A very useful doctor

Janet Fricker

Ferdy Lejeune went into medicine to be 'useful', and he did well. Thousands of amputations have been avoided thanks to a technique he pioneered. His focus on tumour blood vessels and immunology helped pave the way for some of the most exciting areas of cancer research today. For Lejeune, however, 'useful' is as much a matter of finding out what doesn't work as what does.

Growing up in the Belgian Congo, Ferdinand Lejeune (better known as Ferdy) had an idyllic 'Swallows and Amazons' style childhood, messing about on rivers in boats. The only difference between the Arthur Ransome tale and the exploits of Ferdy and his pals on the Stanley Pool (a lake-like widening at the lower reaches of the Congo River) was that the Belgian boys regularly encountered crocodiles. "While swimming we took it in turns to beat the water with sticks to keep the crocodiles at bay," recalls Lejeune, who on one occasion witnessed a dog being eaten by crocodiles just after he'd left the water. "But even that didn't put us off going in again the next day."

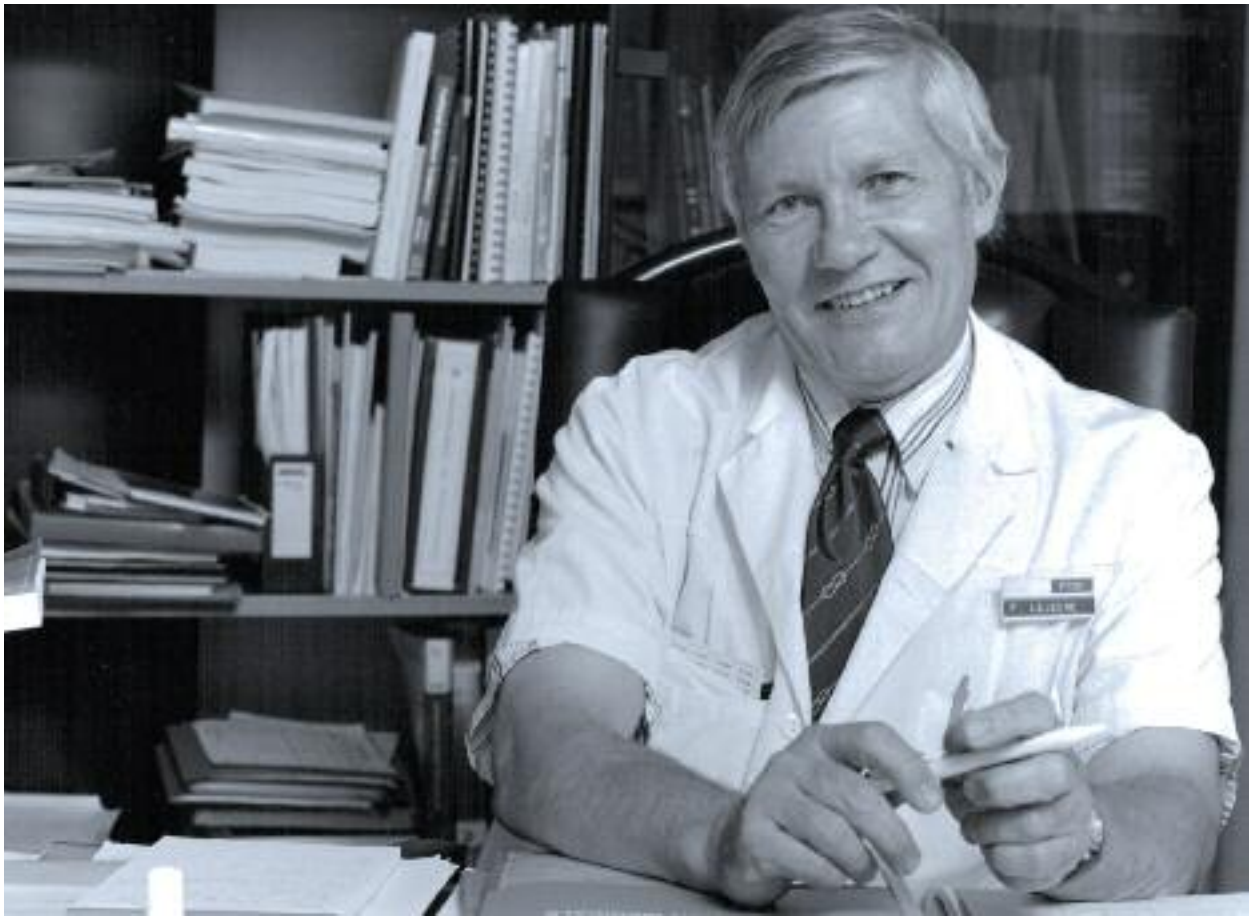
Such *sang-froid* has characterised Lejeune's work as an oncologist and enabled him to take risks, most notably in his pioneering work on use of TNF in isolated limb perfusion. But ironically for someone who has spent a career in melanoma, perhaps the greatest long-term hazard Lejeune encountered as a child was exposure to ultraviolet lamps. "In the Congo, of all places, doctors were worried that UV light was blocked by clouds during the dry season and decided to give us all a course of light treatment. We were herded into big rooms with enormous UV lights and given goggles to protect our eyes."

The Lejeune family settled in the Belgian Congo (now the Democratic Republic of the Congo) in 1946 to escape the deprivation of Belgium after the Second World War. Ferdy's father Ferdinand (who celebrated his 98th birthday last November) had been appointed as an engineer in a cotton textile factory in Leopoldville. The whole experience seemed like a "tropical paradise" to Ferdy, then aged six, and his younger brother and two sisters.

While visiting the factory hospital Lejeune first became interested in medicine. "By becoming a doctor I thought I could make a difference to people's lives. Throughout my life I've wanted to be useful," he says.

In 1957 he enrolled at the Lovanium University, a new Belgian-run college in the Congo staffed entirely by Belgian academics. But the political situation was growing increasingly unstable.

"I remember sitting my pre-clinical exams in the middle of a riot, with shots being fired at the windows," says Lejeune, who despite such distractions still passed with flying colours. In 1960 the Congo gained independence and the Lejeune family relocated to Belgium, with Ferdy switching his medical studies to the Université Libre de Bruxelles. One important legacy from the Congo years was



that it was there Lejeune met his future wife, Claudine Lenain, a biochemistry student. The couple, who married in 1962, recently celebrated their 45th wedding anniversary.

In Belgium Lejeune gained clinical experience at the Jules Bordet Cancer Institute, and felt drawn to oncology. "I appreciated the need for research, because so little was known about cancer. I felt particularly interested in melanoma, since one-third of people getting this cancer are under 40."

In 1970, after training in surgery (where he did breast and melanoma cancer surgery), Lejeune was awarded an International Agency for Research on Cancer (IARC) grant to work at the Chester Beatty Research Institute at the Royal Marsden Hospital in London. At the same time his wife Claudine had been awarded a Royal Society fellowship to research radio-immune assays at the Middlesex Hospital, also in London. Lejeune was trained in electron microscopy by Michael Birbeck (who gave his name to the Birbeck organelles), and used this newly acquired expertise to study melanoma cultures with Peter Alexander and Gordon Hamilton Farley.

Lejeune discovered that there were macrophages within the tumour that were not malignant and were able to eat away at the melanoma cells. The work formed the basis of his PhD thesis (awarded in Belgium in 1976) showing that macrophages are cytotoxic to melanoma.

Magic bullet with a dark side

In 1975 Lloyd Old from the Sloan-Kettering Institute identified 'tumour necrosis factor', or TNF, as the substance secreted by macrophages that attacked tumours. Along with interferon and interleukin, TNF was heralded as one of the most promising 'magic bullets' in molecular biology's assault on cancer, and the race was on to clone the gene. By

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1984, the availability of recombinant TNF had paved the way for extensive studies in animals. But to everyone's surprise the studies proved disappointing. TNF had antitumour properties, but it was also a mediator of septic shock and caused hypotension. By 1988 TNF was being described by the *New York Times* as a molecule with a "dark side", with "too much toxicity and too little efficacy".

Back at the Jules Bordet, Lejeune established a thriving melanoma clinic, attracting patients from all over Belgium. The London experience had got him "well and truly hooked on tumour immunology", and he negotiated to spend half his time running a lab exploring the biology of melanoma.

In one of those career-defining, serendipitous moments, Lejeune was offered free access to the disgraced TNF by a drug rep visiting his clinic. "Chance smiles on those with a prepared mind," says Lejeune. "I thought TNF might enhance the melphalan cocktail we were already using in isolated limb perfusion."

Working with Danielle Lienard, Lejeune was performing an innovative procedure known as 'isolated limb perfusion' (ILP) in patients with intransit melanoma metastasis confined to the limb. ILP involved tying off the affected limb from the rest of the body with a surgical tourniquet to minimise the systemic effects of chemotherapy, and subjecting the tissues to high doses of melphalan. Since the treated limb is attached to a heart lung machine, there's no limit to how long it can be exposed to the drug. While elegantly simple in concept, the procedure is technically complex, requiring continuous monitoring of leakage by introducing radio-labelled proteins and probe recording over the heart.

Prior to ILP, intransit melanoma metastasis (a condition occurring in 5%–8% of melanoma patients) was largely treated by palliative amputation. The introduction of ILP with melphalan produced a complete response rate of 50 %.

"We just copied what we were already doing with chemotherapy, and gave ten fold the maximum tolerated dose of TNF. The effects were awesome," recalls Lejeune, who acknowledges that he benefited from the regulations being "extremely relaxed" in Belgium. "We saw something that's very uncommon in oncology – the effects of therapy could be seen in a few hours. The tumours just melted away."

To achieve an even better result, Lejeune devised a combination therapy with TNF, melphalan and gamma interferon. The triple therapy was well tolerated with a complete response rate of around 80%, and an overall objective response greater than 90%. In soft tissue sarcomas that are inextirpable, the technique has resulted in salvage in 80% of cases, a complete response rate of 20% and an objective response rate of 80%. There is, however, no effect on overall survival in either melanoma or sarcoma.

From the outset Lejeune was not without detractors who told him TNF would kill patients. Here he acknowledges the debt he owes Alexander (Lex) Eggermont, now professor of surgical oncology at the University of Rotterdam in the Netherlands, who believed in the data at a time when everyone else put the positive results down to "hyperselection" of patients. "Alexander persuaded his hospital authorities to implement an ILP-TNF programme. Ultimately it was thanks to our synergy that we persuaded Boehringer Ingelheim to invest in the clinical programme, resulting in the development of the appraisal file," says Lejeune.

Today ILP-TNF is widely acknowledged as a

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The TNF trio. Lejeune (left) with Danielle Lienard and Lex Eggermont, Rotterdam 1996

success story for both melanoma and sarcoma, and is available at 40 hospitals in Europe. Triple therapy is recognised as one of the first attempts at combining immunotherapy and chemotherapy.

Later, working with Curzio Ruegg in Lausanne, they demonstrated that the antivascular activity of TNF results from reduced activation of the adhesion receptor integrin alpha(v) beta(3), which decreases endothelial cell adhesion and blood vessel survival. Further elucidating the mechanisms mediating suppression of integrin, he says, could result in more specific and less toxic TNF treatments.

"Ultimately our work on TNF and integrins sensitised the medical world to the importance of blood vessels in cancer treatment and encouraged people designing anti-angiogenic drugs," says Lejeune.

In 1992 Lejeune was appointed professor of oncology and director of the Multidisciplinary Oncology Centre at Lausanne University Hospital. He had a joint appointment with the Ludwig Institute for Cancer Research, where he was recruited as a clinician with experience in basic science to enhance the translational aspects of Jean-Charles Cerottini's melanoma vaccine research programme.

Slow progress

Treatment options for melanoma have advanced little over the course of Lejeune's forty-year career – surgery is limited to early tumours, regional treatment has only a regional effect with little influence on survival, and there is still no standard of care for stage IV disease. Even the much-touted immuno-therapy still hasn't reached the point of showing a clinical effect.

As chairman and secretary of the EORTC Malignant Melanoma Cooperative Group, Lejeune was instrumental in initiating a number of key melanoma trials, but with disappointing results. In two separate phase III EORTC studies, the group, then led by Lex Eggermont and Ulrich Keilholz, showed that combining cisplatinum plus DTIC (dacarbazine) chemotherapy with either interferon alpha and interleukin 2, or with interferon alpha alone, produced no survival benefits in metastatic melanoma. "Such studies are enormously important because, for me, giving false hope is worse than discovering a treatment to be ineffective," he says.

One reason melanoma has proved so challenging, suggests Lejeune, is that melanocytes come from the ectoderm and are endowed from the outset with the capacity to migrate through the body and invade tissue. "We just need to find melanoma's Achilles heel and decipher the molecular mechanisms responsible for melanoma's high metastatic capacity," says Lejeune, who refuses to be disheartened by the current lack of progress.

He is dismissive, however, of the hundreds of 'promising' agents for melanoma that are touted in journals and at meetings, but which then regularly bomb in clinical trials. "Pharma companies just don't appreciate that implanting pea-like tumours under the skin of mice produces tumours with totally different biological properties from a true metastasis. Progress won't be made unless they start to introduce better animal models."

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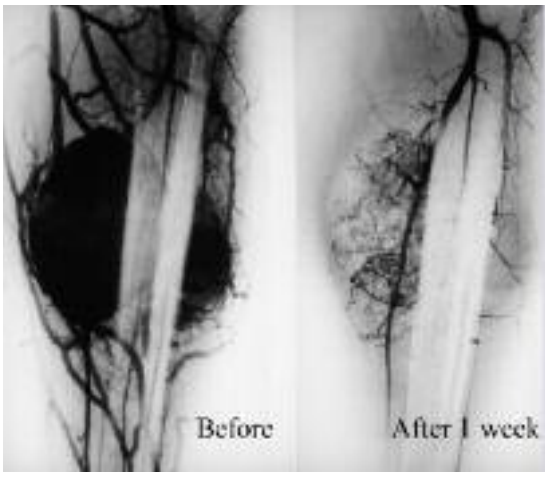
Towards a vaccine

Since joining the Ludwig Institute 15 years ago, Lejeune and his colleagues have been engaged in the quest for the holy grail of melanoma research – an effective vaccine. The team have progressed from injecting tumour cells to utilising the pure peptides found on the surface of tumour cells recognised by lymphocyte receptors. But the whole area has proved unexpectedly complicated. "We've discovered there are several steps in the maturation of lymphocytes, using new tools to gauge whether the resulting lymphocytes are mature enough to kill," says Lejeune.

More recently, they discovered in an *in vivo* model of melanoma that, while CD8 T cells generated in peptide vaccination display robust cytotoxic actions in blood, those extracted directly from tumours are not active. "It appears there's something in the tumour milieu preventing lymphocytes from becoming killers," says Lejeune, who hopes that greater understanding of the mechanism involved will ultimately improve the efficacy of immunotherapy.

The Lausanne team has succeeded in curing mice with a 10^5 melanoma tumour load (100,000 cells, roughly 1/10,000 of 1 cm^3) through vaccination, but found it impossible to cure higher loads.



For the last four years the group has participated in clinical trials, vaccinating patients with metastasis in one lymph node.

But the real future of melanoma vaccination, says Lejeune, may be in protecting individuals deemed to be at high risk of developing the disease.

Lejeune has always been an advocate of melanoma prevention. There are two strategies, he maintains. Persuade people to refrain from sun exposure and make them aware of early warning signs.

"The messages are getting through – the incidence of big melanomas has gone down, and small melanomas up, suggesting earlier diagnosis is occurring. But we're still not identifying medium-sized melanomas quickly enough, and this is serious since any melanoma over 1 mm in thickness can metastasise."

Surprisingly, Lejeune doesn't advocate use of sun screen. In 1999 he took part in a double blind study randomising Swiss and French students to either (sun protection factor) SPF 10 or SPF 30 before they embarked on their holiday. Sun exposure diaries revealed that those allocated the higher factor had 25% longer sun exposure.

The longer exposure, it seems, was subconscious – sun screens delayed sunburn so people felt able to stay out longer. "But burning is a good sign. Burnt cells die, they don't mutate," says Lejeune. "To me the best protection remains wearing a hat and staying in the shade."

Unproven medicines

One negative aspect to practising medicine in Switzerland, he has found, is the tolerance of alternative/complementary medicine. "About 50% of melanoma patients use complementary medicine and I was really shocked when the minister of health decided to allow insurance companies to

Melted away. High-dose TNF has a dramatic impact on leg sarcoma associated vasculature and spares vessels in normal tissues

Student days. Lejeune met his future wife, biochemistry student Claudine Lenain, while studying medicine at a Belgian-run college in the Congo

reimburse alternative medicine without any proof of efficacy," says Lejeune.

His outrage launched his son Stephane on a career debunking complementary medicine. Stephane, who is now married with a daughter, trained first as a sociologist, did his masters in public health and epidemiology and now works for the EORTC. He was instrumental in gaining EORTC funding from the European Commission's 5th Framework to review scientific evidence on complementary medicine and launch a website providing information on the efficacy and safety of alternative medicines used in cancer for the public and health professionals.

Lejeune and his wife also have a daughter, Padmini, whom they adopted in 1978. "Padmini came to us at the age of eight from Madras. She adapted quickly to life in Belgium and spoke fluent French after just three months," remembers Lejeune.

Today Padmini is a dress designer in Belgium and, in addition to looking after two young children, has established her own dress label, making garments with Indian material for Western women.

"It's perfect – Padmini is based in Brussels, but travels regularly to India to source material and keep in touch with her roots."

When Lejeune 'retired' in 2004, his wife and children hoped he'd spend more time with them in Brussels. But today he remains very much at the forefront of melanoma research, and the fact that he no longer has an administration or surgery role gives him the time to think and explore ideas. "I hate games and playing cards and have an obsession with keeping useful," he says.

He still gains enormous pleasure from editing *Melanoma Research*, the translational research journal he launched 17 years ago with Giuseppe Prota and Patrick Riley. Recently, without the pressure to publish, he has found time to write reviews pulling together the latest information on TNF and metastatic melanoma.

A new retirement venture is as a freelance evaluator for a privately owned Swiss research and development company that specialises in partnering opportunities with promising biologics and small-molecule drug candidates.

"In my journal work I've access to developments six months ahead of publication. But here I'm getting fascinating insights into the drugs that'll be around 10 years into the future," says Lejeune.

One hobby he does, however, find time to follow is scouring antique markets for African masks. "I'd completely forgotten about Africa until I came to Lausanne, where something about the reflection of the light from the lake brought it all back and gave me a yen for African culture," says Lejeune, who has accumulated a collection of 30 masks.

"Traditionally the masks are regarded as being inhabited by the spirit of the ancestors, with the concept that everything that happens in life is due to your forebears. I'm very receptive to this message, because as a scientist I make the link between the genes of my ancestors and the masks."