Presentation of Leslie Brent, 1994 Medawar Prize Awardee

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LESLIE Brent was the youngest member of the so-called British "holy trinity" whose description of acquired immunologic tolerance 41 years ago launched the modern era of transplantation. Brent, who was 28 years old at the time, had been only 22 in 1947 when he first met Medawar, then chairman of the Department of Zoology at the University of Birmingham.

However, like many children of this turbulent century, Brent already had been through a lifetime. This distinguished Englishman actually was born in Koslin (Germany) and came to Britain alone at the age of 13 as one of 10,000 children saved by "Operation Kindertransport" (Fig 1). The rest of his family was lost in the holocaust.

Between the ages of 18 to 22, he became an infantryman, rising to the rank of captain. However, his ambition was to be a teacher, not a soldier. This came to pass, but on a scale he scarcely could have imagined. After discharge from the army, 4 years at the University of Birmingham, selection in 1951 as the outstanding graduating student, and a term as president of the Student's Union, he received a Bachelor of Science degree.

Fig 1. The young Brent.

That spring, Medawar accepted the Chair of Zoology at the University College, London, and invited Billingham and Brent to move with him. Billingham, who had completed his graduate studies with Medawar over the preceding 4 years, was already an established investigator. Brent became their graduate student. Fig 2 shows Professor Medawar and his star pupil Brent who was then 33 years old.

The holy trinity was intact for 6 golden years—1951 to 1957. In between times, the two conceptual brackets enclosing the fundamental principles of transplantation immunology were put in place: at one end the acquisition of immunologic tolerance by Billingham, Brent, and Medawar,[1] and at the other the troublesome handmaiden of tolerance, graft-vs-host disease (GVHD).

The latter discovery (GVHD) was made by Billingham and Brent[2] and independently by Simonsen.[3] Both reports indicated that the engrafted donor leukocytes (in these experiments, splenocytes) upon which tolerance depended could turn the tables and reject the defenseless recipient unless the tissue match was a close or perfect one. The dream of 1953 was suddenly a nightmare. Or was it?

On the contrary, the work took a straight line to clinical application. The immunologically pristine state of Billingham, Brent, and Medawar's fetal mice could be simulated in adult mice and in human recipients by irradiating them, and then reconstituting their ablated bone marrow with the bone marrow of adult donors. In 1968, 15 years after the epic Billingham, Brent, and Medawar publication, Robert Good[4] and Fritz Bach[5] reported in the *Lancet* the first successful human bone marrow transplantations. Both of these recipients are still alive. However, the GVHD delineated by Billingham, Brent, and Simonsen could be avoided or managed only with MHC-matched donors.[6]

The conceptual vacuum left by these developments was that there was no explanation why mismatched whole organs could be successfully transplanted and could often induce donor-specific nonreactivity. Here, the original discoveries by Billingham and Brent and by Simonsen eventually cast a clarifying light. It was found about 2 years ago that donor leukocytes of bone marrow origin, which are part of the structure of all organ grafts (the so-called

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Fig 2. The professor and the student.

"passenger leukocytes"), migrate from the organs and survive throughout the recipients where they can be found as long as 30 years later.[7] Under immunosuppression in patients, and in some animals without therapy, a small fragment of what can be construed as a disseminated pocket of extramedullary donor bone marrow became assimilated into the overwhelmingly larger immunologic network of the host.

Thus, whole organ transplantation involved a mutually cancelling GVH as well as a host-vs-graft (rejection) reaction. These two components of graft acceptance (and tolerance), which originally had been defined separately, were in fact interactive. Now, the original observations of GVHD made by Billingham and Brent and by Simonsen were belatedly realized to be the missing piece of the puzzle as had once been suspected by Simonsen.[8]

Professor Brent, your legendary contributions (along with those of Billingham and Simonsen) to an understanding of *both* limbs of the bidirectional immune reaction involved in transplantation are being acknowledged and honored today. Congratulations!!!

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