

## OBITUARY

# Fred S. Rosen (1930–2005)

Immunologist, paediatrician and polymath

Fred Rosen, who died on 21 May — four days short of his seventy-fifth birthday and three days after a celebration to mark his retirement as president of the CBR Institute for Biomedical Research in Boston, Massachusetts — combined in his person a range of attributes unparalleled among his contemporaries. His scientific achievements, as one of the most cited authors in biomedical science, were allied to a legendary clinical acumen, and a warmth and authority that secured the trust and devotion of his patients.

Rosen passed most of his professional life at Harvard — at the Medical School, the Children's Hospital and the Center for Blood Research. This last he transformed, by dint of his formidable persuasive powers as a fund-raiser and his unerring eye for young talent, from an obscure relic into one of today's foremost centres of biomedical research. In his own field, that of hereditary immunodeficiencies — failures, commonly calamitous, at various sites in the labyrinth of the human immune system — he was undisputed monarch.

Rosen gave early proof of his scientific mettle. He took special pride in the discovery, while still a resident, of a disease (X-linked hyper-IgM syndrome), the manifestations of which had long baffled paediatricians. The antibodies, or immunoglobulins, in the blood are the first line of defence against infection, and one form, IgM, predominates at birth. Rosen had already established that what were known as 'natural' antibodies to preceding generations of immunologists were in fact IgM molecules, which are unable to cross the placenta: this is the basis of the susceptibility of babies to bacterial infections. IgM is normally supplanted soon after birth by gamma globulin, or IgG. Rosen showed that the lack of IgG in his patients arose from an absence of the population of cells (B cells) in which it is normally made. This in turn resulted from the primary defect, which lies in the complementary cells (T cells) that in the normal state activate the B cells; and finally Rosen and his colleagues identified the aberrant gene.

He went on to show that another lethal immune deficiency (X-linked agammaglobulinaemia) was characterized by a lack of all circulating B cells, and that the so-called common variable immunodeficiency could have a variety of causes; this revelation stimulated the search for unrecognized gene defects. All these discoveries shed new light on the workings of the normal immune system and redirected

much of the thinking in the field.

The complement cascade, a set of surveillance proteins circulating in the blood, is another part of the immunological armoury. These proteins act by attracting phagocytes, specialized cells that engulf and destroy bacteria or other interlopers. Rosen and his colleagues made a lasting impact on many aspects of this system — by the discovery, for example, of an inhibitor that lies at the root of hereditary malfunctions of one of the proteins (C1). Perhaps the most spectacular coup concerned another complement constituent, C3, a deficiency of which Rosen was able to link to a previously unfathomed disease in children. This proved the key to several other hereditary conditions, and further studies by Rosen and his associates eventually uncovered the chemical route by which C3 provokes phagocytosis.

Rosen's last great contribution centred on an anomalous molecule found on the surface of T cells in patients suffering from a severe malady called Wiskott–Aldrich syndrome. Its chemical nature led Rosen to divine that the anomaly might engender a disturbance in the cell's internal network of filaments governing shape and movement. So indeed it proved, and the discovery initiated a new departure in cell biology.

There was more, but what united all of Rosen's undertakings was an acute sense of purpose, for his concern throughout was to understand the genesis of diseases, and to devise methods of treatment. He promoted the now universal treatment of immune deficiency with intravenous IgG, and thereby saved many lives and much misery. He and his colleagues performed the first successful bone-marrow transplants for two of the most dire immune conditions. This was quintessential 'translational research', long before that dispiriting term was invented.

Albert Szent-Györgyi viewed the practice of science as "seeing what everybody else has seen, and thinking what nobody else has thought". This was Rosen's supreme gift, and his capacity to discern an interesting, important and, above all, soluble problem attracted a succession of talented and percipient colleagues, all eager to take up the challenges that he defined, and with all of whom he worked closely. Through everything, he treated, comforted and cheered his paediatric patients, for he had an especial rapport with the young, and he taught generations of students. His very appearance, that of an ample, genial teddy



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bear, radiated reassurance. His prodigious knowledge and sagacity made him a universal fount of information and good sense — the "primal Google", in the words of one of his acolytes.

Fred Rosen had friends in all parts of the world. He could converse, write and lecture in any of a half-dozen or more languages. He was especially drawn to Russia and its literature, music and culture. He was instrumental in setting up a paediatric leukaemia unit in St Petersburg. On a typical occasion, he returned from South Africa, having interviewed and collected blood samples from a family with a new type of complement anomaly. They were Afrikaaner farmers, he recounted, and he had been surprised to find that they spoke no English at all. How then could he communicate with them? He looked mildly surprised at such an inane question: why, you could speak Dutch to them, of course.

Rosen, in short, was a formidable polymath. He read omnivorously and retained it all. He knew more about antique furniture and silver than the dealers whom he patronized. He shopped at Fauchon and Hermès, had his shirts made in Jermyn Street and took tea among the dowagers at Fortnum & Mason. His friends were astonished that this archetypal urbanite should have built a graceful house on the island of Anguilla in the Caribbean, and have found a warm affinity with the local community. It was there that he decided his remains should rest. ■

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