclard (translated by José María de Aguayo y Trillo in 1832). In addition to disseminate the important ideas of Bichat on the properties and classification of the tissues, these books included an update on the work of the French microscopists of the first third of the XIX century, as well as their impact in pathology and in the case of Beclard´s Treaty a summary on comparative anatomy (P. A. Béclard was a great admirer of G. Cuvier). The biographies of two of the translators, Ramón Truxillo and Cayetano Balseyro, are

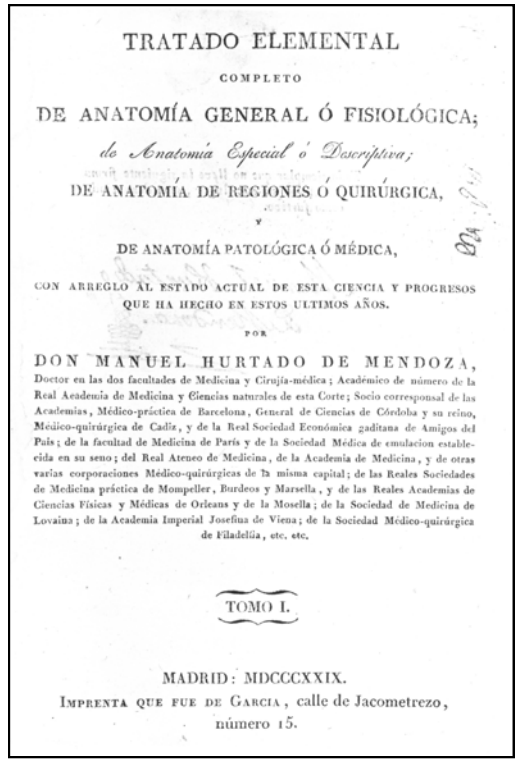
TRATADO ELEMENTAL
COMPLETO
DE ANATOMÍA GENERAL Ó FISIOLÓGICA;
de Anatomía Especial ó Descriptiva;
DE ANATOMÍA DE REGIONES Ó QUIRÚRGICA,
Y
DE ANATOMÍA PATOLÓGICA Ó MÉDICA,
CON ARREGLO AL ESTADO ACTUAL DE ESTA CIENCIA Y PROGRESOS QUE HA HECHO EN ESTOS ULTIMOS AÑOS.
POR
DON MANUEL HURTADO DE MENDOZA,
Doctor en las dos facultades de Medicina y Cirujía-médica; Académico de número de la Real Academia de Medicina y Ciencias naturales de esta Corte; Socio corresponsal de las Academias, Médico-práctica de Barcelona, General de Ciencias de Córdoba y su reino, Médico-quirúrgica de Cadiz, y de la Real Sociedad Económica gaditana de Amigos del Pais; de la facultad de Medicina de París y de la Sociedad Médica de emulacion establecida en su seno; del Real Ateneo de Medicina, de la Academia de Medicina, y de otras varias corporaciones Médico-quirúrgicas de la misma capital; de las Reales Sociedades de Medicina práctica de Mompeller, Burdeos y Marsella, y de las Reales Academias de Ciencias Físicas y Médicas de Orleans y de la Mosella; de la Sociedad de Medicina de Lovaina; de la Academia Imperial Josefina de Viena; de la Sociedad Médico-quirúrgica de Filadelfia, etc. etc.
TOMO I.
MADRID: MDCCCXXIX.
IMPRENTA QUE FUE DE GARCIA, calle de Jacometrezo, número 15.

Fig. 7. Cover page of volume one of the encyclopedic work of Manuel Hurtado de Mendoza (1829-30). *It contains the first modern Spanish* Histology (General Anatomy) *and* Anatomic Pathology.

representatives of the liberal period, taking part in the *War of Independence (1808-1814)*. Truxillo was a representative in the Cadiz Parliament that wrote and voted the first democratic Constitution in Spain in 1812. The conservatives harassed him until 1829, when he regained his positions in Madrid as Full Professor and Director of the Madrid Medical School *(Real Colegio de Medicina y Cirugía de San Carlos)*, dying shortly afterwards.

The more important work published in this period was the treatise of Manuel Hurtado de Mendoza (1783-1849) entitled "*Tratado Elemental Completo de Anatomía General o Fisiología, de Anatomía Especial o Descriptiva, de Anatomía de Regiones o Quirúrgica y de Anatomía Patológica o Médica, con arreglo al estado actual de esta ciencia y a los progresos que ha hecho estos últimos años*" (Complete Elementary Treatise of General Anatomy or Physiology, of Special or Descriptive Anatomy, of surgical Anatomy and Medical Anatomy or Pathology, with respect to their actual state and the progress made in the last few years) published between 1929-1930 (Fig. 7). Hurtado de Mendoza, a former student of the *Royal College of Surgery* of Madrid and military surgeon during the war of 1808-1814, emigrated to France at the end of it, probably because his liberal character and empathy with the invaders. In France, he developed an intense activity assisting to curses and public demonstrations at the Medical School of Paris and the Hospitals of Saint Antoine and Charenton by the main figures of the French medicine at that time, like Pierre A. Beclard, Jean N. Marjolin, Jules G. Cloquet, etc., some of them direct disciples of F. Xavier Bichat, and was especially influenced by Joseph V. Broussais (1772-

1838), a former physician of the French Napoleonic Army in Spain during the war and, later, professor in Paris. Broussais ideas of the unity between physiology and pathology influenced Claude Bernard but were at the same time mixed with many other old fashioned concepts, particularly those linked to the treatment of diseases. Hurtado de Mendoza came back to Spain probably at the beginning of the liberal triennium (1820-1823) but kept fluid relationships with medical circles of France (Paris, Bordeaux, Montpellier, Marseille, Orleans), Austria (Vienna), Belgium (Louvain) and USA (Philadelphia) along his life. His excellent book above mentioned, really encyclopedic, was clearly up to date in the anatomical, histological, embryological, evolutionist and pathological ideas of the early Romantic France, and of German *Naturphylosophen* (mainly Karl F. von Kielmeyer, Lorenz Oken and Johann F. Meckel) and British comparative anatomists (i.e.: Richard Owen), but mainly through French authors (Geoffroy Saint-Hilaire, George Cuvier and, particularly, Etienne Serres). Its actualized content is of superior quality of any other book of Spanish morphologists in several decades. In the matter we are dealing of in this article, we must enhance his role in the introduction in Spain, among many others, the concept, classification and early descriptions of the human tissues (his book of 1929-30 is the first Spanish one about Histology and Pathological Anatomy) and the *Globular Theory*, mainly after the interpretations of J.F. Meckel (1815), G.R. Treviranus (1816) and H. Milne-Edward (1823) (Aréchaga, 1973, 1974, 1976, 1977b). Hurtado is a typical representative of the intermediate period between de *Fibrilar Theory* and the *Cell Theory* of Schwann, according to A. Berg (1942) periodical description.

The reception in Spain of the *Cell Theory* of Schleiden and Schwann and the new Histology founded on it took place during the reign of Queen Isabel II (1833-1868). We should subdivide this period in two parts, the one that ended in 1854 when the progressive, more left wing, liberals controlled the government for two years and the final moderate (conservative) period, from 1854 till 1868, that we will call the "transition stage" (Aréchaga 1973, 1977b; López-Piñero 1971, 2006, 2008; Marco-Cuellar 1966).

The characteristics of the first part are the following: the number of publications is still rather low and modest. The more significant of them were the *Compendio de Anatomía General y Descriptiva* (Compendium of General and Descriptive Anatomy) of Agapito Zuriaga (1838) and the *Tratado de Anatomía General, Descriptiva y Topográfica* (Treatise of General, Descriptive and Topographic Anatomy) of Lorenzo Boscasa (1844). Although with merits as manuals for students, with important contributions to the improvement of the anatomical terminology, both authors were still supporters of ancient *Theory of the Fiber* and of the old Bichat points of view about the structure of the tissues, ignoring all recent European progress in the field of Microscopy (Aréchaga, 1976b, 1977b; Aréchaga and Guirao, 1987). The first mentions of the primitive *Cell Theory* in Spain are included in the anonymous translations of the *Treatise of General Anatomy* of Jakob Henle (1843) and of the *Treatise of Physiology* of Johannes Müller (1844), but the introduction of the new ideas about the cellular organization of the body in plants (Schleiden) and animals (Schwann) do not appear in texts of Spanish authors until the publication of the *Manual de Botánica* (Handbook of Botany) of Manuel González de Jonte in 1849 (Gomis-Blanco, 1987) and of the *Tratados de Histología y Ovología* (Treatises of Histology and Ovology) of Mariano López-Mateos in 1853, although it was written and ready publish in 1948, but the author delay its print by bureaucratic circumstances (Aréchaga, 1974, 1976a, 1976b).

Mariano López Mateos (1800-1863) was professor of Anatomy at the Granada and Valencia Universities and later of Physiology. He was quite appreciated by the students, who tried to update the information available so that they could adapt to the changes in the teaching programs introduced in 1847 by the Spanish Government. He was not a real practical microscopist, although he gave a very small reference to the use of compound microscopes in his book. López Mateos neither was exposed directly to the European science like Manuel Hurtado de Mendoza, but he was well informed of the progress of his discipline and had a strong influence on some anatomists and histologists of the next generation like Aureliano Maestre de San Juan, Juan Creus y Manso, Rafael Martínez Molina, Antonio García Cabrera and Eduardo García Solá, all of them students and/or academic colleagues of him in Granada University Medical School. As a consequence of the Government decision of 1847 to introduce in the Spanish Medical curriculum, for the first time, a subject on *"histology and anatomy of tissues and the ovology and development of organs and systems",* López Mateos book was entitled *Treatises of Histology and Ovology* when most books of his time, for example the one from Henle (1841), were still called *Allgemeine Anatomie*; even Kölliker´s title of 1852 is *Handbuch der Gewebelehere*, reflecting the still great influence of the Bichat´s original book title and tissue concept (Fig. 8).

The microscopic elements listed in López-Mateos book are multiple and tissue-specific, as they appear in French books of the preceding period. The *Ovology Treatise* is much more interesting, at least in terms of the little attention that had been paid to Embryology until then in Spain. From his descriptions is almost undoubtedly that López Mateos was updated, especially through the French literature. In this regard, he was very much influenced by the still incomplete encyclopedic work of Louis Mandl (*Anatomie Microscopique. Histology and Histogénèse,* Paris´1838-1857) and, with the brevity of a handbook for students, he incorporated clearly the present state of the *Cell Theory* in 1847*,* just before the definitive contributions of R. Remak and R. Virchow (Aréchaga, 1974, 1976a,b). Unfortunately, his valuable work has been recently not properly appreciated (López-Piñero, 2006)

The situation began to improve in Spain in what we can call the "transition stage" (1854-1868**)**. In addition to the political and educative reforms that established the organization of the high education in the country, it can be defined by three features: 1) the practical introduction of the microscope across Spain, b) the increase in the number of translations and original publications dealing with the microscopic organization of the living organisms both under normal and pathological conditions (if the years 1833-54 *vs.* 1854-68 are compared: translations 12 *vs.* 150 and original publications 9 *vs.* 160), c) the slow but continuous introduction of the new and final histological synthesis, that was taking place in Europe, the one based on many investigations starting in the 1840s and culminating with Rudolf Virchow and other, mostly German, histologists. This was not easy, the influence of the French ideas was still important and many more conservative, vitalistic oriented people (for example Martín de Pedro in Madrid) counterattacked claiming that the studies using the microscope were not trustworthy. It was necessary to wait until the next stage to find in Europe and also in Spain the full incorporation of the definitive *Cell Theory.*

The main sites of this development in Spain (Barcelona, Madrid, Valencia and Granada) show the same features at that time: the anatomy professors and the surgeons working in combination (Fig. 9), the protection of the scientific societies and the existence of at least one scientific medical journal supporting these developments (López-Piñero 1992, 2006, 2008; López-Piñero *et al.,* 1979, 1986; Marco-Cuéllar 1966, 1969; Terrada *et al.,* 1963).

In Barcelona, possibly the part of Spain where the spirit of the *enlightenment* had survived to a higher degree, being closer to Europe (the initial steps of the industrial revolution were imported there), may explain why the studies using the microscope started (or remained operative) earlier than in the rest of Spain. The professor and surgeon was Antonio Mendoza y Rueda (1811-1872). Born in Málaga; he studied in Madrid and became a military surgeon, participating in the *First Carlist Civil War* before settling in Barcelona. In 1843, as a consequence of the refunding of the Medical Sciences Schools by the Provisional Government, he occupied the chair of *General and Descriptive Anatomy*. Two years later he took the chair of *Surgical Anatomy*. He had a good command of several languages, including Latin, Greek, French, English, German, Italian, Portuguese and Catalan. He was an excellent clinical teacher, very proficient in all types of complementary techniques, including Microscopy. In 1850 published the *Estudios Clínicos de Cirugía* (*Clinical Studies of Surgery)* in 3 parts. An extensive section on the Microscope and its practical applications was included (almost a literal translation of Alfred Donné´s *Course de Microscopie Complémentaire des Études Médicales*, Paris 1844-45). In terms of the cellular composition of the living organisms, he is still completely in accordance with the current ideas in Europe (mostly in France and Germany) including the ideas of Lionel S. Beale (*The microscope, and its application to clinical medicine*, London 1854). In 1857, Carlos Silóniz(1815-1892), born in Cadiz where he studied Medicine, traveled to Paris (1840-43), London (1859) and Paris (1862). From 1843 on, he was professor of Anatomy in Barcelona and published a similar booklet, *Del Microscopio en su aplicación al diagnóstico* (Of the Microscope in its diagnostic applications) and later an extensive *General Anatomy* (1871-72) that reproduced the framework of the *Cell Theory* with the most recent information from German, French and English microscopists (Fig. 10A). The group of medical doctors in Barcelona, members of the *Academy of Medicine and Surgery* in Barcelona, started editing a Journal in 1865 *El Compilador Médico* (The Medical Compiler), The clinical histories of Mendoza´s practice published in this Journal testify the almost routinely use of the Microscope and the ideas derived from its use corresponding to that period in Europe.

This trend is even clearer in Madrid. The new Military Hospital of this city (adaptation in 1836 of the previous *Real Seminario de Nobles,* after Mendizábal economic reforms) had from the 1860´s decade one of the earliest *Histological Laboratory* of the country (predecessor of the present *Instituto de Medicina Preventiva Capitán Médico Ramón y Cajal*). Its used microscopical techniques were oriented, at the beginning, only to Histopathology but, after, also to Microbiology. Anatomists and surgeons like J. Fourquet, R. Martínez Molina, F. Rubio and M. Soler, the dermatologist J. E. Olavide, the otolaryngologist R. Ariza, the gynecologists F. Alonso y Rubio, the expert on Medical Legislation, P. Mata, and his student T. Yañez, among others, used the histopathological information on the microscopic constitution of the living tissues, led to the founding in 1865 of a micrographic department in the Medical School under the direct supervision of the surgeon A. Moreno y Pozo. Different free schools independently organized by the more important medical practitioners (the surgeon P. Gonzalez de Velasco, the ophthalmologist S. Delgado Jugo) included the teaching of the use of the Microscope in their programs. In 1855 the *Academy of Sciences*, and in 1864 and 65 the *Royal Academy of Medicine* announced competitions on the distinctive characters of the gametes and on the impacts of the new anatomical concepts on the Medical Progress. Several Journals like *La Gaceta de Sanidad Militar* (Military Health Gazette) *La Iberia Médica* (The Medical Iberia), *La España Médica* (The Medical Spain) and, especially, *El Pabellón Médico* (The Medical Pavilion), later becoming *El Anfiteatro anatómico español* (The Spanish Anatomical Anphitheater), and *El Siglo Médico* (The Medical Century) opened their pages to any new scientific advancement with an impact on Medicine, including of course, the microscopical theories. In fact, the two main journals, *El Pabellón (The Pavilion)* and *El Siglo* (The Century) aligned themselves in opposite sides of the dispute between the French and the German Schools respectively.

We will only review the work of Rafael Martinez Molina (1816-1888), as an example of the "intermediate generation" (López-Piñero, 1971). Born in Jaen in a

TRATADOS

DE

HISTOLOGÍA Y OVOLOGÍA,

ARREGLADOS

AL PROGRAMA REMITIDO AL GOBIERNO

por el Dr. en Medicina y Cirugía

Don Mariano Lopez Mateos,

Catedrático propietario por oposición de Anatomía en la Universidad de Granada, despues en la de Valencia y al presente de igual asignatura en la facultad de Medicina de segunda clase de esta Universidad; socio de diferentes Corporaciones científicas, condecorado con varias cruces, etc.

GRANADA: 1853.

Imprenta de D. Juan María Puchol.

Fig. 8. Mariano López-Mateos (1800-1863) and cover page of his book *(written in 1848, although its publication was delayed until 1953 for bureaucratic circumstances). Actually, he was one the last romantic Spanish anatomists and the introducer of the Schwann* Cell Theory *in our country. He also deserves recognition to be among the first movement to arrive to the great figure of Santiago Ramón y Cajal (1852-1934), through his influence, at the University of Granada, on several important members of the so-called* "Intermediate Generation". *(Oil portrait in the* Royal Academy of Medicine of Granada*).*

Fig. 9. Oil painting of a representative group of professors at the *Real Colegio de Medicina y Cirugía de Madrid* (Madrid Medical School) in Romantic Spain. *The professor of Surgery, Diego de Argumosa (1792-1865), is operating a corpse under the attentive glance of the rest of the academics, among them the professors of Anatomy, Juan Fourquet (1807-1865) and of Surgical Anatomy, Juan Creus (1828-1898). Painting entitled "*Operación del Dr. Argumosa". *Faculty of Medicine, Complutense University of Madrid, Spain.*

modest family, after trying a religious career in Granada, began Medical studies in 1839, where he distinguished himself in the eyes of the professors. After, he earned after a Doctor degree in Natural Sciences. He had extensive knowledge of foreign languages; his clear and extensive explanations gave him the consideration of a "sabio" (wise). He taught at the Madrid Medical School where he was eventually named to the chair of Anatomy. He founded *The Biological Institute*, a private venture, where students could learn in a practical way Microscopic Anatomy and Histology as well as Chemistry and Pharmacology. He translated the Anatomy treatise of Philibert C. Sappey and the Histology from Van Kempen (see later), as well as the Treatise of Surgery from August Nelaton and Jules R. Guérin. We can find a summary of the ideas that he taught in his address published in 1867: *The anatomy, its progress and applications*. He is a representative of the intermediate situation in Europe caught in the dispute between the French School of Robin, Lebert, Broca, etc. and the German one of Virchow. Martinez Molina as many other practitioners due to the influence of the near country, initially supported the ideas of the French School. We have to wait until the next phase to witness the final triumph of the German School as it happened in all Europe, including France (Fig. 11).

Similar trends can be found in Valencia with the anatomist José María Gómez Alamá (1815-1875) (Fig. 10B) and his practical *Arte de Disecar* (Art of Dissecting) with extensive descriptions on microscopical techniques. A medical society, the *Instituto Médico Valenciano* (Valencian Medical Institute) organized several competitions on the application of the microscopical ideas to Pathology and a journal, *La Fraternidad* (The Brotherhood) also published the microscopical examination of clinical cases.

In 1860 arrived in Granada as professor of Anatomy the vigorous personality of Aureliano Maestre de San Juan (1828-1890), former pupil of Mariano López-Mateos in Granada and the grandfather of the Spanish School of Histology, who was already engaged in practical microscopical research; see, for instance, his reception address of 1860 in Granada, entitled *Consideraciones sobre la anatomía de los ganglios nerviosos* (Considerations on the anatomy of the nervous ganglia). On the other hand, anatomists and clinical practitioners such as Juan Creus y Manso (1828-1897), Eduardo García-Solá (1845-1922) and Antonio García-Cabrera completed the group of academicians and medical doctors interested in Microscopical studies in Granada at that time (Fig. 11).

The foundations of the Spanish Scientific Recovery in the second part of the XIX Century. The forerunners of Santiago Ramón y Cajal (1852-1934)

Even though the situation was still far from satisfactory, the preceding description indicates how slowly but steadily some-

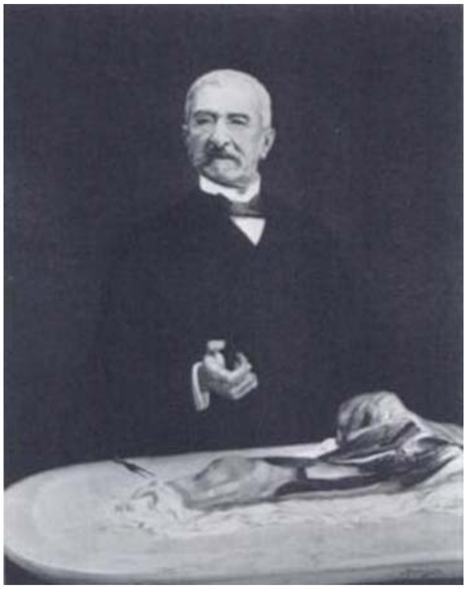


Fig. 10. Carlos Silóniz-Ortiz (1815-1898) and José María Gómez-Alamá (1815-1874). *Representative histologists of the Universities of Valencia and Barcelona before Santiago Ramón y Cajal (1853-1934).*

thing was changing in Spain. After the turmoil's of the years 1868-1874, the political restoration of Isabel II son, Alfonso XII, and the posterior social and economic development brought back the tranquility that made possible to continue with the improvements already described. The previous restrictive and detailed legislation was reinstated and the official University continued its growth. The more progressive professors that had been supporting the political changes in the preceding period were separated from their positions and founded in 1876, a private learning institute, the *Institución Libre de Enseñanza* (Free Learning Institution) that was important for the cultural development of the country.

Although minority and exceptional, catching up the level of the European Science continued to be one of the objectives of the more active professionals. In Life sciences, microscopical and histological studies were one of the topics where this trend is more clearly visible. They provide the environment where the work of the next generation including Santiago Ramon y Cajal could take place. Several characteristics are worthwhile noting of this new period: 1) The final incorporation of the definitive *Cell Synthesis* with the victory of the German School as it was happening at the same time in the rest of Europe (Histology Chairs began to be established in all the Spanish universities). The interest in Microbiology was also increasing during these years. 2) The maintenance and increase in the practical and experimental work and 3) The existence of two separated areas, the one carried out in the official Universities and a second one, that we can call para-university institutions.

The described development achieved in the previous years in Madrid, Barcelona, Granada and Valencia was maintained during the following period and extended to the rest of Spain. We will just describe in more detail the situation in Madrid where the first chair on Histology at the Medical School was endowed in 1873. Aureliano Maestre de San Juan, whom we have seen in Granada, teaching *General and Descriptive Anatomy* from 1860, took the position. He was born in Granada but had lived in Madrid from 1841 till 1851 when he obtained the Doctorate degree. His interest in anatomical studies comes from this time. His initial microscopic publications started in 1860 and he traveled to Paris, Berlin and London in 1863 and 1865 and to France, Belgium, the Netherlands and Germany in 1867, visiting the laboratories in the main Universities. His pivotal role as introductory of the definitive concepts in Histology and the practical work with the Microscope is clear. From his 53 publications, 16 are on histological topics, 3 Textbooks on Histology and many histopathological analyses in the micrographic laboratory of the Madrid Medical School founded in 1865 and expanded in 1873, with the new Histology chair. Santiago Ramón y Cajal saw for the first time microscopic slides in this laboratory shown by Leopoldo López-García (1854-1932), the main disciple and graduate student of Maestre de San Juan. López-García had spent three years in Paris completing his training under the supervision of L. Ranvier at the College of France. In 1886 he did another stay learning Microbiology at the *Institut Pasteur*, moving to the chair of Histology in Valladolid in 1888 in a School of Medicine without laboratories! Thus, he initiated his work there in a private laboratory at home and in a small room in the Medical School attic, just equipped with a table and a *Nachet* microscope that he had personally purchased. In Valladolid, López-García later trained Pio del Río Hortega (1882-1945), the discoverer of *microglia* and the second more important name in the *Spanish School of Histology* after Cajal. Another disciple, Manuel Tapia Serrano was a surgeon that actively used the microscope in his practice. In this direction, he joined other professors of *Surgery* at the Madrid Medical School (such as Adolfo Moreno y Pozo, Juan Creus y Manso, Santiago González-Encinas) of *General Pathology* (Andrés del Busto), of *Anatomy* (Julian Calleja, pupil of Juan Fourquet), etc.

In Barcelona, J. Giné y Partagás (1836-1903) and B. Roberts, established the use of *Histology* in the clinical studies. R. Coll y Pujol and I. Valentí y Vivó did the same in *Physiology*. Giné and Robert's annotations in their translation of R. Virchow's *Cellular Pathology* indicate that were still influenced by the French School of Ch. Ph. Robin. In Granada, we find to Eduardo García Solá (1845-1922), Profesor and Rector of his University, trained by López-Mateos and Maestre de San Juan and author of important textbooks of Histology, Anatomic Pathology and the first Spanish text on *Clinical Micrography* (Fig. 11).

In Valencia, P. Casanova, E. Martínez-Gil and the group around the chemist J. Montserrat, developed the interest on bacteriology and parasitology. F. Campá (1838-1892) in Gynecology, the internist J. Crous y Caselles (1846-1887) contributed to the introduction of laboratory practices in Spanish Medicine. Crous published a *Treaty on the Anatomy and Physiology of the Nervous System* (1878), six years before the arrival of Cajal to this University. The surgeon E. Ferrer Viñerta (1838-1891) strongly supported the introduction of the histopathological analyses in surgical practice as performed by Martínez-Gil in the samples

Fig. 11. Rafael Martínez-Molina (1816-1888), Aureliano Maestre de San Juan-Muñoz (1828-1890) and Eduardo García-Solá (1845-1922). *Three prestigious Spanish histologists, former students or academic comrades of Mariano López-Mateos (1800-1863) in the University of Granada Medical School, and members of the generations previous to Santiago Ramón y Cajal (1853-1934).*

coming from Ferrer's practice.

One important demonstration of the degree of penetration in the medical environment in Spain is the extensive dissemination of the ideas and activities linked to the Histology, Histopathology and Micrography in general. Without being exhaustive, we will give some examples at the time. The *Histological Society*, founded in 1874 with Maestre de San Juan as first President, met weekly and soon organized a practical school. The subjects that were discussed in their weekly sessions were half applied, histological preparations of clinical cases, half theoretical, including the *Cell Theory*. After very hot discussions, Maestre supported as conclusion Virchow´s and Cohnheim´s views in front of the French School and the vitalistic ideas. More or less simultaneously, Pedro González de Velasco (1815-1882), the more successful surgeon in Madrid, founded the *Anatomical Society*, used large amounts of money that he had obtained in his practice to build an important museum, still active, the *Anthropological Museum*, that included an important micrographic laboratory. Velasco´s support of the histological ideas was quite old; already in 1856 he defended building anatomical museums in Spain that included microscope equipped laboratories. Velasco founded also several scientific journals, such as the *Anatomic Anphiteater* where many contributions on microscopical pathology problems were published. A similar support to microscopical studies was exhibited by another successful surgeon, Federico Rubio (1827-1902) and his fellow companion in the medical studies, the otolaryngologist, Rafael Ariza (1826-1887) who was a known practitioner of the microscopical techniques, professor in a private School of Medicine established by F. Rubio in Sevilla in 1868. Rubio, Ariza among other founded in Madrid of the *Instituto de Terapeútica Operatoria* (Institute of Surgical Therapeutic) where Eugenio Gutiérrez (1851-1914) also trained in Paris by Ranvier in the College de France where he were head of the histopathological laboratory. A similar development was undertaken by the great dermatologist J. E. de Olavide (1841-1901) in the Hospital de San Juan de Dios, that also included a microscopical laboratory. The ophthalmologist S. Delgado Jugo (1830-1878) founder of the *Instituto Oftálmico* (Ophthalmological Institute), born in Venezuela and trained in Paris with A. L. Desmarres, and his fellows R. Cervera and E. Sobrino extended the use of the microscope and the histological approach on eye diseases.

Similarly, in Barcelona, the ophthalmologist school of B. Carreras and J. Barraquer (1852-1924) in similar lines than Delgado and his successors in Madrid, making extensive use of the microscope in their studies. The scientific societies in Barcelona, starting from the *Sociedad Médica "El Laboratorio"* (Medical Society "The Laboratory"), the *Academia i laboratori de Ciences Mediques de Catalunya* (Academy and Laboratory of Medical Sciences of Catalonia), etc. were all sites of at least the discussion of the new microscopical techniques in pathology. In Valencia, it is interesting to mention, in addition to the continuing activity of the already mentioned *Valencian Medical Institute*, the activities of the students participating in the *Medical Student Association*. In addition to many talks and activities, they complimented T. Schwann for his retirement in Liegé in a congratulation letter that was answered by Schwann in September 1878. Schwann´s words remembered the role that Spain had played in the world in the past and showed his unhappiness that the Country had failed to maintain this status.

This trend was not limited to medical activities but extended to Natural Sciences. The *Spanish Society of Natural History* (founded in 1871) was at similar times encouraging its members to apply the microscope in their research. J. Macpherson Hemas (1839-1903), born in Cadiz, was one of the first scientists in the world to apply the achromatic microscope to geological investigations while the Catalan J. M. Castellarnau y de Lleopart (1848-1943), working on the microscopical anatomy of plants, developed a classifications of woods based on their histological characteristics. However, the sad commentaries reproduced in the preface to his excellent 414 pages book entitled *Teoría general de la Formación de la Imagen en el Microscopio* (General Theory about Microscopical Image Formation) in 1911 is a good example of the unjustified bad exterior image of the Spanish Science in the last quarter of the XIX century:

…De seguro que hoy tienen de nosotros en el extranjero una opinión muy distinta de la que tenían en 1885, cuando

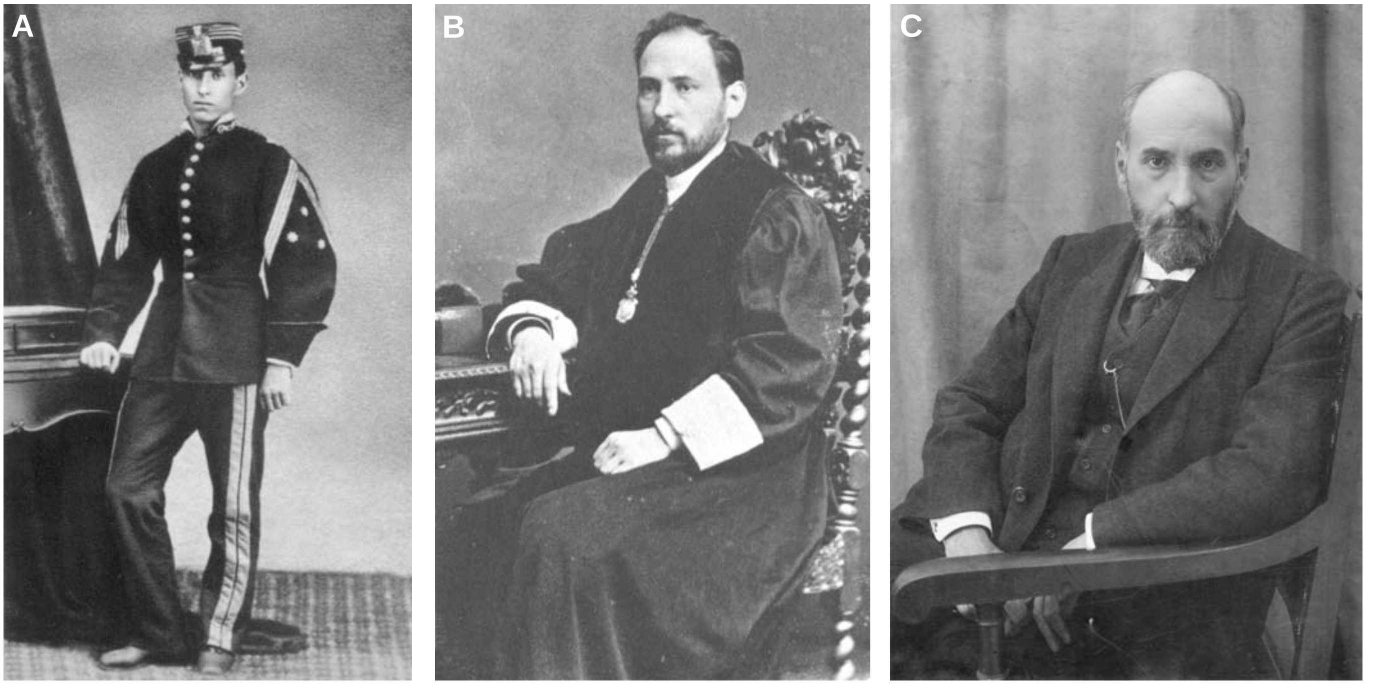

Fig. 12. Portraits of Santiago Ramón y Cajal (1852-1934). (A) *As captain of the Spanish Army Medical Corps (1874);* **(B)** *dressed in his academic suit as professor of Histology at the University of Barcelona (1887) and* **(C)** *in the year he received the Nobel Price for Medicine (1906).*

publiqué mi estudio las *Condiciones de verdad de la Imagen microscópica*, y que ya no causará extrañeza el que un español pueda escribir de asuntos del microscopio. El entonces Secretario de la Real Sociedad de Microscopia de Londres, Mr. Crisp, decía así al dar cuenta de mi trabajo: *"We were not a little surprised to receive lately an elaborate discussion on Aperture and Microscopical Vision written in Spanish which we should have supposed to be one of the most unlikely language of the Western Europe in which such a subject would be treated of. It is from the pen of D. Joaquin María Castellarnau y de Lleopart, who in other papers previously published has shown himself to be much in advance of the majority of his countrymen…"*

Fig. 13. Luis Simarro-Lacabra (1851-1921) *working in his private laboratory with students and collaborators. Painting entitled* Una investigación *by Joaquin Sorolla, friend of Simarro (1897).*

The initiation of Santiago Ramon y Cajal (1852-1934) in Histology

Our essay has the obvious goal to establish how much of the European scientific movement had been introduced in Spain when Santiago Ramón y Cajal (Fig. 12) was able to perform his titanic work in our country. Nevertheless, it is logical to extend our review to the times when he was beginning his training and his work. Born in 1852 in Petilla de Aragón in a humble family, Cajal overcame his difficult origin in a relatively retarded part of Spain due to the strong determination of his father, a former barber surgeon that did not gave up also his own goal of becoming a physician, finally obtaining the corresponding degree in Valencia in 1862 and settled first in a series of villages in Aragon and later in Saragossa in 1870. In a similar way as it has been described in the case of Pasteur, Cajal was a difficult and mediocre student, attracted to artistic practices such as drawing, in which he was strongly opposed by his father. Cajal became interested in learning photography during his early years. Both hobbies were much later, at least in the case of Cajal, fundamental for his scientific activities.

Having completed his secondary education in Huesca in 1869, he registered at the *Free School of Medicine* in Saragossa in September 1969. These were turbulent politic years in Spain. As a consequence of the liberty during these years, free Schools of Medicine sprang in many places in Spain. After graduating in 1873, he joint, after competitive exams, the Spanish *Army Medical Corp*, participating in the end of the *Third Carlist Civil War* and in the war against the revolts the in the still Spanish Cuba as Medical Captain (Fig. 12). There, he contracted malaria and dysentery and had to be discharged from the active service and sent back to Spain, now determined to pursue an academic career in Anatomy. For this purpose, he received his doctorate from the University of Madrid in 1877, becoming professor extraordinary of Anatomy the same year. During his trips to Madrid, he visited often the laboratory of Aureliano Maestre de San Juan, where especially Leopoldo López-García guided him in his autodidactic training in Histology. As already mentioned, López-García himself had been trained in Paris in Louis Ranvier laboratory. It was at his return from Madrid, when Cajal began his histological studies in a private micrographical laboratory that he mounted at home in Saragossa. With his scarce resources, he bought a *Verick* Microscope and a *Ranvier* microtome. It is interesting to cite the list of books he purchased at this time: Henle´s *Anatomie Génerale* and Frey´s *Histologie et Histochemie* in French translations, the French books on the subject by E. M Van Kempen´s and Ch. Robin and for the technical part, Beale´s *The Microscope in Medicine* as well as Latteux´s *Manuel Technique*. He subscribed to two Journals, the English *Quaterly´s microscopical Science* and the French *Journal de Micrographie*. Among them, Van Kempen´s treaty is interesting since it incorporated the main concepts developed by German schools. He was professor in Louvain (Belgium) and originally trained by Th. Schwann during his years in this University, before moving to Liege. The book provides information on the posterior views of Schwann about the developments that he so much had helped to initiate. In 1879 Cajal became head of the *Anatomical Museum* in Saragossa and, finally, after a second attempt, he was appointed in 1884 to a chair of Anatomy this time in Valencia, remaining there until 1887. During these years, he explored several possible scientific disciplines, such as Bacteriology and vaccination (in 1885, the last big cholera epidemics affected Spain) and Comparative Anatomy in which he did not had such a good background as in Histology. Possibly for this reason, he moved back to histological work. His visit to the Madrid laboratories in 1888 and his contact with Luis Simarro Lacabra (1851-1921) was decisive. Simarro, born in Valencia and trained in his Medical School during his *Golden Age* (1868-1873), had been also later student of Louis A. Ranvier (1835-1922) in Paris (Kaplan 1969). He showed to Cajal the first preparations of the Golgi technique and the Weigert-Pal technique for staining myelin (Fig. 13). With this and his own background in photography, Cajal jumped into the field of the silver staining techniques that proved crucial to the advancement of the information on the nervous system and provided the final piece completing the *Cell Theory*, demonstrating that neurons were not forming a reticulum, as still defended by many scientists in Europe, including C. Golgi himself, but were also single isolated cells that strongly interacted with other cells in different parts of the body (Albarracín 1978, Fernández-Santarén *et al.,* 2006, Laín-Entralgo 1961, 1978, López-Piñero 2006, Marañón 1951, Mazzarello *et al.,* 2006, Vera-Sempere 2001). Th Spanish School of Neurohistology, initiated by Ramón y Cajal (Fig. 14) laid the ground work of our present knowledge of the microscopic anatomy and pathology of the nervous system. Cajal had particular interest in the embryonic development of the nervous system (see Puelles, 2009).

The weaknesses of the Recovery

The situation of the University in Spain remained tight up by the XIX Century legislation and the adherence to the French model. The growth and the strengthening of the research structures continued during the first third of the XX Century. Nevertheless, it was a difficult and unequal race since the stronger countries in the World continued to grow, new countries like the United States, Japan, etc. continuously arrive and the distance separating Spain from them remained large. The situation in Spain was broken again by the *Civil War of 1936-39* and the difficult post-ward period. The *Second World War (1939-1945)* also produced a discontinuity in the growth of research in all developed countries, but after its conclusion, the growth and the intellectual effort was renewed with increasing strength. The recovery in Spain, although initiated in 1950s, was insufficient to breach the distance that had widened again enormously.

In Spanish we say *a la tercera va la vencida* (the third attempt is the winning) We are once more trying to become part of the advanced nucleus of Science and Technology in the world. The challenges are enormous and few people, certainly not yet our politicians, understand which will be the new objectives of the scientific movement in the XXI Century. Competition from powerful and populous societies is going to be increasingly hard. This time hopefully there are no internal forces capable of stopping the

Fig. 14. Studio photograph of a simulated autopsy by Santiago Ramón y Cajal. *Two very representative disciples of his were Nicolás Achúcarro (1880-1918), third from the right (smiling), and J. Francisco Tello (1880-1958), in light grey coat, second from the right.*

movement as in previous times; this is the current challenge for our national scientific community and for our political leaders. The more general quantitative indicators support this contention, but..have we really achieved the right place among the leading agents in Science and Technology? And, as importantly, are we heading in the same direction that the new countries joining the race? Many of the structural weaknesses of our previous Science system have not been totally removed and we are still far to be part of the advanced nucleus of research and development in the world. Lets expect that the still very difficult objective of becoming part of the more advanced and progressive scientific and technological movement in the world is finally successful in XXI century Spain!

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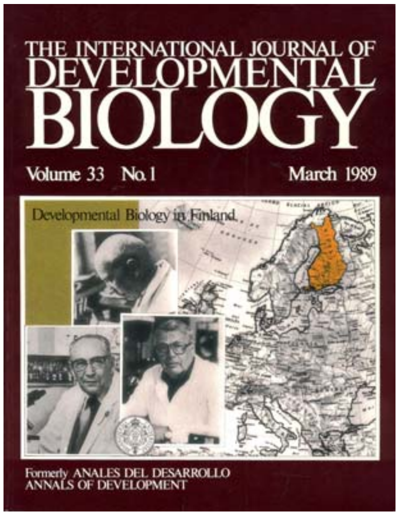

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