James Edmond Wraith

Paediatrician whose research crucially contributed to treatments for lysosomal storage diseases

James Edmond Wraith, consultant paediatrician (b 1953; q University of Sheffield 1977), died from a neurodegenerative disorder on 10 April 2013.

Ed Wraith chose a specialty that, at the time, some doctors might have seen as a career cul de sac. He trained as a general paediatrician but his career focus was on lysosomal storage diseases (LSDs), a group of progressive neurological conditions. At the start of his career these conditions were untreatable, with symptom control being the only option. His interest was prompted by wanting to improve the care of these patients with rare, life limiting, and disabling conditions. It was certainly not seen as an area where a young doctor could make their mark.

Wraith worked with a paediatrician at the Royal Manchester Children's Hospital. He had an interest in metabolic diseases and started to investigate what could be done to help patients with these disorders. During his career he identified many major genetic mutations in storage diseases, including mucopolysaccharidosis (MPS) types.

He undertook several natural history studies on the diseases, which led to better treatments and clinical classifications. He also wrote the NHS guidelines for management of MPSI, MPSII, and MPSVI; Niemann-Pick type C disease; infantile Pompe disease; and paediatric Gaucher disease.

Wraith became the UK expert on these diseases, and Brian Bigger, lead scientist for the stem cell and neurotherapies laboratory in Manchester, says that Wraith saw roughly half of the 1500 patients in the country. "Manchester does a huge amount of diagnostics, and that was largely driven by Ed," says Bigger. Patients came to Manchester from all over the world for diagnosis, and Wraith travelled widely, lecturing and running clinics. From the beginning he developed close links with patient groups, and the MPS Society funded his first consultant post for two years.

Because of the large numbers of patients coming to the unit it was an obvious base for conducting clinical research, and Wraith led or was the co-investigator on more than 20 clinical trials—notable as drug trials are so rare in paediatrics. These trials resulted in the development of enzyme replacement therapy (ERT) for many of the LSD disease types and a substrate reduction therapy drug for Niemann-Pick type C disease. Six licensed drugs came out of these clinical trials and new products were developed to treat mucopolysaccharidosis types; Fabry disease; and Pompe disease.

Bigger says Wraith had a real compassion for patients, and his work was driven by a desire to help children deemed untreatable. "First there was a treatment for Gaucher disease in 1994, and then along came ERT, and then more therapies. It must have made a huge difference to him, being able to see patients improve," he says.

Wraith also had an interest in stem cell transfer as a treatment for LSDs, which led to a collaboration with the bone marrow transplantation group at Royal Manchester Children's Hospital. Rob Wynn, consultant paediatric haematologist on the group, says his own interest in transplantation for metabolic diseases was driven entirely by Wraith.

He adds: "He [Wraith] was among the first to recognise the utility and role of transplants in these rare disorders, and through referral to transplant teams, support of those teams, and his pivotal role in fostering important collaborations between centres he helped to improve outcomes. Ed did not directly make the decisions in the unit and always left that to us, but he was always absolutely aware of where his patients were up to during the transplant process."

Wraith was born in South Shields in Tyne and Wear to working class parents and won a place at the local grammar school. He trained at Sheffield University, worked for a few years in hospitals in the city, and then moved to Manchester. He took up a clinical research fellow post at the Murdoch Institute for Research into Birth Defects in Melbourne between 1986 and 1988.

He became the clinical director of the Willink Biochemical Genetics Unit at Royal Manchester Children's Hospital in 1993 and insisted that it follow the Australian model with the merger of clinical and metabolic genetics. Bronwyn Kerr, a consultant clinical geneticist at the unit and close colleague, says this was important. "He believed firmly that this was the way forward as the work becomes synergistic. It gave people the chance to collaborate on understanding these diseases," she says.

He pushed for LSDs to get specialist commissioning status and was the lead clinician on the national commissioning group from 2007.

Patient group representatives speak of a doctor who spent his career giving bad news but to whom the families were also incredibly grateful

Wraith had a long ponytail, rarely wore a suit, and was seen as something of a maverick. He was a lifelong Newcastle United supporter but was also very private and outside work was happy at home with his family and two lurchers.

He was also devoted to his patients, giving them his phone number and making himself available to them—perhaps too available sometimes, says Wynn. He even moved within walking distance of the hospital so he could be on hand in emergencies.

Patient group representatives speak of a doctor who spent his career giving bad news but to whom the families were also incredibly grateful. Toni Mathieson, executive director of the Niemann-Pick Disease Group, says: "He recognised that parents were very knowledgeable about the disease and that they knew what was best for their children. He always allowed you to ask questions."

He travelled widely, and his expertise and knowledge were recognised around the world. When he was diagnosed with a rare degenerative disorder in 2009 he cut back on his travelling but retained his clinics and saw patients on the day he died.

Kerr says that he was a true advocate for people with storage diseases. "Not only did he pioneer new drug treatments he gave a voice to people with these diseases," she says.

He leaves his wife, Sue, and three children.

Anne Gulland freelance journalist, London
annecgulland@yahoo.co.uk

Cite this as: *BMJ* 2013;346:f3238

François Jacob

Molecular biology pioneer and Nobel prize winner

François Jacob (b 1920, q University of Paris 1947), died in Paris on 19 April 2013.

In the late 1940s no one suspected that François Jacob was a future Nobel prize winner. Jacob, approaching the ripe age of 30, was not yet sure what he wanted to do in life. He had a medical degree, but a wartime injury prevented him from pursuing his interest in surgery.

He dabbled in various possible careers, such as acting, journalism, and banking, and then became intrigued with science. In 1950, after several rejections, he finally talked his way into a fellowship at the Pasteur Institute to work in the nascent field of molecular biology. At the time, in his own words, he was an "ignoramus" in science. "I knew nothing in science," he admitted a half century later. "I decided that I give myself five years (in science)—either I find something in five years or I do something else."

Jacob found something. Indeed, a lot of things. In 1965 he and two Pasteur Institute colleagues—André Lwoff and Jacques Monod—were awarded the Nobel prize in medicine or physiology "for their discoveries concerning genetic control of enzyme and virus synthesis."[1]

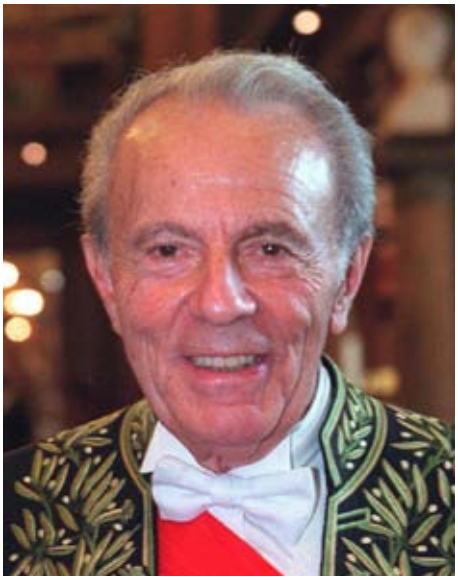
His science education began in 1950 in Lwoff's laboratory which was located in a secluded "stifling" attic at the Pasteur Institute. Jacob worked mainly with the genetic mechanisms existing in bacteria and bacteriophages and with the biochemical effects of mutations. In 1954 he started a collaboration with Élie Wollman to establish the relations between the prophage and genetic material of the bacterium. Their work led to a definition of the mechanism of bacterial conjugation and an analysis of the genetic apparatus of the bacterial cell.

By then he was hooked on science. In his 1988 memoir, *The Statue Within*,[2] Jacob says that during these intense years of scientific discovery he rose from bed each morning eager to get to the laboratory to set up experiments. With each experiment he felt "like a kid unwrapping an unexpected toy."

"I am bored by what has been done, and excited only by what is to do," he wrote, adding: "It took me a long time to realise that this drive toward tomorrow has an advantage in at least one domain: in research."

In 1958 he teamed with Monod to study the mechanisms responsible for the transfer of genetic information as well as the regulatory pathways in the bacterial cell that adjust the activity and synthesis of macromolecules. They would eventually propose a series of new concepts—including messenger RNA, regulator genes, operons, and allosteric proteins.

Michel Morange, a biologist who worked in Jacob's laboratory in the 1980s, says that Jacob's and Monod's "operon model" was the first to describe the mechanisms that regulate gene expression. It had a major impact on biology by demonstrating the value of pooling experience in biochemistry and genetics. "François Jacob's particular skill in all of these major research projects was his ability to conceptualise specific molecular mechanisms underlying complex observations and abstract paradigms," says Morange, now a professor at the University of Paris and École normale supérieure. "He was able to start from very complex observations and to explain them as simple mechanisms."



In his 1988 memoir Jacob said that during these intense years of scientific discovery he rose from bed each morning eager to get to the laboratory to set up experiments. With each experiment he felt "like a kid unwrapping an unexpected toy"

François Jacob was born 17 June 1920 in Nancy, France, but was schooled for 10 years at the prestigious Lycée Carnot in Paris. In 1938 he began studying medicine at the University of Paris, intending to become a surgeon. After Germany invaded France in 1940 he fled to London to join the Free French Forces under Charles de Gaulle. He served first in northern Africa as a battlefield medical officer before contracting a minor arm wound in 1943.

In early August 1944 he landed on Utah Beach in France. Eight days later he was severely wounded during a German attack while using his body to protect another soldier. He was awarded the Croix de la Libération, France's highest second world war military honour. His death in April was announced by France's Defence Ministry.[3]

He returned to medical school, earning his medical degree in 1947 and his doctorate in 1954. He spent his whole scientific career at the Pasteur Institute, serving as head of cellular genetics from 1960 until retirement in 1991, and as the institute's chairman of the board from 1982 to 1988. He was also professor at the College of France from 1965 to 1992.

In the late 1960s, after winning the Nobel prize, Jacob quit using bacteria as research models and switched to mice, which are genetically closer to humans. For his studies into embryonic development in mice he chose to use teratocarcinoma cells, the ancestors of the stem cells now grown in laboratories across the world. His later work included studying how cancer grows and spreads.

In addition to his memoirs, Jacob wrote four acclaimed books exploring science and the history of the life sciences. In 1994 he was awarded Rockefeller University's Lewis Thomas prize for writing about science. "All his (written) works demonstrate a substantial degree of originality in both style and content," says Morange.

Jacob was an honorary member of several scientific academies, including the Royal Society in London. In 2012, the Pasteur Institute inaugurated the new François Jacob Centre. "From the new building I can see my old (attic) laboratory," Jacob wrote, adding: "It was a hive of activity and really quite extraordinary. It was one of the most enjoyable and productive periods of my life."

Jacob leaves four children from his first wife, the pianist Lise Bloch, who died in 1983; and his second wife, Geneviève Barrier, and grandchildren.

Ned Stafford freelance journalist, Hamburg
ns@europefn.de

References are in the version on bmj.com.

Cite this as: *BMJ* 2013;346:f3611