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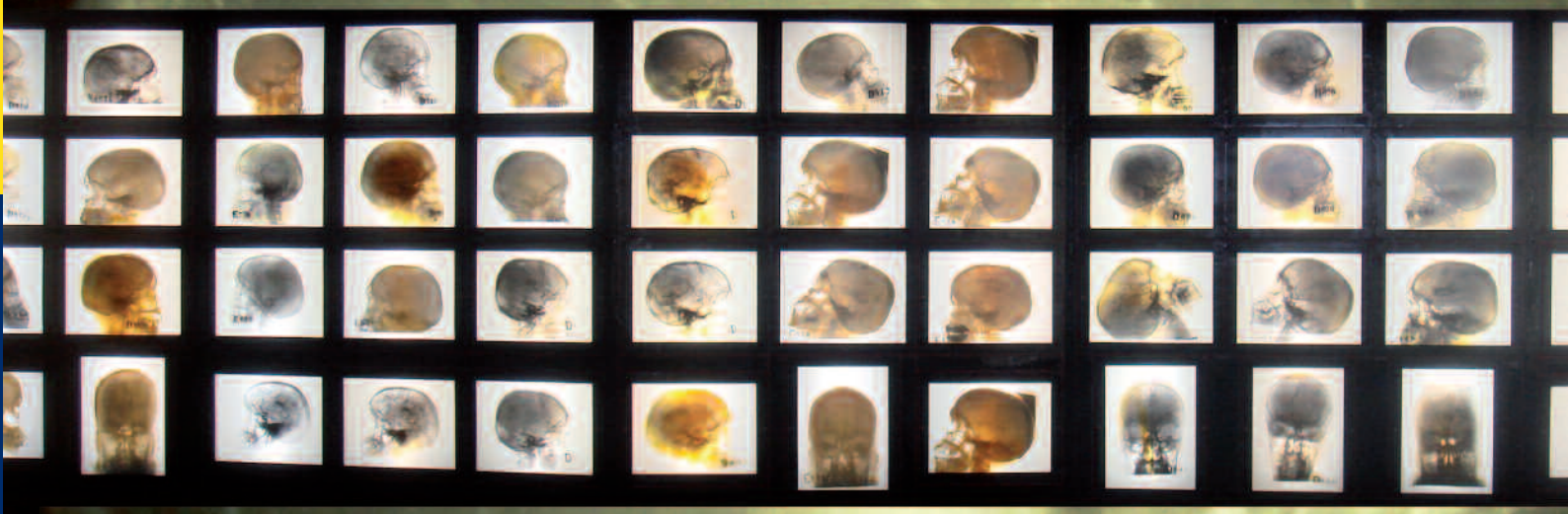
Publicação da Sociedade Portuguesa de Neurologia

SUPLEMENTO 1 | Volume 11 | Nº1 | Maio de 2011

100 YEARS OF PORTUGUESE NEUROLOGY



1911-2011

Sinapse®

Publicação da Sociedade Portuguesa de Neurologia

Órgão oficial de: Sociedade Portuguesa de Neurologia; Grupo de Estudos de Envelhecimento Cerebral e Demências;Grupo de Estudos de Esclerose Múltipla; Liga Portuguesa Contra a Epilepsia; Secção da Neurologia do Comportamento da SPN; Sociedade Portuguesa de Cefaleias; Sociedade Portuguesa de Doenças do Movimento; Sociedade Portuguesa de Estudos de Doenças Neuromusculares; Sociedade Portuguesa de Neurocirurgia; Sociedade Portuguesa de Neuropatologia; Sociedade Portuguesa de Neuropediatria

Versão electrónica: www.spneurologia.com
Indexada nas bases bibliográficas: EMBASE / Excerpta Medica Database (Elsevier), SCOPUS (Elsevier), www.indexrmp.com

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Design: Isabel Monteiro, Next Color – Sol. Digitais, Lda., Porto
Produção gráfica: Multitema – Sol. de Impressão, S.A., Porto
Produção da versão electrónica: CGMdesign.NET

Propriedade: Sociedade Portuguesa de Neurologia
Registo de Marca: 358 268
(Instituto Nacional de Propriedade Industrial)
ISSN: 1645-281X
Depósito Legal: 172 674/01
Tiragem: 600 exemplares
Edição: Publicação semestral;
SUPLEMENTO 1 - Volume 11 – Número 1 – Maio de 2011
Preço unitário: €10; **Assinatura anual:** €15

Editorial

One hundred years of Neurology is for sure a date to remember and celebrate.

In fact the first university chair devoted to neurology was created in Portugal by decree of the new republican regime in February 1911. This was just four months after the collapse of monarchy (October 5, 1910) and shows the concern of politicians with medical education. Among the parliament representatives at that time, were a significant number of physicians including the most influential who were aware of the medical developments in Europe.

The political influence of Professor Egas Moniz was determinant for the creation of the chair of Neurology at Santa Martha School Hospital in Lisbon and latter, his pioneering work on angiography was also determining in the foundation of the first department of neurosurgery in the Iberian Peninsula.

One hundred years may not seem a long time for a country with nine hundred years of history and reviewing our past we should not forget other distinguished Portuguese physicians, some of whom are known only by the name of a street, a school or a hospital.

Pedro Julião also known as "Pedro Hispano" (Peter of the Spains) was born in Lisbon circa 1226 and made a double career being a physician and priest and died in Viterbo (Italy) in 1277. He was appointed as principal physician (*archiathros*) to Pope Gregory X and finally he himself became Pope as "John XXI." Pedro Hispano is the only Pope in history who was also a physician.

His legacy was perpetuated in the book "Liber de Conservanda Sanitate" where he states that disease prevention is better than cure.

Garcia de Orta (1501-1568) was a physician who dedicated his life to clinical practice in India during the golden age of Portuguese discoveries. He moved to Goa (India) and there he remained until his death. His main contribution was the study of the effects of medical herbs in the book "Coloquium of the Simple and Drugs of India" were he made an extensive description of many Indian plants with therapeutic properties.

More recently Ribeiro Sanches (1699-1783) achieved a European reputation. He made his studies at Coimbra, Salamanca and Leiden (with Boerhaave). He was physician for Czarine Ana Ivanova in St.Petersburg and was appointed to the most respected European scientific societies.

At present Neurology in Portugal is practiced aiming the most developed standards and in this brochure we try to establish a link between the past, the present and future of the Portuguese Neurology.

Vitor Oliveira
President of the
Sociedade Portuguesa de Neurologia


CITOMAS—EPENDIMOMAS
QUISTO HIDÁTICO — ABCESSO
COLESTEATOMAS — HEMATOMAS SUBDURAIS

PAST AND PRESENT

Cloister of the School Hospital of Santa Martha, Lisbon

One hundred years of Portuguese Neurology

Vitor Oliveira

Although some Portuguese physicians devoted interest to neurology since the end of XIX century it was in early XX that neurology achieved the attention and made the first neurologists as so.

Portugal in the track of European Medical Science.

Medicine at the western end of Europe was agitated in 1906 when Portugal harboured the XV International Congress of Medicine held in Lisbon in April 1906, after the well succeeded efforts of Dr. Miguel Bombarda Professor at Medical-Surgical School of Lisbon and director of the Psychiatry Hospital *Rilhafoles* in Lisbon, who submitted the application of Lisbon at the previous congress that took place in Madrid in 1903.

He took full charge of the organisation of the event as General-Secretary of the congress.

O amphitheatro das projecções durante uma conferencia

Portugal was at that time out of the tracks of medical events and the distance from the heart of Europe was reflected in an old fashioned practice.

The XV International Congress of Medicine brought to Lisbon 1762 delegates from 35 countries. More than 500 communications were presented distributed by 17 sections.

The 7th session was devoted to: Neurology, Psychiatry and Criminal Anthropology, were the subjects of dementia, paranoia, anthropology and medical-legal aspects were discussed.

With this event many young Portuguese physicians and students got contact with the advances of medicine and so disclosed the new era of scientific development.

Contacts and future relationships were established at that time.

In that same year of 1906 the young Portuguese doctor António Flores left Portugal to acquire expertise in Neurology in Germany with well names of neurology such as Alzheimer, the couple Vogt and Forester.

He returned in 1911 and was a mainstay in the teaching of Neurology at the Faculty of Medicine in Lisbon.

Since 1902 another well known name of Portuguese physician (Egas Moniz) spent his summer holidays in France to learn Psychiatry and Neurology first with Souques in Bordeaux and then in Paris at Salpétrière with Babinski and other French neurologists.

In October 5, 1910 Republic replaced the monarchic regimen. Professor Bombarda who organized the 1906 congress in Lisbon was one the most active republican leaders, unfortunately he was shooted to dead by one of his patients precisely the day before the revolution.

His name was given to his psychiatric hospital and to an avenue in Lisbon.

With the new regimen the Medical-Surgical Schools of Lisbon and Oporto were switched to the Faculties of Medicine (1911) and a new era of development in medicine began.

School Hospital Santa Martha. Ward of Neurology was located on the first floor.

Before this, only the University of Coimbra, created in 1290, one of the older universities in the world, harboured a course of Medicine in a department that held the title of "Faculty of Medicine"

In Lisbon this was the most important period of Portuguese medicine of the XX century, with the so-called "1911 Generation".

Many professors in different fields of medicine spread their teachings and mainly their method to future generations of teachers and practitioners.

(School Hospital of Santa Marta (Faculty of Medicine since 1911 to 1953)

The first Service of Neurology in Portugal where Egas Moniz worked and where angiography was developed.

In this brochure we aimed to point out Portuguese contribution to the Neurology since the creation of the first service and chair of Neurology (1911), to date. ■

Egas Moniz

Vitor Oliveira

António Caetano de Abreu Freire **Egas Moniz** (Avanca 1874-Lisboa 1955) is unquestionably the best knonw figure of portuguese neurology and even portuguese medicine.

Graduated at Coimbra Faculty of Medicine (1899) he divided the first two decades of XX century between politics and medicine. In politics the reached the places of leader of Parliament, Minister of Foreign Affairs and President of the portuguese delegation at the Peace Conference in Versailles (1918-1919). In medicine he created the first chair and service of neurology in Portugal.

Since 1902 he visited regularly Salpétrière and other neurological clinics in Paris.

Disillusioned with politics he returned to his Hospital in Lisbon and dedicated to the puzzling issue of the diagnosis of intracranial tumours. He wondered if it will be possible to conceive a method that even indirectly could identify space occuping lesions as it was seen with myelography.

He decided to study the possibility to inject the intracranial circulation with an harmless product opaque to X Ray in order to suspect the location of a tumour by the distortion of the vessels.

By opacifiing intracranial vessels with iodine solution he was able to visualize intracranial circulation in vivo for the first time in June 1927. In his patient's brain vessels were distorted by a pituitary tumour, latter on confirmed at autopsy.

Soon after he realised that angiography was useful not only to identify tumours by the distorted position and abnormal vessels but the intracranial vessels deserved themselves to be studied.

He described the "S" shaped appearance of intracranial carotid segment named after him as "Siphon" .Many different abnormalities were then identified: Carotid bifurcation, stenosis and occlusions, intracranial arterial occlusions, aneurysms, vasculitis, arterio-venous malformations etc.

Angiography was also used in other territories namely aorta (Reynaldo dos Santos), lungs and limbs.

Latter, Egas Moniz described a series of surgical attempts to treat agitated psychiatric patients through the so called "Leucotomy".

This procedure was abandoned after the first anti-psychotic drug (Chlorpromazine) was synthesized (1950).

Moniz published more than three hundred papers and several books not only on scientific subjects but also in fields of literature and few auto-biographic volumes.

Performing an angiogram about 1940 at Hospital Escolar de Sta Martha - Lisbon.

He was awarded with many distinctions worldwide being the Noble prize in 1949 shared with Rudolf Hess the most relevant one. ■

João Afonso Cid dos Santos
(1907-1975)

Vitor Oliveira

Professor and chair of Surgery at Faculty of Medicine in Lisbon. He was son of Professor Reynaldo dos Santos (1880-1970) a prominent surgeon and also Professor at the Faculty of Medicine in Lisbon., remembered as the inventor of Aortography by injecting contrast media directly in aorta. He was also an expert in art with a monumental work published "Eight Centuries of Portuguese Art" among many other titles.

Not being a neurologist Cid dos Santos gave an important contribution to the progress of neurology by discovering endarterectomy.

In August 1944 Cid dos Santos operated a 66 year-old male with a critic limb ischemia and renal failure. He attempted to perform a thrombectomy of the superficial femoral artery under heparin aiming to remove the thrombus by finding a plane of dissection between the thrombus and the intima. By accident he removed intima and media with the thrombus and the unexpected occurred: blood flew normally through over the muscular layer without any complication. "It seemed unbelievable!" he wrote.

This finding destroyed the previous assumption that blood would clot while running out of the intima, over the muscular layer. He coined the procedure as "disobliteration" but latter it was called endarterectomy (Razy) and thrombendarterectomy (Leriche).

This procedure was latter used to disobliterate carotid stenosis. The first operation was performed in 1953 at the Methodist Hospital by deBakey and the first paper published reporting this procedure appeared in The Lancet in 1954 by Felix Eastcott, from the St Mary's Hospital, London.

Carotid endarterectomy continues to be the first choice procedure for symptomatic carotid stenosis.

He died suddenly at 68 years of age.

As Connoly and Price wrote: "The beginning of modern vascular surgery received its greatest impetus on August 27, 1946, when Cid dos Santos performed the first thromboendarterectomy with the aid of untried heparin". ■

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Corino de Andrade
(1906-2005)

Familial Amyloidotic Polyneuropathy and beyond

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Hospital de Santo António and Instituto de Ciências Biomédicas Abel Salazar,
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Mário Corino da Costa Andrade, known as Corino de Andrade, was a clinical neurologist and is most often remembered for his description of Familial Amyloidotic Polyneuropathy (FAP-I) in 1952[1]. He was born in Moura (Alentejo, Portugal) on June 10, 1906, son of Francisco Andrade (veterinarian from Goa, Portuguese India) and Amélia Alves (housewife from Beja, Portugal).

Corino de Andrade lived through the 20th century, witnessing and experiencing significant events. He faced many difficulties, fought consistently and obtained results. He built a "Neurology School" from the ground up, discovered and named an illness. His life is documented in a biography[2] and articles written by physicians[3-17], scientists[18, 19, 20] and intellectuals[21, 22].

Lisbon, Strasbourg and Berlin.

Corino de Andrade attended the Lisbon Faculty of Medicine from 1923 to 1929. He came into contact with Egas Moniz (1874-1955) and Almeida Lima (1903-1985), at Hospital de Santa Marta in Lisbon, but it was António Flores (1883-1957) who sparked his love for neurology and his will to train abroad.

In 1931 Corino de Andrade began a six-year residency with Jean-Alexander Barré (1880-1967), in Strasbourg. He dedicated his work to neuropathology, especially focusing on the meninges. In 1993 he became the first non-French researcher to win the Dejerine Prize. Shortly afterward he was appointed head of the Neuropathology laboratory.

Corino de Andrade won the Dejerine Award in 1933. Next to him are Jean Alexander Barré and Sorrel-Dejerine, daughter of Joseph Julles Dejerine (1849-1917) and Marie Augusta Dejerine-Klumpke (1859-1927).

He moved to Berlin, in 1936, where he studied with Cécile Mugnier Vogt (1875-1972) and Oskar Vogt (1870-1959). His father died in 1938. He took on his family responsibilities and decided to return to Portugal. There was no place for him at Hospital de Santa Marta. Probably, it was, once again, António Flores who suggested a career path.

Porto, the early days.

He arrived in Porto in the summer of 1938 with letters of recommendation from Barré and Vogt. There had never been a Neurology department in the city. In spite of this, he was not welcomed by the Faculty of Medicine.

Corino de Andrade strengthened his friendship with mathematician Ruy Luís Gomes (1905-1984), who introduced him to Porto's intellectual milieu, including Abel Salazar (1889-1946), histology professor, essayist and plastic artist, dismissed from the university due to the "inconvenience of his political and social action".

Corino de Andrade was hired as head of the "Infirmary of the Filthy and Agitated Patients" of Hospital de Alienados do Conde Ferreira. He simultaneously began to visit Hospital Geral de Santo António (HGSA). He met the individual who would become his first resident and right-hand man, João Resende (1913-2003). In January 1939 he signed a six months unpaid contract with HGSA. He created a biweekly Neurology clinic in a room borrowed from the Homeopathy Department.

An intriguing disease.

In 1939 Corino de Andrade was saddened by the dismissal of his friends (the Vogts) from the Kaiser-Wilhelm Institut für Hirnforschung, who were replaced by the Third Reich scientists Julius Hallervorden (1882-1965) and Hugo Spatz (1888-1969). During that year, at the request of Américo Graça (1902-1972), he observed a woman from Póvoa de Varzim, a fishing town near Porto, with an intriguing and complex neuropathy. During the following decade he frequently visited the north Atlantic coastal villages to observe families afflicted with a peripheral neuropathy that the locals called "doença

dos pezinhos" (foot disease). At one point he considered an environmental etiology, describing in detail the fishermen's extremely poor eating habits, but he soon discovered the hereditary nature of the disease.

Events and achievements in wartime.

In 1940 he created the Department of Neurology at HGSA. During that decade he worked with João Resende, Jorge Campos, Pereira Guedes and Castro Alves. He promoted the first neurosurgical interventions with the help of general surgeons and orthopedists. João Resende described his polyvalent work this way: "I was Corino de Andrade's assistant during the difficult early days of neurosurgery (struggling against a structural aversion to these kinds of activities). I also improvised as a neuroradiologist (percutaneous carotid angiographies, gaseous encephalographies, myelographies) and performed autopsies".[3]

Corino de Andrade remained close to the Egas Moniz team, going to Lisbon by train on weekends to observe surgeries performed by Almeida Lima (1903-1985) and Gama Imaginário (1909-1970).

In the meantime, he continued to study the new polyneuropathy. In 1943 João Resende conducted an autopsy and Corino de Andrade took the organs to Lisbon, carefully packed in cookie boxes. Histologist Silva Horta (1907-1989), identified the amyloid substance. The nature of the disease had been unveiled.

In 1944 Corino de Andrade married Juliette Möes, a Luxembourgian pediatrician, he had met in Strasbourg. She had fled the war, entering Portugal as a stateless person. Juliette died in 1945 while giving birth to her first son, José Miguel.

On his 38th birthday Corino de Andrade denounced the formalism of medical education on a radio broadcast: "Book based education creates cultural pedants who are unable to face concrete and real life problems."

Postwar: a concerned citizen and hospital clinician in his prime.

In the postwar period he collaborated with the MUD (Democratic Unity Movement), as a scientific advisor. Mário Soares wrote about those times: "He was a discreet man, friendly, always listened to us attentively, as if we were his equal."[22] In 1946 Abel Salazar died; his beliefs had a major impact on Corino de Andrade and influenced his future projects.

In 1948 Corino de Andrade married Gwendoline Gething (1914-1983), an English teacher, later known in Porto as Mrs. Gwen Andrade, director of the British Council. The couple would have two children: Amália (1949) and Carlos (1954).

He made friends within the Lisbon School, particularly Miller Guerra (1912-1993) and João Alfredo Lobo Antunes (1915- 2004). Writer António Lobo Antunes, son of João Alfredo, remembered his visits:[21]

"We knew he was arriving because of the telephone ringing at seven in the morning which woke up the entire house. Between the telephone rings we could hear my father's steps going from the bedroom to the living room, sleepily tripping along the way and his furious voice uttering,'I bet it's that pain in the neck Corino', and he would pick up the receiver and to my surprise the voice would go from furious to enthusiastic in a surprising metamorphosis: 'You're here? What a surprise!'"

In 1951 a "peculiar form of peripheral neuropathy" was publicly introduced. António Flores proposed the eponymous name of "Corino de Andrade Para-Amyloidosis".

During one of his returns from Lisbon, he was arrested by the PIDE (political secret police) at São Bento railway station. He remained in prison for several months without a trial. In Christmas of 1951, still in prison, he received a letter from Egas Moniz: "And all this happening when you were about to present in Paris one of the best clinical works ever conducted in Portugal, one that will immortalize your name! But what can we do? Now they're after the doctors. Absolutely horrible!"

Gwen Andrade and Lobo Antunes translated the original text into English and in 1952 it was published in *Brain*. "A Peculiar Form of Peripheral Neuropathy"[1] remains one of the most highly cited papers from a Portuguese author.

In the beginning of the 1950's Corino de Andrade and João Resende were alone in the field. They then received help from Rocha e Melo (1923-2007) and António Coimbra.

Reanimation and trauma: foreseeing the future.

In 1961 Corino de Andrade promoted the "Lecture on Provoked Hypothermia" motivated "by the varied and rich perspectives of its application to clinical and surgical practice and even to science fiction literature". The following year he founded the Respiratory Reanimation Centre. In 1964 he hosted the International Meeting of Respiratory Reanimation with the presence of Maurice Cara (1917-2009), creator of the mobile reanimation service. Also in the 1960's, Corino de Andrade launched a rescue project for the streets of Porto that was subsequently vetoed by the police hierarchy. In 1967 he created the Cranioencephalic Trauma Unit. He defended the legalization of the concept of brain death and speculated on the future challenges of transplantation: "We must accept the possibility that, in an already dead individual, there are human structures that have their own circulation, or not, in an already dead individual."

Port of call.

During the 60's and 70's the Department of Neurology began to grow on the basis of young volunteer doctors attracted by fame or by the master's charisma. In the words of Paula Coutinho, "It was like a port of call. Many would arrive. Many would leave too. (…) A sort of natural selection took place"[5]. Corino de Andrade maintained privileged relations with many other doctors from the hospital, especially important to the advent of Neuroanesthesia and Respiratory Reanimation. In the beginning of the 1970's he headed the Centro de Estudos de Paramiloidose and defended the creation of centres for genetic diseases because "little by little hereditary illnesses will become avoidable illnesses".

Corino de Andrade's heterogeneous staff, in 1968. In the first row, Pinho Costa (Researcher), João Resende (Neurologist), Corino de Andrade, Paula Coutinho (Neurology resident) and Rocha e Melo (Neurosurgeon).

Retirement and new challenges

For several years, Corino de Andrade had been planning a biomedical research institute, inspired by the thinking of Abel Salazar. In 1975, a few months after the democratic revolution, he worked on the committee for creating the Instituto de Ciências Biomédicas Abel Salazar (ICBAS), together with Ruy Luís Gomes (Dean of the University of Porto), Nuno Grande, Aloísio Coelho, João Monjardino, Neves Real and Pereira Guedes. He became the ICBAS's scientific mentor for the rest of his active life. For thirty years, he followed up on the development of the ICBAS scientific and other academic fields: Medicine, Aquatic Sciences, Veterinary Medicine, Biochemistry and Bioengineering. He was able to witness the ICBAS popularity among young university applicants and the progress of biomedical research programmes.

In 1976 he retired from the hospital. During that year he accompanied Paula Coutinho to the Islands of the Azores, taking part in the field work that helped define a new spinocerebellar ataxia (future Machado-Joseph Disease/ SCA3).

He inspired strong biomedical groups and several lines of research around FAP-I and SCA3. Up until the 1990's he remained linked to the work being developed at the Centro de Estudos de Paramiloidose and ICBAS. He had the privilege of describing a new disease (FAP-I), confirming its genetic nature, and witnessing proactively seven decades of progress: identification of the amyloid, abnormal transthyretin and mutation cause (TTRV30M); hepatic transplantation; development of preventive genetics; advent of pharmacological strategies.

He always paid great attention to people and teams, never seeking easy popularity or privileges. António Coimbra stated: "He had always worked for free at the hospital and for that reason he had a meagre pension, he never owned a car or a house."[9] However, Corino de Andrade's work and approach were recognized by society. His clinical life and civic action received tributes and honours awarded by universities, municipalities, foundations and scientific societies. The Portuguese Republic awarded him the "Ordem de Sant'lago de Espada" (Grand Officer) and the "Ordem de Mérito" (Grand Cross).

Corino de Andrade died at his home in Porto on June 16, 2005, at the age of 99. Paula Coutinho was able to identify unmistakable traits of Corino de Andrade among the small crowd of people present at the farewell ceremony, describing them elegantly: "I'll never forget when Dr. Corino died, the walk to the crematorium on a sunny morning along the 'Prado do Repouso'. Not too many people were there, but it was an enormously rich group of people, very diverse, of all ages and classes, no one dressed in mourning attire, almost no crying. Everyone had a good story about Dr. Corino, many people whose lives he had certainly changed in some way: a timely gesture of sorts, a great conversation or a good swift kick in the behind. It was wonderful being out there in the sunshine, with the breeze blowing across the river, watching the people passing, meeting, talking and smiling. Anyone who knew these people and understood who they really were would see this was an extraordinary product of life"[17]. ■

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SINAPSE: Centennial of Corino de Andrade

Photo courtesy:
Andrade's Family: 1; Luís de Carvalho: 2.

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You know that in the impossibility to reach perfection I always looked for precision!
Fernando Tomé

For those who know Professor Fernando Tomé, those few words define his personality.

While reading his CV, I understood the life of a man somehow nomadic, beginning his journey from the small village of Vila Nova de Foz Côa where he was born in 1933. He graduated at the University of Lisbon Medical School (Faculdade de Medicina – Universidade de Lisboa) in 1958. He made Lisbon his residency and remained as a neurologist at Hospital Santa Maria in Lisbon until 1969 when he left Portugal. Philosophy and literature were two of his passions. During his residency in Neurology he took a course of philosophy at the University of Lisbon but he had to quit in order to devote full time to medicine. Nevertheless his humanistic values were kept up in the field of his intellectual curiosity.

As he said in a speech in 1998, when he received the french decoration of *Chevalier de l'Ordre National du Mérite* : *"Je ne prétends pas que mon âme soit plus grande que mon corps ne le laisserait croire, mais j'ai toujours essayé de l'agrandir en suivant l'exemple, les enseignements, les bonnes paroles, de ceux qui m'ont élevé (mon père, ma mère, ma tante préférée - que j'évoque avec tendresse), et de ceux qui m'ont formé, soit mes maîtres à Lisbonne (en particulier deux dont je tiens à dire le nom: Miller Guerra et Lobo Antunes), soit mes maîtres à Queens Square (et je ne cite que Bill Mair, sans lequel rien n'aurait été possible). Ils m'ont inculqué des principes, l'exigence morale et l'amour du travail. Ils m'ont fait comprendre que dans la vie, comme dans la clinique ou au laboratoire le but à atteindre était celui de l'excellence.*

In his academic career, out of Portugal, Professor Fernando Tomé attained the position of Assistant Professor of Neuropathology at the Institute of Neurology – Queen Square in London. There he began to dedicate his attention for the study of the peripheral nervous system.

He learned with Bill Mair and with him published an Atlas on the *Ultrastructure of Diseased Human Muscle* (WGP Mair and FMS Tomé), one of the rare atlases in this field. In 1973 he obtained his PhD at the University of London.

In 1971 he attended a fellowship in France at the Risler Departement of the Hôpital de la Salpétrière with Michel Fardeau beginning a partnership that remains to this day.

In France he made a successful career:

INSERM (Institut National de la Recherche et de la Santé Médicale):"Chargé de Recherche" at unit 106 (1973-1976) and unit 153 (1976 - 1981). "Maître de Recherche" (DR2) INSERM na Unit153 (1982-1993) e latter "Directeur de Recherche" (DR1) (1994-1998).

His name is related to the description of tubular inclusions in oculo-pharyngeal Dystrophy (1980) and a large number of papers about sarcoglycoproteins, congenital muscular dystrophy with deficiency in merosin.

He has published more than 150 scientific articles, written numerous chapters in scientific books and received many prizes: The INSERM-Academy of Sciences Award (Paris) in 1995, The Gaetano Conte Academy (Naples) Basic Research Prize em 1997, The Peter Emil Becker Prize in 1998, The "Dedication Prize" of the "Sociedade Portuguesa de Estudos de Doenças Neuromusculares" in 2003 and The "Lifetime Achievement Award" at the X International Congress on Neuromuscular Diseases (2006).

Prof. Fernando Tomé with colleagues (first row in dark jacket)

He was a member of the Advisory Board of the INSERM and of the scientific committee of the "Association Française contre les Myopathies – AFM", and of the *editorial board of several scientific journals such as Clinical Neuropathology, Acta Neuropathologica e Acta Neurologica Scandinavica. He was also associated editor of Neuropathology; Applied Neurobiology, Neuromuscular Disorders and Acta Myologica.* ■

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About the identification and research of Machado-Joseph disease in Portugal

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The first families

The official story of Machado-Joseph disease is relatively recent. It began in the 70s by the description of two large American families of Azorean origin. The first was the Machado family[1]. All its members descended from William (Guilherme) Machado who lived in Bretanha, in the Northeast of S. Miguel Island. Some of his 13 children migrated to Massachusetts in the 19th century, 9 of them were affected. The family's disease was described and published in 1972, as a late-onset cerebellar ataxia associated with a peripheral neuropathy. Meanwhile, another family of Azorean ascendancy was beginning to be studied in the West coast[2]. They all descended from António José Bastiana, who had migrated from the Island of Flores, in a whaler boat, to North of S. Francisco, in California, around 1815. He got rid of his difficult family name, and was thereafter called Anton Joseph. In the Joseph family, the disease began rather early, under the form of generalized spasticity and dystonia, the cerebellar ataxia being seldom mentioned. Therefore, the two entities, both affecting families of Azorean descent, both transmitted as autosomal dominant traits, were fiercely considered as different entities both by family members and a few, but influent, American neurologists. In part because of this controversy, in part because of the considerable influence of family members lay associations, a vibrant controversy rose and got to the press. It raised the attention of the Portuguese Ambassador in Washington, who sent a note the health authorities in Lisbon. That's how Arnaldo Sampaio, by then the major Public Health authority in Portugal, invited Corino Andrade to go the Azores and put some order in these sparse information of these diseases "exported" from the Azores to the States.

Fieldwork in the Azores

I had the chance of participating in all expeditions to the Azores, the very first in February 1975, and the following in subsequent years until 1994. With very little money to spend, and no commercial flights for many of the islands, we used, through the influence of President Eanes, Portuguese and French military old airplanes to and between islands in the Azores. There was at the time a French military base in Flores – *La Station Française de Mesures* – that gave us accommodation and food. Most employees of the French Mess volunteered to give us information about the disease and affected persons, some of them belonging to affected families. We opened a free consultation every morning at the French Hospital, and all kinds of neurological diseases began to appear, mainly patients with this at the time odd disease. Family trees were drawn (occasionally the families were so big that we used the back of MFA Movement posters, at the time very popular). In the afternoon we visited older or renitent members of the families at home. During many years, we returned to the Azores, involving other neurologists and a young candidate to neurogenetics (Jorge Sequeiros), establishing the epidemiologic pattern: many affected families in Flores and S. Miguel, no families in the other islands, with just one exception, in Graciosa. The same peculiar patchy distribution was to be found, years later, in the mainland.

The unification and the name of the disease

Ignoring previous reports, we were able to examine, without any prejudice, many patients in many families with extremely variable clinical expression, covering in fact the clinical spectrum described. It was probably the innocence of our approach that allowed a free, non-prejudiced analysis and the subsequent clinical grouping.

Little by little, the puzzle began to make sense: we examined young patients with very severe dystonic and spastic picture, older patients with the ataxic and neuropathic picture of Machado family. And when we arrived, after Flores, to S. Miguel, we saw members of the Machado family in Bretanha with the Joseph severe phenotype. By a chain of hazards, by the end of the Seventies we were able to examine the first mainland family that included all the clinical types we had seen in different families: young, very severe dystonic patients, middle-aged cerebellar patients and old cerebellar and neuropathic patients. So the circle was closed[3,4]. Meanwhile, the first post-mortem study was obtained[5], confirming a multisystem involvement centred in the basal ganglia and brainstem, relatively sparing the cerebellar cortex.

In the first meeting on the disease at the Gulbenkian Foundation (the "International Symposium on Autosomal Dominant Motor System Disorders in Persons of Portuguese Ancestry", (and this long vague label still translated the general feeling…), Jorge Sequeiros and I proposed the name Machado-Joseph disease (MJD)[6], gathering the first and the largest families described, the East and the West coasts in the States, the two affected Islands in the Azores, Flores and S. Miguel. The name was approved, not without many discussions and pacifications. Now it corresponds to a single name and number – SCA3 (spinocerebellar atrophy 3, by order of gene identification).

Molecular studies: the gene and its functions

Since the second travel to the Azores and along the subsequent travels, blood samples were collected from all willing members of the families, and genetic studies began, first in Paris, then in Montreal, through different research collaborations organized by Jorge Sequeiros. The disease locus was mapped to chromosome 14q32.1 in 1993 in Japan[7], and the gene (an expansion of a CAG trinucleotide repeat) identified in 1994 by another Japanese group[8]. These findings were confirmed in the Portuguese kindreds by Jorge Sequeiros group in the same year[9]. The diagnosis of SCA3 rests on the use of molecular genetic testing to detect the abnormal CAG trinucleotide repeat expansion in ATXN3. Affected individuals have alleles with 52 to 86 CAG trinucleotide repeats. Many lines of research on the gene are going on in several centers (Universities of Porto, Azores, Minho and Coimbra), mainly focused on the mechanisms of the disease processes and the gene product, the protein ataxin 3[11,12,13].

Phenotypic variability and variable CAG expansions

From our first travel to the Azores, it was clear the extreme variability of the clinical expression of MJD and of its link with the age of onset: since the very young patients, so spastic and dystonic, whose cerebellar ataxia was no longer evident to the old patients, were ataxic and had with peripheral nerve or anterior horn cells involvement. In between stayed the middle-aged patients, only ataxic - a common feature to all patients - but with variable degrees of external ophthalmoplegia. Common to many patients were also the typical staring eyes, often associated to lid-retraction, which allow neurologists to recognize the disease among all the other ataxias. Parkinsonian features may be present and may respond to L-dopa. The size of the CAG has some influence in this phenotype, but other genetic or epigenetic factors are still to ascertain[14,15].

Fieldwork in the Mainland and prevalence studies

Between 1993 and 2004, a systematic population-based survey covered all the Portuguese population in the 18 mainland districts and Madeira Island[16]. Adding previous to more recent results of the Azores[17], 207 families with dominant ataxias with molecular diagnosis were identified in Portugal: 54% of them correspond to Machado-Joseph disease. The main clusters of MJD in Portugal are well defined: besides the islands of Flores and S. Miguel, the Northeast of Beira, the sea border region of Figueira da Foz and South of Coimbra, the Tagus Valley, the North of Alentejo. The prevalence of DMJ in Portugal is estimated in 40:100 000 inhabitants (contrasting with the average of 4.2 for dominant ataxias). In the main clusters it reaches very high numbers: 835.2: 100.000 in Flores, 102.3 in Chamusca (a small town in the Tagus Valley), 27.1 in S. Miguel.

Meanwhile, multiple surveys (most of genetic laboratories basis) demonstrated that MJD may in fact be the most frequent dominant ataxia in Europe, Brazil and North America, Japan and China. That is to say, the most frequent dominant ataxia worldwide.

Not Azorean, not Portuguese, very old mutations travelling all around the world

By haplotype studies in 264 affected families in 20 different populations[18,19,20], probably only two mutational events explain MJD geographic distribution. One mutation, ACA, about 5774 +/- 1116 years old, has a worldwide distribution. It is suggested that it could be a postneolithic mutation that may have occurred in Asia, with more recent introductions in North America, Germany, France, Portugal, and Brazil. A second, more recent (about 1416 +/- 434 years old!) and less frequent mutational event, CTG, was also identified. Most of the kindreds with this haplotype are of Portuguese ascendancy, and, this fact, in spite of less gene diversity, suggests it may have occurred in Portugal.

Looking back

Looking back now, the Portuguese contribution to knowledge on Machado-Joseph disease is a fine combination of hazard, right timing and involvement of some right persons. This is probably the case for success in any research. The attention paid by the Portuguese people in Washington could be a hazard or the product of a good routine of information. Corino Andrade was unquestionably the right person to lead the research. The series of people involved, in the Azores, mainland Portugal, and abroad, in very different fields of research was almost ineluctable (the subject of research was fascinating and

progressed with the progress of science in every field of knowledge), and very fruitful indeed.

After all, looking back the progresses in the research on Machado-Joseph disease always gives me a kind of pleasure and remote pride. ■

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Paula Coutinho

Paula Coutinho is a clinical neurologist with a special interest in neurogenetic diseases and neuroepidemiology, particularly in the diseases once linked to Portuguese communities outside Portugal and Portuguese migrations – first amyloid neuropathy and subsequently Machado-Joseph disease.
She is head of the Department of Neurology at Hospital S. Sebastião, Santa Maria da Feira, Portugal. Since its foundation, she has been a clinical researcher at UnIGENe, a neurogenetics research unit, and of CGPP, a centre for genetics services in neurological diseases, at IBMC, Univ. Porto.
She has authored or co-authored over 100 original articles in refereed international journals, including three chapters, one on Machado-Joseph disease and two on hereditary spastic paraplegias, in reference books. She has supervised or co-supervised a considerable number of PhD theses concluded.
She is a member of the scientific councils of the Portuguese Association of Inherited Ataxias and the Portuguese Association of Paramyloidosis (both of which she helped to create), and also of the International Joseph Diseases Foundation until its extinction.

Previously, Paula Coutinho was associated professor of Neurology at the Instituto de Ciências Biomédicas Abel Salazar, Univ. of Porto, Portugal (1987-1999), consultant of Neurology at the Centro de Estudos de Paramiloidose, Porto (1975-1992), "chef de clinique" at the Clinique Universitaire de Neurologie of the Geneva Cantonal Hospital, Switzerland (1973-1974), assistant of Neurology at the Clinique Universitaire de Neurologie (Prof. G. Gauthier) of the Hôpital Cantonal de Genève (1973) and assistant of Neuropathology (Prof. E. Wildi) at the Institute of Pathology of Geneva University, Switzerland (1971-1972).
Paula Coutinho was awarded with the first Bial prize of Medicine in 1992 for her work on Machado-Joseph disease.

Special interests outside Neurology: football, detective stories, dogs and birds, camellias and roses.

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Fernando Henrique Lopes da Silva

José Mendes Ribeiro
Dept Neurophysiology

Education and Training

– Received his Medical Degree from the University of Lisbon in 1959.
– Received a Gulbenkian Scholarship (1962—1964) - 1st year: to receive training in Physiology at the Department of Physiology and Pharmacology (Head: Prof. Dr. W. Feldberg) of the National Institute of Medical Research (Mill Hill, London UK); 2nd year: to follow a post-graduate course on Engineering and Physics for physiologists (Head: Prof. Dr. B. McA. Sayers) at the Imperial College of the University of London; 3rd year: to acquire training in neurophysiology at the Department of Brain Research of the Institute of Medical Physics (TNO) in Utrecht, The Netherlands (Head: Prof Dr. W. Storm van Leeuwen).

Main Positions

– In 1965, joined the scientific staff of the Brain Research Group of this Institute as assistant researcher. He got his Ph.D. from the University of Utrecht in 1970 His supervisors were: Prof. Dr. W. Storm van Leeuwen (Neurophysiology) and Prof. Dr. H. van der Tweel (Biophysics).
– In 1973, he followed Prof. dr. W. Storm van Leeuwen as Head of the Brain Research Group.
– In 1980 was appointed Full Professor of General Physiology at the Faculty of Science at the University of Amsterdam (since 2002 part of the Swammerdam Institute for Life Sciences).
– From 1993 to 2000, Director of the newly created Institute of Neurobiology of the University of Amsterdam, and member of the Scientific Directorate of the Graduate School Neurosciences Amsterdam.
– In 2000, when he reached the retirement age of 65, he became Emeritus Professor of the same University, and has at present a free-lance contract with the Swammerdam Institute for Life Sciences.
– For the past 10 years, he has enhanced his work as an scientific member and adviser for several Medical Faculties and Scientific Societies, namely the Lisbon, Porto and Minho Medical School e hi is an honorary member of the Portuguese Society of EEG and Clinical Neurophysiology.
– In 2000 appointed visiting professor of the Faculty of Medicine of the University of Lisbon and co-ordinator of the new Course 'Bio-Medical Engineering'; in 2005 he was also appointed Professor at the 'Instituto Superior Técnico' of the Technical University of Lisbon with the same task.

Main Research Interests

– His research interests are centred on the biophysical aspects of electrical activity of the brain and the functional organization of neuronal networks, namely of the cerebral cortex and the limbic system, with a special interest in the generation and functional significance of brain rhythmic activities. A main topic of research is the generation of epileptic phenomena, both at the cellular/molecular level, and at the neuronal network level. The main scientific achievements can be summarized under 3 headings:

1. The finding of the origin and functional organization of alpha rhythms: In a series of experimental studies performed on dogs, Lopes da Silva and colleagues established that alpha rhythms, in the awake state, are the undertaking of the cerebral cortex, mostly in the visual areas, although they can also be recorded in the visual thalamus (lateral geniculate and pulvinar nuclei) (Lopes da Silva et al., 1973). In the visual cortex, alpha waves are generated by an equivalent dipole layer centred at the level of the somata and basal dendrites of pyramidal neurons in layers IV and V (Lopes da Silva et al 1980). Furthermore, the coherence of alpha waves within the visual cortex is only partially dependent on thalamic sources measured in the same animal (Lopes da Silva et al., 1980) leading to the conclusion that horizontal intracortical linkages are essential to the spread of alpha activities, with only moderate implication of the thalamus. The cortical generator of alpha rhythms was recently confirmed and extended by more recent studies performed in awake monkeys using fine microelectrode arrays implanted (Bollimunta, et al J Neurosci. 2008, 28:9976-9988).

2. The finding of the cortical driver of Absence seizures. We revealed that spike and- wave discharges (SWDs) characteristic of epileptic absences are driven by a cortical network situated in the area of the somatosensory cortex where the perioral region is represented, in a rat genetic model of absences (Meeren et al 2002).

   Furthermore we found that at the onset (first 500ms) of a burst of SWD the cortical sites are leading and the thalamus follows this lead. In the course of the evolution of a SWD burst, however, these time relations may become variable and the direction of the time delay may even be inverted. The finding of a cortical network that is the driver of SWDs in rats with absence epilepsy is leading to a number of further studies of different groups that revealed that the SWD onset site presents specific abnormalities at the molecular level (Blumenfeld et al Epilepsia. 2008 Mar;49(3):400-9). The finding of the cortical driver of absences in the rat was confirmed in human subjects (Holmes et al Epilepsia. 2004 Dec;45(12):1568-79,Tucker et al Epilepsy Behav. 2007 Dec;11(4):546-57, Westmijse et al Epilepsia. 2009 Dec;50(12):2538-48; Polack et al Cerebral Cortex 2009).

3. The development of Neural Mass Models of EEG rhythms. The 1st model was published by Lopes da Silva et al (1974) that was able to simulate the generation of alpha rhythms. The model consisted of lumped sub-populations of interconnected excitatory and inhibitory neurons with properties of thalamocortical cells and a special sub-population of interneurons. More recently this kind of models were extended to account for other EEG frequency components other than the alpha rhythm. Using this Neural Mass Model we were able (Suffczynski et al 2001) to account for the origin of a specific EEG/MEG phenomenon, the so called "Focal ERD – surround ERS", where a given event (e.g. finger movement) can cause at the same time a decrease (event-related desynchronization or ERD) and an increase (event-related synchronization or ERS) of EEG/MEG power within the alpha frequency range (mu rhythm) depending on the site over thescalp (Pfurtscheller and Lopes da Silva 1999). This approach has led to the development of models of neural masses by many research groups with a variety of applications, namely to make a bridge between the activity of neuronal networks as reflected in EEG signals and hemodynamic signals as measured by way of functional MRI, as in a number of studies (David and Friston NeuroImage 2003,20: 1743 – 1755, Stephan et al J Biosci. 2007, 32(1):129-44., Valdés-Sosa et al Hum Brain Mapp. 2008, 23;30(9):2701-2721). Another important line of research that emerged from these Neural Mass Models is the development of models that can account for the transition between normal and epileptic seizure activity (Suffczynski et al 2004, Wendling et al Eur. J. Neurosci. 2002, 15(9):1499–1508, Lytton, W.W., Nature Revs. Neurosci. 2008, 9:626 – 637). This was followed by theoretical studies of the non-linear dynamics of neuronal networks and to the formulation of a general hypothesis about how the transition between normal and epileptic activity may take place. The hypothesis is that this transition can take place according to two basic models (Lopes da Silva et al 2003): the "bifurcation model" and the "deformation" model. The former takes into account the existence of bi- (or multi-stable) systems where jumps between two or more coexisting attractors can take place, caused by stochastic fluctuations (noise) of any input. In this case the transition between the interictal state and a seizure may occur at random due to some fluctuations in input conditions or in some system's parameters, or in other words seizures can be generated autonomously due to internal instability as occurs in Absence seizures. The latter i.e. the deformation model accounts for systems with deformable parameters such that their dynamics may evolve from one attractor that represents the normal state, or interictal state, to another attractor, typical of a seizure, as may occur in temporal lobe epilepsy (Richardson and Lopes da Silva .

4. The introduction of a new method for forecasting the occurrence of epileptic seizures. The finding in photosensitive epileptic patients (Parra et al 2003, Kalitzin et al 2002) that relevant information about the probability of a seizure occurring could be extracted from the phase of specific frequency components elicited by a periodic light stimulus, using a new index – the phase clustering index (Kalitizin et al 2005) - led to the hypothesis that a similar "active stimulation paradigm" might also be used in patients with temporal lobe epilepsy in order to forecast seizures.

   This implied the application of deep brain electrical stimulation using electrodes that were implanted for long-term EEG monitoring in these patients. Thus we developed an active electrical direct-stimulation paradigm and found that using the phase clustering

index it is possible to forecast the probability of a seizure occurring within a certain time interval. This was supported by a theoretical study using a computational model (Suffczynski et al 2008, Kalitzin et al 2010).

5. The development of a new parametric hemodynamic response model to account for our recent findings (De Munck et al 2007, 2008, 2009) of the correlations between EEG signals (namely alpha rhythms) and fMRI BOLD signals, both in cortical and sub-cortical regions. We apply a response function called the "Alpha band Response Function" (ARF) that combines the effects of local changes in electrical activity and the resulting hemodynamic response. This new model allows to study timing effects on a time scale shorter than the fMRI repetition time.

Scientific Awards

– 1975 He received the Winkler Medal from the Netherlands Association for Neurology for scientific contributions in the field of neurosciences.
– 1985 Elected member of the Royal Netherlands Academy of Arts and Sciences.
– 1990 "Lord Adrian" Lecturer at the 12th World Congress of Electroencephalography and Clinical Neurophysiology in Rio de Janeiro, Brazil.
– 1992 Honorary President of the VIIth European Congress of Clinical Neurophysiology, Budapest, Hungary.
– Honorary President of the First European Congress of Epileptology, Oporto, Portugal.
– Honorary member of the Dutch Society of Clinical Neurophysiology.
– Geoffrey Parr Memorial Lecturer at the Annual General Meeting of the British Society for Clinical Neurophysiology in London
– 1995 Honorary Life Member of The British Society for Clinical Neurophysiology (Formerly The EEG Society), London, United Kingdom.
– 1997 Doctor Honoris Causa of the University of Lisbon (Portugal).
– 1997 Special "Berger" Lecturer at the 14th International Congress of EEG and Clinical Neurophysiology in Florence, Italy.
– 1999 Recipient of the Herbert H. Jasper Award, selected by the American Clinical Neurophysiology Society for his (sic) "lifetime of outstanding contributions to the field of clinical neurophysiology."
– 2000 Recipient of the 'Storm van Leeuwen/Magnus Prize' of the Dutch Society of Clinical Neurophysiology for his (sic) 'outstanding contributions to the field of clinical neurophysiology'.
– 2000 Honorary member of the Portuguese Society of Electroencephalography and Clinical Neurophysiology.
– 2002 Recipient of the Ragnar Granit Prize for his work on the field of Bioelectromagnetism at the 4th International Congress in Montreal (Canada).
– 2002 Doctor *Honoris Causa* of the University of Porto (Portugal).
– 2004 Recipient of the first Prize "Universidade de Coimbra" for a (sic) "person of Portuguese nationality who has made a particular relevant and innovative contribution in the fields of culture or science."
– 2007 Doctor Honoris Causa of the University of Helsinki (Finland).

Teaching Activities

Since 1970, he supervised a large number of student trainees from different Universities and Faculties: Medical, Biology, Sciences, (Bio-medical) Engineering.

He was the coordinator (1988 - 1998) of the educational programme of the new Graduate School Neurosciences Amsterdam, which provides research training for about 90 PhD students in different branches of the Neurosciences.

Supervised 65 PhD students (up to 2007)

Selected Publications

He published more than 220 papers in peer-reviewed journals and contributed chapters to 10 books (among which, he is the co-editor of six), including the EEGers sacred book "The Electroencefalography: basic principles, clinical applications and related fields"; Niedermeyer, E.and Lopes da Silva, F. H. (Eds), published by Lippincott, Williams and Wilkins, Baltimore; 6 editions: 1982, 1987, 1993, 1998, 2004 and 2011.The last very recent edition has changed the title to "Niedermeyer's Electroencephalography: Basic Principles, Clinical Applications, and Related Fields" and the co-editor joining Prof. Lopes da Silva is now Prof. Donald Schomer.

H-factor: 54 according to "Harzing.com." (Feb 2011)

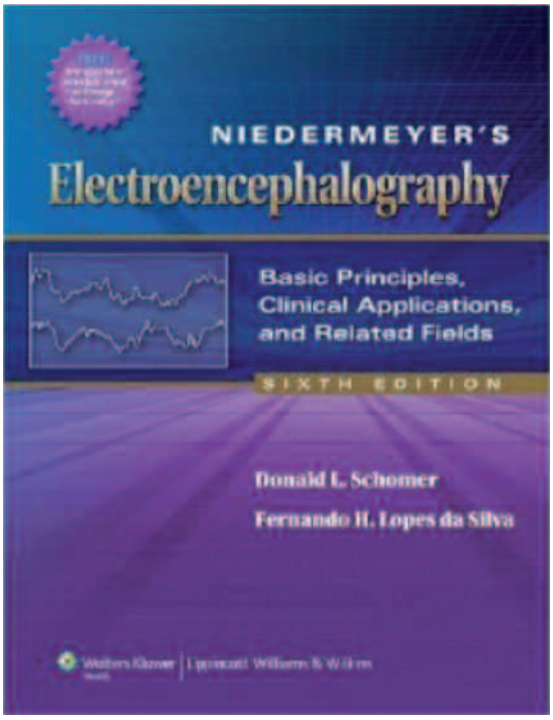
Five most Cited Publications:

– 1085 citations - Pfurtscheller G, **Lopes da Silva FH**. Event-related EEG/MEG synchronization and desynchronization: basic principles. Clin Neurophysiol. 1999 Nov;110(11):1842-57.
– 887 citations - Niedermeyer E, **Lopes da Silva F**, eds. Electroencephalography. Basic Principles, clinical applications, and related fields. Lippincott Williams & Wilkins, 1256 pp. 5th Edition 2004.
– 529 citations - Witter MP, Groenewegen HJ, **Lopes da**

Silva FH, Lohman AH. Functional organization of the extrinsic and intrinsic circuitry of the parahippocampal region. Prog Neurobiol. 1989;33(3):161-253.

– 543 citations - Steriade, M., Gloor, P., Llinás, R.R., **Lopes da Silva, F.H.** and Mesulam, M.-M.Basic mechanisms of cerebral rhythmic activities. Electroenceph. clin. Neurophysiol., 1990, 76:481-508.

– 343 citations - **Lopes da Silva FH**, Witter MP, Boeijinga PH, Lohman AH. Anatomic organization and physiology of the limbic cortex. Physiol Rev. 1990 Apr;70(2):453-511. ■



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António Damásio
The Neurologist of Emotions

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António João Rosa **Damásio** is possibly one of the best known neuroscientists and a world authority in the field of cognitive neurosciences. Although most of his scientific career has taken place in the United States, his interest in the understanding of the interface between the mind and the brain began during his early years as a young researcher in Portugal.

António Damásio was born in Lisbon in 1944. He completed his Medical Degree at the Lisbon Faculty of Medicine and undertook his training in Neurology at the University Hospital of Santa Maria. During his internship, in the early 70´s, he pioneered research in Behavioural Neurology and founded the Language Research Laboratory, dedicated to the study of Aphasia and other cognitive disorders. At that time aphasiology and behavioural sciences were emerging as new disciplines, especially in North America. António Damásio visited and established collaborations with Arthur Benton and Norman Geshwind in Iowa and Boston respectively, organized courses and produced the first Aphasia Battery for the Portuguese Language (Bateria da Avaliação da Afasia de Lisboa - BAAL), that is still used nowadays. He published articles on aphasia, relying on clinical assessment and angiography, the only imaging available at that time, but was also one of the pioneers of the study of the therapeutic effect of L-Dopa in Parkinson's disease. Despite his young age he was well succeeded in obtaining funding from the Gulbenkian Foundation (Portugal) to support research activities, and was able to assemble a team of active young researchers that he mentored and stimulated. Among those were medical students who, like Alexandre Castro Caldas, José Ferro and others, were to become outstanding academics and clinicians in Portugal.

In 1974, after completing his PhD thesis in Lisbon, António Damásio and his wife Hanna Damásio moved to the United States. He began his activity as a research fellow at the Aphasia Research Center in Boston and later became Director of the Department of Neurology and Van Allen Professor of Neurology at the University of Iowa. There he developed one of the most relevant Laboratories of Cognitive Neurosciences and pursued his study on the neural organization of language, emotions and the processes involved in decision-making, taking advantage of recently developed advanced brain imaging techniques. Both António and Hanna Damásio gave outstanding conceptual and methodological contributions to the study of the biological basis of behaviour, namely about the participation of emotions in decisions, the cerebral organization of knowledge and the construction of social cognition. He and his co-workers produced more than two hundreds of publications in well known scientific journals.

In addition António Damásio authored several books that contributed to bringing science and scientific discussions to the public at large: "Descartes' Error: Emotion, Reason and the Human Brain" (1994); "The Feeling of What Happens: Body and Emotion in the Making of Consciousness" (1999); "Looking for Spinoza: Joy, Sorrow, and the Feeling Brain" (2003) and "Self Comes to Mind: Constructing the Conscious Brain" (2010).

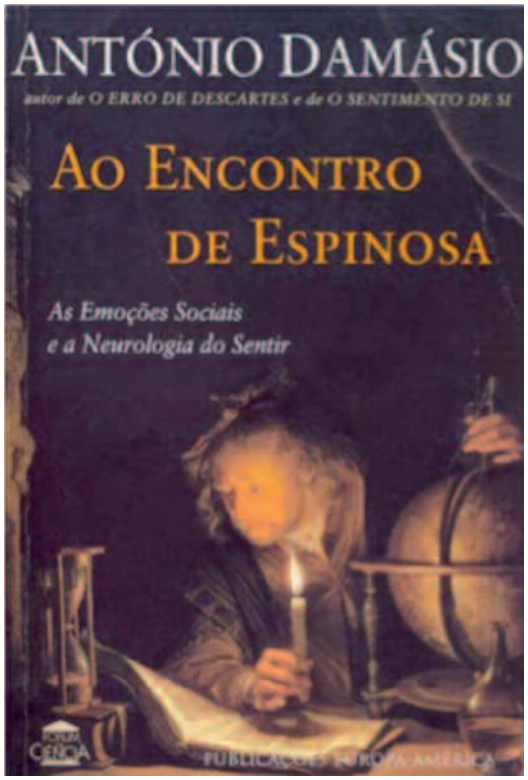
António Damásio is a member of renowned scientific societies, namely the National Academy of Sciences, Institute of Medicine, American Academy of Neurology, American Academy of Sciences and Arts, Academy of Aphasia and the Behavioral Neurology Society (that he presided) and the European Academy of Sciences and Arts. He has been awarded several prizes like the William Beaumont Prize of the American Medical Association (1990), Prémio Pessoa (1992), the Prince of Astúrias Award in Science and Technology, the Kappers Neuroscience Medal, the Golden Brain Award (1995) and recently the Honda Prize.

In the last decade António Damásio's interests expanded to the study of creativity, social cognition, moral judgments, ethics, drug addiction and also the very core of human nature, the understanding of the biological basis of consciousness. He has approached this topic in depth and from multiple perspectives from its neuro-anatomical

basis, the phylogenetic predecessors of conscious awareness, their advantages for the species, as well as the philosophical and methodological constraints in which those studies involve, somehow narrowing the gap between biology and philosophy.

He has given a substantive contribution to the understanding of human nature, balancing creative hypothesis with sound scientific methodology and the ability to integrate results with other areas of knowledge, opening new pathways for neuroscience research.

At present António Damásio is David Dornsife Professor of Neuroscience at the University of Southern California, Director of the Brain and Creativity Institute USC and is Adjunct Professor at the Salk Institute. ■



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CITOMAS—EPENDIMOMAS
QUISTO HIDÁTICO — ABCESSO
COLESTEATOMAS — HEMATOMAS SUBDURAIS

PRESENT AND FUTURE

Institute of Phamacology and Neurosciencies - Faculty of Medicine University of Lisboa and Neurosciencies Unit - Institute of Molecular Medicine (IMM)

Ana M. Sebastião e Joaquim Alexandre Ribeiro
Inst Pharmacol and Neurosci, and Unit of Neurosci, IMM, Univ of Lisbon

The present Unit of Neurosciences integrated in the Neuroscience Programme of the Institute of Molecular Medicine (IMM) and presently based at the Institute of Pharmacology and Neuroscience of the Faculty of Medicine, University of Lisbon, was structured as such in 2004, due to the merger of the laboratory of Neurosciences with the Institute of Pharmacology, both at the Faculty of Medicine. The Laboratory of Neurosciences was created in 1997 at the Faculty of Medicine following the invitation of the President of the Scientific Council at the time, Prof. João Lobo Antunes, to move from the Gulbenkian Institute of Science (IGC) in Oeiras, where a Neuropharmacology laboratory (Laboratório de Farmacologia) was developing its research activity between 1973 and 1997 (to see achievements and publications related to its performance visit the Web of Science of ISI Web of Knowledge, introducing the address Gulbenkian Inst Sci). The Neuropharmacology lab at the IGC was part of the Centro de Neurociências de Lisboa (CNL) network, since its creation in 1990. CNL was merged with other research centres of the FMUL classified by international evaluation panels as excellent or very good, to create the IMM, which from the beginning therefore included, a well reputed and structured programme of Neurosciences.

he main aims of the Neurosciences programme at the IMM were, and still are, in order of priority by, strengthening 1) basic and clinical research, 2) teaching and 3) to promote public perception in neurosciences. Public perception of Neurosciences has been developed through close relations between our labs and the DANA/EDAB for Brain initiatives, namely implementing the Brain Awareness Week (BAW), which was started in Portugal by Unit members; by promoting interviews in the media, activities with schools, etc. BAW initiatives by the Unit grew in diversity and recognition and were then extended to many other Units across the country, as well as organizations such as Sociedade Portuguesa de Neurociências e Ciência Viva.

The actual members of the Unit have been directly involved in important steps in developing Neurosciences in Portugal, namely: in 1988 with the foundation of the Portuguese Society for Neurochemistry, a joint initiative with other groups in Coimbra and Porto, which made possible the organization in 1989 of the International Society of Neurochemistry Meeting; in 1995 with the establishment of the Portuguese Society for Neuroscience also jointly with other groups in Porto and Coimbra, making it possible the organization of the meeting of the Federation of the European Neuroscience Societies (FENS); Unit members have also been involved as advisors and consultants in Neuroscience meetings and scientific events throughout Europe, USA and Japan

The teaching initiatives of the Unit include: **Pre-graduate teaching** namely, an optional **Course in Basic Neurosciences** designed for third year medical students aiming to establish a link between basic neuroscience research and clinical practice. In the last three years, after a curricular reform in the Medical Course, the Unit members are coordinating and teaching a block of vertical **Neurosciences** block that includes Neuroanatomy, Neurophysiology, Neuropharmacology and Psychology, therefore covering topics from the Molecule to the Mind. **Post-graduate teaching**, namely, **1) a PhD program in Neurosciences and, 2) a Masters course in Neurosciences**, which gives a focused perspective on current neuroscience research providing both theoretical and experimental fundamental knowledge suitable for different scientific backgrounds. These programs are part of the European Network Neurosciences Schools (NENS) under the umbrella of FENS.

Major Research interests and objectives of the Unit are the elucidation of cellular and molecular mechanisms involved in tuning and fine-tuning of neuronal communication, in particular at synaptic level, including receptor mobility, pre- and post-synaptic receptor activation and the transducing systems operated by receptors as well as the systems involved in neurotransmitter/neuromodulator inactivation including membrane transporters. The impact for nervous system function and dysfunctionis

also evaluated in the context of behaviour, memory and learning. The unit is now composed of five independent groups. The following, specific research objectives of each group in the Unit are:

The Neuromodulation and Plasticity Group - To elucidate fine tune regulation of the chemical synapses by neuromodulators (e.g. purines, neuropeptides). The idea is to recognize the way neurotransmitters are controlled at the synaptic level and the implications for plasticity and in neuronal dysfunctions (for a review see e.g., Ribeiro et al., 2002, *Prog Neurobiol, 68, 377-392*). A project aiming to identify a role for adenosine in animal models of amyotrophic lateral sclerosis (ALS) has been initiated.

Neuroprotection Group - To investigate mechanisms involved in neuronal protection, focusing on the control of a delicate balance between neuronal inhibition/excitability. (for a review see e.g., Sebastião et al.,1996, *Prog Neurobiol, 48, 167-189*). Adenosine besides acting itself as an endogenous neuroprotective agent, interacts with other substances also relevant for cell survival. The aim is to evaluate the interplay between different neuroprotective substances and, therefore, to contribute for the understanding of how neurones can be helped to survive and recover from insults.

Receptor Biology and Cognition Group - To understand how brain structures involved in memory are affected in situations of cognitive decline namely interested in changes occurring with ageing and whether these changes are hastened or exacerbated by several pathological conditions, namely depression and anxiety, epilepsy, neurodegenerative diseases. With the use of experimental models, (for the chronic stress model see e.g. Lopes et al., 2008 J. *Proteomics* **71**, 80-88) mimicking these situations, the impact on cognition both at neuronal and behavioural levels is investigated.

Regulation of Neuronal Death Group - To get a better understanding of neuronal cell death mechanisms induced by noxious conditions. Interest to the loss of endogenous neuronal trophic support observed in Alzheimer's disease patients, and the potential of direct involvement of A, which aggregates this loss. The age-related changes of neurotrophins-mediated control of synaptic transmission (for a recent publication on the topic see Diógenes et al., 2007, *Hippocampus*, 17: 577-585) and plasticity are also a focus of the group.

Inhibitory Synapses Group - Understanding the molecular mechanisms of inhibitory synapses, focusing upon glycinergic ones, and their modulation in the brain. It aims to elucidate the glycinergic neurotransmission in the hippocampus, both at molecular and functional levels, and to clarify the role of glycine-mediated inhibition within the context of neuronal hyperexcitability, as occurs in epilepsy (MS on the topic in the press at *J Neurochem*).

Following the broad objective of the Unit – to understand how neurons are finely tuned, or in other words, how neuronal activity is metamodulated (to better understand the concept see Ribeiro & Sebastião, 2010 – *Acta Physiol 199, 161-169*) by adenosine – **major scientific achievements of the Unit** during 2010 include the following findings:

1) By the first time it was observed the influence of adenosine A2A receptors on receptor mobility, namely upon TrkB translocation to lipid rafts (signaling specialized membrane domains). Doing this we identified a key step in the understanding of the molecular mechanisms through which adenosine A2A receptors trigger synaptic actions of neurotrophins.
2) Also, we found that A2A receptors influence AMPA receptor mobility. Thus, A2A receptors are responsible for setting part of the endogenous phosphorylation tonus of glutamate GluR1 subunits and hence, the availability of the GluR1-containing AMPA receptor extrasynaptic pool for synaptic insertion and reinforcement of synaptic strength.
3) While carefully looking at the influences of adenosine A2A receptors on synaptic transmission in very young (peri-weaning) animals, we could identify for the first time that, at least at the neuromuscular junction, tonic activation of A2A receptors predominates over A1 receptor activation, challenging an old paradigm that inhibition by adenosine predominates over excitation.
4) In a study aiming to evaluate reciprocal influences between adenosine A1 and cannabinoid CB1 receptors (the two main targets of the most widely used psychoactive and recreational drugs, caffeine and tetrahydrocannabinol) we clearly found that A1 receptors exert a negative modulatory effect on CB1-mediated inhibition of GABA release, and in collaboration with the University of Strathclyde, Glasgow, provided first evidence that chronic caffeine consumption induces alterations in the cannabinoid system with functional implications in spatial memory. That caffeine in concentrations selective for

adenosine receptors affects synaptic plasticity has been identified in another study by the Unit.

5) While investigating the mechanisms behind the neuroprotective actions of pro-inflamatory interleukin-6 (IL-6)-type cytokines, in a collaboration with Knut Biber (Univ Groningen) we found that IL-6 and oncostatin (OSM), but not the leukemia inhibitory factor (LIF), are neuroprotective because they induce an upregulation of A1 receptors in neuronal cells, strongly suggesting that IL-6 type cytokines, despite known structural and functional similarities, use different mechanisms to achieve neuromodulation and neuroprotection.

In conclusion, the above major scientific achievements reinforce concepts that have been developed and highlighted by the Unit members over the last years, that adenosine A2A and A1 receptors, via regulating mobility and action of other agents that protect and/or reinforce synapses, have a major role in the balance between neuronal inhibition and excitation, therefore 'synchronizing' or 'desynchronizing' directly or indirectly neuronal synaptic activity.

Publications in peer review Journals

Since its foundation the Neurosciences group published about 200 articles (original articles, reviews, letters, notes) (see e.g PubMed or Web of Science introducing: JA Ribeiro, who as a leader has been co-authoring practically all publications). The address: Edinburgh or Oeiras or Lisbon and as Authors: Ribeiro JA or Sebastiao AM receives **6135 citations** (includes auto-citations) and an **h-index : 45**, which means that at least 45 publications received at least more than 45 citations, Average Citations per Item : 31.62 (data obtained 22 March 1911).

The most recent Publications include:

Aroeira RI, Ribeiro JA, Sebastião AM and Valente CA (2011). Age-related changes of glycine receptor at the rat hippocampus: from the embryo to the adult. (***J Neurochem,*** **on line pub med Jan**).

Dias R, Ribeiro J A and Sebastião A M. (2011). Enhancement of AMPA currents and GluR1 membrane expression through PKA-coupled adenosine A2A receptors. *Hippocampus*, **on line pub med Nov**)

Sebastião AM, Assaife-Lopes N, Diógenes MJ, Vaz S, Ribeiro JA (2011) Role of adenosine A2A receptors on the brain derived neurotrophic factor (BDNF) actions in the nervous system. *BBA Biomembranes*, **on line pub med July**).

Sousa, VC, Assaife-Lopes N, Brett RR, Ribeiro, JA, Pratt JA, Sebastião AM. (2011) Regulation of hippocampal cannabinoid CB1 receptor actions by adenosine A1 receptors and chronic caffeine administration: implications for the effects of tetrahydrocannabinol on spatial memory. *Neuropsychopharmacology*, **36: 472-487**.

Assaife-Lopes N, Sousa VC, Pereira DB, Ribeiro JA, Chao MV, Sebastião AM (2010). Activation of adenosine A2A receptors induces TrkB translocation and increases BDNF-mediated phospho-TrkB localization in lipid rafts: implications for neuromodulation. *J Neurosci. **30**: 8468–8480.*

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Pedata, F , Pugliese, A M, Sebastião A M and Ribeiro J A. (2010). Adenosine A3 receptor signaling in the central nervous system. A3 Adenosine Receptors from Cell Biology to Pharmacology and Therapeutics, P.A. Borea (ed), Springer Science Business Media B.V.

In Future Research we expect to achieve a deeper knowledge on how neuronal excitability and survival, in adult and ageing animal tissue models are regulated. We will use slices, isolated neuronal substructures (nerve terminals, membranes) cultured neurons and glia, KO and transgenic mice, drugs and antibodies directed towards

receptors and transducing pathways. We propose to evaluate synaptic transmission via patch clamp, field potentials and intracellular recordings, and also astrocytic Ca^{+} signaling, neurotransmitter transport, neuron and astrocyte survival, expression of receptors and relevant transducing pathways, as well as behavioral testing. With this plan, we believe to take a step further in understanding the ability of the brain to remodel and adjust itself. ■

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Center for Neuroscience and Cell Biology (CNC): A New Culture Through Scientific Research

Catarina Resende Oliveira MD PhD
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AN OVERVIEW

The Center for Neuroscience and Cell Biology (CNC) was founded in 1990, aiming to foster biomedical research at the University of Coimbra, Portugal. Established in 2000 as an "Associate Laboratory", its main mission is to promote excellence in fundamental and translational research. This is best expressed in the high quality publication record and international recognition, including invitations to join international networks such as the Network of European Neuroscience Institutes (ENI-net), the MIT-Portugal Program, the Harvard Medical School-Portugal Program, and more recently the European Neuroscience Campus Network (ENC Network).

CNC is a multidisciplinary research Center that, besides its own staff researchers, brings together scientists from the Faculties of Medicine, Pharmacy and Sciences and Technology, and from the Coimbra University Hospitals (HUC), Paediatric Hospital and Portuguese Institute of Oncology (IPO). CNC has over 100 members holding a Ph.D.

The core scientific activity of CNC is the study of the molecular basis of brain function with a focus on neurodegenerative processes and mechanisms of neuroprotection and regeneration which may act as future candidates for the development of disease biomarkers and novel therapeutic strategies. This activity of the Neuroscience and Disease research area is potentiated by a multidisciplinary approach involving other research areas, opening the scope of intervention of CNC in the biomedical field: biomedical NMR, cell and molecular toxicology, microbiology, stem cell and regenerative medicine, human genetics and pharmacogenomics, oncology, gene therapy, immunology, inflammation, high throughput analysis (genomics, transcriptomics, proteomics, lipidomics, metabolomics), systems biology, structural biology, etc.

Translational research and technology transfer have been progressively developed in CNC leading to a promising interaction with industry and local authorities. The outcome of this interaction was the participation of CNC as a founding member of the Health Cluster Portugal – with the goal of developing internationally competitive and innovative biomedical technologies and healthcare devices --, and of Biocant - Biotechnology Innovation Center in collaboration with "Câmara Municipal de Cantanhede" for the creation of a technology transfer unit and of novel biomedical and biotechnology enterprises. Biocant is organized into eight main functional units with highly qualified teams and state of the art equipment: Bioinformatics, Cell Biology, Genomics, Microbiology, Molecular Biotechnology, Systems Biology, Tissue Engineering, and

Sequencing Advanced Services. Biocant provides services and R&D activities based on post-genomic platforms such as whole-genome sequencing, DNA chips, proteomics, interactomics and metabolomics. Several research projects are currently in progress from which we can highlight the identification of biomarkers for Multiple Sclerosis; the design of novel biomaterials for stem cell differentiation and transplantation; and the development of biomaterials with antimicrobial properties.

The Center has a long tradition in outstanding graduate teaching aiming to provide Master and Ph.D. students with a high-quality multidisciplinary education, through programmes with a strong international component. Education at the CNC focuses on research-oriented graduate training in Molecular Life Sciences and Disease, particularly in the fields of Cell and Molecular Biology, Neuroscience and Biotechnology. Since 2002 CNC organizes its own Doctoral Programme in Experimental Biology and Biomedicine (PDBEB), providing advanced, multidisciplinary, research-oriented training in emerging areas of modern Biology and Biomedicine. CNC also collaborates with other Master and Doctoral Programmes, both at the University of Coimbra and in other Portuguese Institutions. Importantly, as a member of the ENC Network CNC participates in the Erasmus Mundus Joint Doctorate (EMJD) and the Erasmus Mundus Master Course (EMMC) Neurasmus, together with Amsterdam, Berlin, Bordeaux, Göttingen, Zürich, and Québec. CNC is the host institution for 258 Ph.D. students.

Another key mission of CNC is its commitment towards promoting science awareness through an efficient Outreach Programme. This programme offers opportunities to develop partnerships with schools, museums, science centres and other organizations, extending our scientific resources to the community. The programme is designed to engage students in their science studies, promote potential careers related to the life sciences, and to broaden the public's access to science.

RESEARCH AT CNC

Research at CNC is organized in six thematic areas:

Neuroscience and Disease - This Area pursues its research interests on the clarification of molecular mechanisms of synaptic activity modulation and its involvement in neurodegenerative disorders with the ultimate goal of developing new strategies of neuroprotection and brain repair. These objectives are accomplished by the seven groups in this Area. The *Neuromodulation Group* studies the effect of synaptic activity modulators that affect brain metabolism, purines and cannabinoids. The *Glutamatergic Synapses Group* studies the regulation of excitatory glutamatergic synapses. The Neuronal Cell Death and Neuroprotection Group focus on the excitotoxic cell damage, and neuroprotection by neurotrophic factors. The *Neuroprotection and Neurogenesis in Brain Repair Group* is working on the identification of inflammatory mediator's and neuropeptides pro-neurogenic effect. The *Molecular Mechanisms of Disease Group* studies the mechanisms of neurodegeneration associated to peptide aggregation. *Mitochondrial Dysfunction and Cell Death Group* focus on the mitochondrial-driven neuronal death and transcription deregulation in Huntington's disease. Finally, the *Neuroendocrinology and Neurogenesis Group* studies the adrenal-hypothalamic axis and adipose tissue negative regulation of neuronal protection.

Molecular Biotechnology and Health - The general objectives of this Area are to unveil and understand normal interactions that occur in living organisms from a molecular up to a system level; to design vectors to deliver drugs and nucleic acids aiming to modulate or correct abnormal interactions; and to develop new biomaterials for stem cell differentiation, tracking and transplantation as well biomaterials with anti-microbial properties. This line of research encompasses basic and translational research approaches which are conducted by five groups: *Molecular Systems Biology, Structural and Computational Biology, Molecular Biotechnology, Vectors and Gene Therapy*, and *Biomaterials and Stem Cell-Based Therapeutics*. The Molecular Biotechnology and Health research Area, like the most of the research lines of "Associate Laboratories", was originally defined in a broad sense to include and to report the activity of groups developing projects that incorporated a substantial know-how in molecular biotechnology aiming at the development of technologies or products of health care interest. The main objectives thus represent a continuous effort to incorporate new approaches to tackle this central issue on the basis of a deep knowledge of the interactions that occur in the living organisms from a molecular up to a system level.

Microbiology - The Microbiology Area puts an emphasis on the strategies for adaptation of microorganisms to extreme environments, the screening and development of new anti?mycobacterial drugs and the susceptibility to legionella and fungal infection. The *Extreme Environments Group* aims to better understanding the microbial diversity in geothermal areas, hypersaline environments and extremely alkaline springs. One of the primary objectives involves the study of mechanisms that confer radiation and desiccation resistance in species of the genus Deinococcus and Rubrobacter. It also studies the evolu-

tion of genes involved in the pathogenesis of Legionella species in natural environments to define clones that cause human diseases. Yet another line of research focuses on the characterization of the pathways for the synthesis of compatible solutes in hyperthermophiles, which led to the analysis of the synthesis of essential lipopolysaccharides in Mycobacterium species. The *Extreme Environments Group* has described a large number of novel species has now isolated several extremely halophilic organisms from deep anaerobic Mediterranean brines which constitute new lineages of bacteria and archaea. The *Yeast Research Group* is unravelling the resistance of Candida albicans to macrophages as well as the epidemiology of yeast infections in hospitals.

Cell and Molecular Toxicology - This Area maintains a focus on the study of cellular and molecular basis of drug- and disease-related cell dysfunction, in which mitochondria, lipid membranes or free radicals could be involved, for the purpose of translating this knowledge into disease treatment and prevention. Four groups are working to accomplish these goals. The *Mitochondrial Toxicology and Disease Group* is centred on the role of mitochondria as a primary cellular mediator of cell dysfunction and on its potential usefulness as a target in anti-cancer therapy. The *Redox Biology in Health and Disease Group* is focused on mechanisms inherent to neuromodulation and aging involving nitric oxide and on action mechanisms of dietary polyphenols in terms of endothelial dysfunction protection, anti-inflammatory properties and nitrite-driven regulatory processes. The *Membrane Toxicity Group* aims to study the role played by lipids and by the lipid-bilayer component of cell membranes in cell functioning, in health and disease conditions, and in drug-mediated cell dysfunction. The *Pharmacometrics Group* brings a great insight into the optimization of drug efficacy and safety, in order to prevent costly and life-threatening drug-induced toxicity, by developing and apllying mathematical and statistical methods to characterize, understand, and predict a drugs's pharmacokinetic, pharmacodynamic, and biomarker-outcomes behaviour.

Cell and Developmental Biology - Research in this Area focus on human infertility, disruption of human cell function in cancer, contact dermatitis, osteoarthritis, auto?immune disease, obesity, and pathogens biology. Four groups conduct research in this area: *Biology of Reproduction and Human Fertility; Cellular Immunology and Oncobiology; Infection and Pathogens; Molecular and Translational Medicine;* and *Immunology Group*. A key identifying feature of this area, and one of its major strengths, is the close partnerships with clinicians at FMUC/HUC and IPO, allowing the collection of human tissues and samples both for basic research, setting up novel clinically-relevant services and trials, and hopefully for furthering translational research.

Biophysics and Biomedical NMR - This Area is characterized by a strong focus on the development of inorganic compounds for medical diagnosis (e.g. MRI contrast agents) and therapy, and on intermediate metabolism and diabetes. The *Inorganic Biochemistry and Molecular Imaging Group* studies new diagnostic imaging tools – metal based nanoparticles and chelates as multimodal (MRI, nuclear imaging) targeted agents – *in vitro* and in animal models. This group is also working on the development of inorganic drugs for therapy – like lithium compounds for bipolar disorder, and vanadium complexes as oral insulin-mimetic agents – and their mechanisms of action in cell and animal models. The *Intermediary Metabolism Group* is developing stable-isotope tracer measurements of glucose, fatty acid, and amino acid metabolism in humans and in animal models of diabetes, in order to integrate the analysis of carbohydrate, lipid and protein metabolism disruption that occurs in insulin resistance and Type 2 Diabetes.

BIOMEDICAL INTER-INSTITUTIONAL RESEARCH PROGRAMME

The Biomedical Inter-Institutional Research Programme emerged from the strong and valuable partnership developed between CNC and the Clinical Faculty - University Hospitals of Coimbra (HUC), the Hospital Center of Coimbra (CHC) and the Portuguese Institute of Oncology (IPO) -, allowing for the translation of basic knowledge into clinical applications, enhanced by partnerships with the pharmaceutical industry. The following joint research projects are being developed:

Psychiatry research – Molecular and phenotypic studies of complex disorders

These studies have focused on the identification of candidate genes for schizophrenia and bipolar disorder; and on the clarification of the phenotypic definitions and boundaries of complex disorders

Neurology research – Biochemical and DNA studies on neurodegenerative disorders

This area of research has developed expertise in the identification of biomarkers in the cerebrospinal fluid (CSF) for the early diagnosis of neurodegenerative disorders; in the clarification of the genetic basis of Alzheimer's disease, Parkinson's disease, and frontotemporal dementia; and on the identification of common genetic variability that confers risk for neurodegenerative diseases

Brain cancer research – Genetic heterogeneity of gliomas

This project has been assessing the intratumoural genetic heterogeneity in gliomas, and evaluating possible predictive and prognostic markers.

Paediatric research – Metabolic disorders

The main goal of these studies has been to provide tools for the diagnosis of mitochondrial respiratory chain diseases, and a better understanding of the pathogenic mechanisms leading to the clinical phenotypes

Dermatology research – Contact dermatitis

These studies have focused on the identification of new therapeutic targets for allergic contact dermatitis; and on the identification of cellular markers that allow the in vitro recognition of the skin sensitization potential of environmental chemicals.

Arthritis research – Inflammation

The main goals of this research area have been: the elucidation of the role of high and low glucose concentrations as effector mechanisms modulating the chondrocyte functions, in order to identify cellular and molecular links between diabetes and osteoarthritis (OA); the development of a method for the cryopreservation of osteochondral allografts that maintains chondrocyte viability and metabolic activity; and understanding how CD8+ T cells participate in the recruitment and/or regulation of other immune cells and in the maintenance of the chronic inflammation in rheumatoid arthritis.

Yeast research – Nocosomial infections, oral yeast carriage in type I diabetes, and AIDS progression prediction

The main objectives of this research programme are: to type yeast isolates using restriction endonuclease analysis (REA) of mitochondrial DNA, in order to trace and prevent possible yeast infection outbreaks in healthcare units; to characterize the yeast species of normal and type I diabetic children, together with the yeast load in each individual; and to study, in the Portuguese HIV-1 population, the naturally occurring genetic variants of HIV-1 vpr gene and to assess the resulting functional variability, using yeast as a cell model, and its potential impact on disease progression.

Novel techniques for the diagnosis and treatment of human infertility

This research programme aims to develop novel assays to monitor human sperm and oocyte quality with the ultimate goal of improving assisted reproduction. In addition, the programme also involves improving the cryo-banking and subsequent use of ovarian tissue for patients undergoing chemotherapy. ■

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Pain Research Group of the Faculty of Medicine University of Porto / IBMC (Institute of Molecular and Celular Biology)

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Experimental neurosciences group of the Faculty of Medicine – University of Porto (FMUP), so called "Group of Investigation on Morpho-Physiology of Somato-Sensitive System" was created at the Institute of Hystology and Embriology of FMUP by Professor António Coimbra when he made his doctoral thesis "The Nervous Cell: Cito-Chemical Aspects" published in 1961.

The focus of investigation at that time was on spinal cord and in particular the dorsal horn. By the decade of 1980, a new field of interest aroused: Pain and other related areas.

Progressively our team enlarged, becoming a part of the IBMC as associated laboratory.

Some other groups of investigation developed from the original one, namely the "Group of pain at the University of Minho, the team of neuronal network IBMC and the group of Translational Neuro-Urology (IBMC/FMUP).

Among the more significant contribution for progress of science from our group are:

(I) Characterization of synaptic glomerulus form the substantia gelatinosa Rolandi [1], (II)

(II) Classification of the neurons of lamina I of spinal cord [2]

(III) Characterization of the neurons lâmina I sharing different tracks to the supraspinal projection[3,4],

(IV) Findings on differential involvement of the GABAergic spinal system by neurotomy or peripheral inflamation[8],

(V) Demonstration that distinct noxious agents produce distinct patterns of activation at spinal level.[9]

(VI) Identification of a spinalmedullar projection of the medullar reticular dorsal substance.[10,11]

(VII) Demonstration that substantia gelatinosa Rolandi is predominantly filled with excitatory neurons[12].

(VIII) Observation an important nociceptive projection of the substantia gelatinosa Rolandi to caudally medullary ventrolateral reticular substance [-15].

(IX) Characterization of the spinal collateral axons of neurons of the lamina I of the supraspinal projection[16] (Fig. 1),

(X) Identification of a pro-nociceptive nucleus in medulla[17-19].

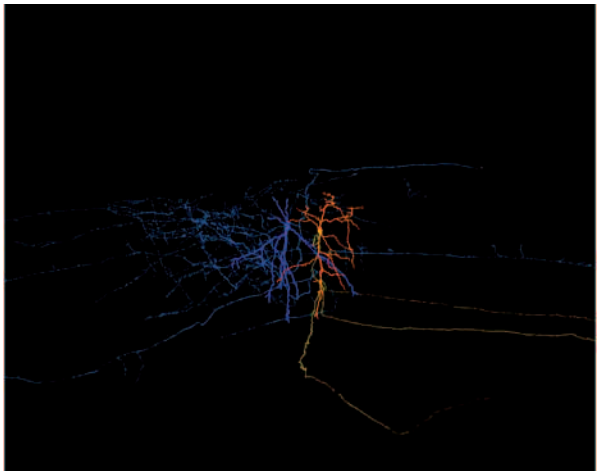

Fig. 1. Yellow: neuron of the contralateral, anterolateral projections with collaterals rostralty distributed through the dorsolateral funiculus (Liliana Luz, Raquel Pinho and Peter Szucs)

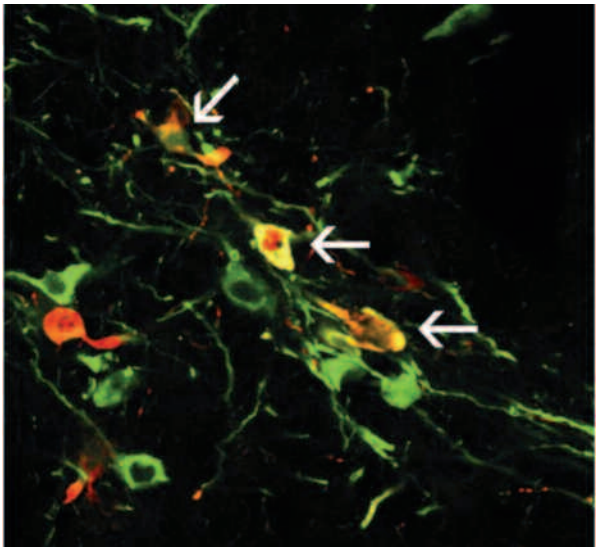

Fig. 2. Noradrenegic neurons A_5 of the pons expressing thyrosine-hydroxilase (green) translated from the meddulary dorsal reticular nucleus of a viral vector (HSV-1), expressing B-galanine (red). On yellow: Neurons expressing both markers. (Isabel Martins and Sara Tavares)

(XI) Identification of a ventrolateral caudal reticular substance as integrative center of nociceptive and cardiovascular functions.[20,21],

(XII) Identification of one circuit at brainstem in connection with the analgesic action of adrenaline at spinal level.[22,23],

(XIII) Observation of central sensitization at the neuropathic pain in diabetes[24].

(XIV) Identification of a transcriptional factor regulating the embrionic spinal nociceptive ganglio-medullar development.[25]

(XV) Demonstration that the pre-frontal cortex regulates cognitive abnormalities in chronic pain[26-29].

(XVI) Demonstration of the efficacy of supraspinal genic therapy to control pain.[30]

(XVII) Identification of TRPV1 as etiological agent and therapeutic target in bladder dysfuncion[31-35]

(XVIII) Demonstration that botulinium toxin is effective in treatment of benign prostate enlargement [36-38].

At present, our team is composed by 24 investigators, including, 7 PhD, 17 doctoral students.

Our work is divided in five areas and producing about 20 papers a year in peer-reviewed journals with a mean impact-factor of 4.5 aside of chapters in textbooks.

In our current focus of interest is the embryonic development of the nociceptive system (Deolinda Lima, Carlos Reguenga e Filipe Monteiro).

Our aim is to identify molecular markers of the different components of the nociceptive system through the understanding of the molecular mechanism regulating its development.

After identifying a transcriptional factor involved in the embryonic development of the nociceptive circuit connecting spinal ganglia to spinal cord, we investigated the molecules whose expression depend on that transcription factor and what is his role in the development of such circuit. At the same time we try to understand the involvement of such molecules in chronic pain.

Another area of investigation deals with the study neurochemical plasticity of the neurons of the nociceptive in several situations of chronic pain, such as monoarthritis and osteoarthritis and diabetic pain (Fani Neto and José Castro Lopes). We found several abnormalities at the level of ionic channels, recptors and neurotransmitters in primary afferent neurons (Fig. 3) spinals and supraspinals that may explain the characteristics sensitivity abnormalities found in those diseases.

Behaviour of the supraspinal control of pain in circumstances such as chronic pain of inflammatory or neuropathic origin is the target of our 3rd line of investigation (Isaura Tavares). Studies are focused on the inhibitory nucleus of medulla to demonstrate. Genetic manipulation of such neurons (Fig. 2) used as pharmacological tool, as shown a powerful tool for pain control.

The 4th area of investigation deals with the study of the anatomical and neurochemical background responsible for the affective-cognitive changes accompanying chronic pain in particular those related to the decision making capacity and sleep. Tha anatomical abnormalities are related with pre-frontal cortex, amygdala and thalamo-cortical loop. The 5th area of investigation is focused on the epidemiology of pain (José Castro Lopes), with results already collected on the incidence of the post-op pain and several other types of chronic pain in Portugal

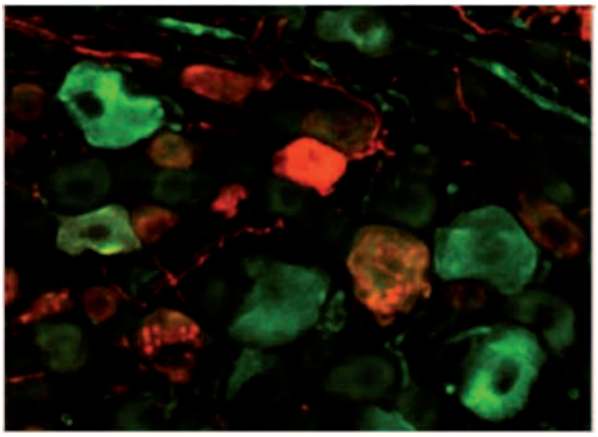

Fig. 3. Immunofluorescence CGRP (red) and NF 200 (green) of a rachidian nucleus innervating an ostheoartritic mouse knee. (Joana Gomes and José Castro Lopes)

For the years to come we are eager to set links with other clinical units in order to contribute solve clinical problems and improve information.

We are indebted to Sociedade Portuguesa de Neurologia for the invitation to participate in this publication. ■

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