

# All in the blood

How the Pavlovsky family put Buenos Aires on the haematological map

→ Peter McIntyre

Despite being home to three generations of Pavlovskys – Alfredo, the founder, Santiago, now medical director, and Astrid a fellow – Fundaleu is no family firm. On the contrary, it was the Pavlovskys' commitment to looking outward to international networks that made it possible to develop this world-class leukaemia centre in Buenos Aires.

Most doctors remember their early successes, so it is no surprise that Santiago Pavlovsky can recall the first adult patient he cured of leukaemia. What is more remarkable is that he still takes a close interest in his first patient, 37 years later.

The year was 1968. At 27, Pavlovsky, back in Argentina from Europe, was scarcely older than his patient. The 23-year-old man had just married, and the diagnosis of acute lymphoblastic leukaemia must have sounded like a death sentence.

Pavlovsky could offer hope. He had recently attended the first international convention on daunorubicin and he treated his patient with this new cytotoxic drug. Being unsure of the side-effects, he asked the young couple to ensure that the wife did not become pregnant. Of course, she did. Pavlovsky and the family waited anxiously to see what would happen to father and baby.

All turned out well. The father went into remission that turned into a cure, and his wife delivered a healthy baby boy. The couple had four more children and the firstborn has chil-

dren of his own. Now aged 60, the patient is still well. Pavlovsky said, "I see him at least once a year. He has never had a recurrence. This was the first adult patient I ever saw cured."

This quietly spoken Argentinean is very aware that this one life saved has led to a whole extended family. A sense of family is part of his personal identity. Fundaleu (Foundation Against Leukaemia), of which he is medical director in Buenos Aires, was founded by his father. His identical twin bother, Miguel, is also a distinguished haematologist in Argentina, and his daughter Astrid works alongside him.

Santiago Pavlovsky winces at the suggestion of a dynasty. He is as proud of dissuading his son (a successful economist) from following him into medicine, as he is proud that his daughter has done so. "Not dynasty, but probably destiny," he says with a smile.

Pavlovsky also has a commitment to internationalism. He sees co-operation between specialists and centres as ever more important to provide sufficient research data on rare cancers and different oncogenes.



Santiago Pavlovsky (seated at the table) with his team of doctors, nurses, scientists and technicians at Fundaleu in Buenos Aires. Standing at his left shoulder is his daughter Astrid

His grandfather, Alejandro Pavlovsky, was born on the banks of the Don in Rostok, in what was then Russia (now Ukraine). Russian Jews were subject to discrimination and pogroms by the Cossacks. Many converted to Catholicism and left. At the age of 18, Alejandro joined older brothers and sisters in Argentina, where he worked his way up to become chief executive of the Buenos Aires municipal authority and married a woman from Mendoza. Santiago's father, Alfredo, was the tenth of their 11 children.

Alfredo graduated from the University of Buenos Aires in 1931, and his PhD thesis on the detection of malignancy made him famous almost immediately.

Santiago says, "His idea was to differentiate a lymph node that was tuberculosis, which was very common, from a lymph node that was malignant disease. They looked the same. My father used a needle to take an aspiration and put the cells in a smear and he looked at them under the microscope. He compared what he saw with what the pathologists said in their

report until he was able to differentiate them based on what he could see."

Alfredo won a top prize in Argentina, and Adolfo Ferrata, 'the father of Italian haematology', was so impressed that he included the thesis as a chapter in his text book in 1936.

Alfredo Pavlovsky spent a lifetime treating haematological diseases. He was one of the founders of the International Society of Hematology in Paris after the war, and in 1954 was President of the Fourth International Congress of Hematology in Mar del Plata, Argentina.

#### BLOOD BROTHERS

He and his wife, Maria, had five children, including identical twins Santiago and Miguel in 1941. The twins went to school together (where they could swap classes without their teachers knowing), and learnt to ride horses together. Both became haematologists. Both work mainly in non-profit organisations. The difference is that Miguel works on coagulation, thrombosis

Santiago Pavlovsky winces at the suggestion of a dynasty – it is more a case of destiny, he says

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and vascular disorders, while Santiago specialises in haematological malignancies.

Santiago began working at the Haematology Research Institute of the National Academy of Medicine in Argentina, where his father was Director. He married young and, with his wife Tatiana, left for France to do his fellowship. Tatiana spoke good French and English and was quickly able to get work in Paris. Pavlovsky recalls, "She was my economic support because my fellowship was very lowly paid, and difficult to live on for one, much less two. Her salary was three times my fellowship."

Professionally, Pavlovsky struck gold at St Louis Hospital, Paris, joining Jean Bernard, then the leading haematologist in Europe, later a French academician, and still alive and lucid at the age of 98. "I had two big inspirations in my career: one was my father, the other was Jean Bernard. He was the big professor type. He ran the best haematology department in Europe and was very well known all over the world. Jean Bernard was very strong in leukaemias and later in lymphomas. I admired him because he started collaboration with the Americans, trialling drugs in acute lymphoblastic leukaemia [ALL] in children."

These Cancer and Acute Leukaemia Group B (CALGB) trials showed the effectiveness of anthracyclines; 40 years later, daunorubicin is still a first-line treatment for ALL.

Pavlovsky returned to Buenos Aires in 1967, to create the oncohaematology department at his father's institute. Other young doctors and scientists were also returning. With Federico Sackmann at the Children's Hospital in Buenos Aires, and other colleagues, Pavlovsky launched the Argentinean Group for the Treatment of Acute Leukaemia (GATLA).

Four institutions grew to 25. They began by copying the work of Bernard, but quickly built their own expertise.

Pavlovsky recruited patients to clinical trials and built a statistics department that could turn data into a coherent story. As chairman of GATLA, he worked tirelessly to collect data and spread treatment protocols across the country.

"We held two big meetings a year in Buenos Aires to which all the physicians from around the country came. Most of them were very young at that time and very enthusiastic about doing clinical trials. We were learning together. Argentina is a huge country with long distances. In the beginning most of the children came to Buenos Aires to be cured, but later many physicians who had trained in Buenos Aires went back to their provinces to treat the children with this new national protocol.

"At that time, in the late 1960s, to tell a patient that the disease could be cured was blasphemy. In the 1970s we started to mention the word 'cure' in relation to acute lymphoblastic leukaemia in children."

By 1973, the team was confident enough to co-organise in Cuba the first Latin American cooperative group on haematology. This inspired clinical trials over a wide range of disorders. Pavlovsky became chairman of the group looking at haematological malignancies, bringing together data from Argentina, Brazil, Chile, Costa Rica, Cuba, Uruguay and Venezuela, agreeing protocols for treatment and publishing in international and peer review journals. The Latin America group developed protocols for childhood leukaemia, Hodgkin's disease, lymphoma and multiple myeloma.

The children's hospitals were good and the paediatricians and young scientists were enthusiastic. "Everybody was looking for new things. The idea of doing a clinical trial was new. The idea of curing a cancer patient was new. Older haematologists had very little knowledge of chemotherapy. For them the most important thing was a diagnosis because there was nothing



Alfredo and Maria Pavlovsky with their children. In the centre picture, Santiago is second from the left with his twin brother Miguel

## They published in leading oncology journals, struggling as much with the English as the science

they could offer as a cure. They were very happy for this new generation to take care of this job.”

Before computers, fax, couriers and e-mail they punched holes in cards to record data, typed up reports on manual typewriters and circulated drafts through slow and unreliable postal services. They published in leading international oncology journals, often struggling as much with the English as they did with the science.

In 1979 the Argentinean group joined a collaborative cancer treatment research programme (CCTRP) sponsored by the US National Cancer Institute. This paired centres in the US with the National Cancer Institutes in Mexico, Brazil, Peru, Uruguay, Venezuela and Chile. The Cancer Research Institute in Buenos Aires was twinned with the Lombardi Cancer Center in Georgetown University, Washington DC.

In 1983, Pavlovsky became co-ordinator of

the CCTRP programme and moved to Washington, where he was also cancer advisor to the Pan-American Health Organization (PAHO). By the time he returned to Argentina in 1986, his father had died and his generation had become the established leaders of cancer research and treatment.

Military dictatorship, a disastrous war with the UK, an economic crisis and ‘Reagonomics’ had a destructive impact on public services in Latin America, and it became more difficult to carry out collaborative work.

### A CENTRE OF EXCELLENCE

In the 1950s, Alfredo Pavlovsky had founded Fundaleu, the Foundation Against Leukaemia, to fund and carry out applied clinical research. Now in the 1980s Santiago Pavlovsky began to build this organisation into a centre of excel-

## His scientists can now identify the molecular structure of cancers and pinpoint the oncogenes

lence. He brought in the best doctors he could find and raised money from private companies and rich individuals. In July 1989, Fundaleu opened the Angelica Ocampo Research and Treatment Centre, dedicated to leukaemia.

In 1991 Fundaleu was one of the first centres in Latin America to start stem cell transplantation to treat leukaemia, myeloma and lymphoma. The team carried out 820 stem cell transplants over the following 14 years, mainly taken from peripheral blood. This required careful selection of patients. Pavlovsky said: "You have to avoid the patients in the late stage because they cannot be cured. We tried to educate the medical profession to transfer the patient early enough to be able to use the transplant."

The reputation of Fundaleu grew throughout the 1990s. In October 2003, it opened an outpatient department complete with molecular biology, flow cytometry, pathology and bacteriology laboratories. Pavlovsky says that his scientists can now identify the molecular structure of cancers and pinpoint the oncogenes for individual patients.

"The objective is not only to achieve clinical remission but molecular remission. Patients who show complete molecular remission have more chance of being cured. If you are able to identify an oncogene that causes the disease you can follow whether this oncogene disappears or at least is reduced many times. If the oncogenes do not decline the disease will come back; if the oncogene disappears they will be in remission for ever."

Fundaleu sees 700 new patients a year and has 7,600 patient visits. Only 20% of patients

are children now that children's hospitals offer excellent treatment. The team carries out stem cell transplants on patients of all ages, including patients over 70 years old.

Most patients receive chemotherapy as outpatients, although a patient who has an infection or a reaction to chemotherapy can stay for 24 hours without being admitted to the hospital. Patients also receive round-the-clock telephone support.

Pavlovsky was determined to attract top-line doctors, nurses and scientists. "Fundaleu is now paying good salaries to doctors, nurses, technicians and scientists and providing good equipment for them to do research. I think that Fundaleu is now an inspiration for many other institutions in the way that we combine clinical practice and research."

Fundaleu employs only graduate nurses, most of whom have a post-graduate qualification in cancer nursing. "We probably have one of the best rates of nurses to patients in the world – one nurse for every two or three patients. All our nurses can deliver intensive care in any of our rooms. Hundreds of nurses come here to learn how to take care of patients with chemotherapy and our oncology nurses do a lot of teaching around the country.

"We educate our nurses to learn about the treatments, side-effects of chemotherapy, and the doses they have to deliver. Well-trained nurses provide a safety net. If they know the doses of the drug and they know the side-effects, they can avert any prescription mistakes by the physician."

Aged 63, Pavlovsky plans to work for another seven years, before focusing on family and

"Fundaleu is an inspiration for others in the way that we combine clinical practice and research"





Santiago Pavlovsky (with the whip) in competition in Argentina with carriage and horses



With his wife, Tatiana, at the meeting of the Challenge Fund in Rome in January 2005

horses in retirement. But retirement must wait. Pavlovsky, who was named Doctor of the Year in 2000 by the Argentine Ministry of Health, is driven by the need to encourage young doctors to support international research. “Clinical research means you do not only follow a protocol but you collect data and help the statistician to evaluate the data, and present the data in a meeting and, last and most important, you publish the data. If you have 800 cases with good information on treatment, outcomes and side-effects, and you enter an international meta-analysis, your 800 patients can become 20,000.”

Fundaleu is collaborating in a study organised from Spain, treating acute promyelocytic leukaemia (APL) with ATRA (tretinoin), a drug developed from Chinese herbal medicine. Fundaleu is part of the extra-nodal lymphoma study group (IELSG) run by Franco Cavalli at the Oncology Institute of Southern Switzerland in Bellinzona. This looks at very rare lymphomas which affect one site, such as the testes or stomach, where international collaboration is the only way to collect enough data. Evidence from Fundaleu was included in international Cochrane Collaboration reviews of multiple

myeloma, Hodgkin’s lymphoma and acute myelogenous leukaemia (AML). Santiago’s daughter Astrid has completed her second year of fellowship at Fundaleu. Her father believes that the changes in her professional lifetime will be even more dramatic than in his own.

“In my lifetime I have passed from practically no cure for haematological malignancies to around 80% of the children with ALL and 80% of Hodgkin’s lymphoma and around 50% of the non-Hodgkin’s lymphoma. I have seen a doubling of the life of multiple myeloma and chronic lymphocytic leukaemia [CLL].

“Now there is a breakthrough in chronic myelocytic leukaemia [CML]. Glivec [imatinib] is the first drug in the world that appears to be killing the neoplastic cells without killing normal cells. Each year, the news improves. More than 80% of patients who were treated four years ago are still alive without disease. It is fantastic.

“In my daughter’s time, I do not think there will be one drug to cure all neoplastic diseases, but there will be other drugs targeted at specific diseases. I am sure that Astrid and her generation will see more and faster changes than I have seen.”

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