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Editorial

Surgery: art or science? Birth of organ transplantation

TE Starzl

The revolution in organ transplantation that occurred between 1950 and 1963 can be used to illustrate the way that surgery has influenced science, all the while preserving a niche as an art form. This modern era of transplantation immunology had begun several years earlier when Peter Brian Medawar, a 24-year-old zoologist fresh from graduate studies at Oxford University, was assigned to the service of the British plastic surgeon Dr Thomas Gibson to determine if skin allografts could be used to treat casualties from the Battle of Britain.

First in human studies [1] and then with simple and logical rabbit experiments [2], it was shown that rejection of the skin was an immunologic phenomenon analogous to the cell mediated delayed hypersensitivity that confers immunity to diseases such as tuberculosis [3–5]. The principal evidence was that repetitive grafts from the same donor were rejected more rapidly with each successive attempt [1, 2]. The donor specific sensitisation caused by repetitive grafting confirmed previous clinical observations by the surgeon Emil Holman of Stanford University in skin grafted burn victims [6].

THE FRENCH "TRANSPLANTATION CLUB"

The potential value of transplantation procedures had attracted the early attention of French surgeons and, eventually, many of the grand figures of French surgery, medicine, and science contributed to the new field. Clinical transplantation activity began in France within the first few years of the 20th century, when Jaboulay in Lyon [7] and others in France and Germany performed animal to human kidney transplantation [8–10]. Although the Russian Yu Yu Voronoy of Kiev reported the first known attempt at human to human renal transplantation in 1936 [11], the clinical field was quiescent until 1951 when René Küss [12] and Charles Dubost [13] of Paris and Marceau Servelle of Strasbourg [14] carried out a series of cadaveric renal transplantations. A short time later, the urologist Louis Michon at the Necker Hospital (Paris) and a team of vascular surgeons reported the now commonplace transplantation of a kidney from a live volunteer donor [15].

Visitors flocked to France in the early 1950s to learn first hand from this experience, including John Merrill from the Peter Bent Brigham Hospital, Boston, who, with the young French physician, Jean Hamburger, founded the medical discipline of nephrology. As important as the early and subsequent contributions of Küss [16] and Hamburger [17] were to transplantation, the scientific basis for this specialty in France went far deeper. The roots of histocompatibility research were nourished in Paris by Jean Dausset (Nobel Laureate, 1980) [18]. In addition, Georges Mathé, the father of bone marrow transplantation [19], was part of the French "transplantation club" of the 1950s and early 1960s.

THE SURGEONS ROLE

At a technical level

The kidneys in the early French cases were removed from convict donors after their execution by guillotine. The pelvic kidney transplant procedure originally used by Küss and refined subsequently by the French surgeons has been used hundreds of thousands of times, including for the celebrated identical

(monozygotic) twin transplantations performed by Murray (Nobel laureate, 1990) and his associates [20] in Boston. The skills necessary to transplant the kidney (the only candidate organ until the 1960s) were applications of what became increasingly sophisticated conventional operative procedures during and after World War II.

The vascular surgical technology originated early in the century in the experimental laboratory of the Frenchman Alexis Carrel [21] (Nobel Laureate, 1912) and had a pervasive effect on essentially all surgical specialties. Although Carrel suspected that transplanted organs were not permanently accepted because of an immunologic barrier, the biologic specificity of the field of transplantation awaited the definitive studies of Medawar and Gibson.

Such experimental work in the laboratory has been critical to each major step in the evolution of organ transplantation. Progress in animal models has been transferred to the clinics, and conversely, problems encountered in the patients have been brought back to the laboratory for clarification, thus a flux has been continuous since the time of Carrel. It resulted in the development of operative techniques, the improvement of immunosuppression, and clarification of previously enigmatic physiologic principles. The objective was to avoid human experimentation, rather than depend on it, when the time came to apply these potentially life-saving procedures in the clinic.

At a leadership level

A co-product of these efforts was the concept of team construction in the laboratory. The more experience gained in the laboratory, the better the team will perform in the human operating room. The actual operations require separate donor and recipient teams, the activities of which must be closely knit. During the transplant operation, co-operation among surgeons, anaesthesiologists, nurses, and technicians is essential. From the very beginning, one of the objectives of laboratory work was to create harmony within the team, and amongst the physician specialists with whom the team would react.

The core roles of the surgeons and the steps involved in transplant operations are identical to those of conventional clinical practice. Someone, most commonly but not necessarily a surgeon, inevitably will emerge from this experience as the team leader. Rigidity, impatience, selfishness, dishonesty, inhumanity, ignorance, and poor organizational skills are disqualifying characteristics. In addition to possessing these graces, as well as professional competence, the leader must have those scientific instincts which allow advances.

PROGRESS AND CULTURE

The Journal of the American Academy of Arts and Sciences (called "Daedalus") is a quarterly publication in which topics of social importance and interest are examined in depth. The winter 1998 issue entitled "Science and Culture" contained two articles that explored the interface between science and art. One was written by Gerald Holton (Mallinckrodt Professor of Physics Emeritus at Harvard) [22], and the other by Lorraine Daston (Director, Max Planck Institute for the History of Science, Berlin) [23].

Both described how the influence of the imagination had long awakened fear among the rank and file of scientists and physicians. Why? Because it could make up a world of its own that was livelier, lovelier, or more logical that the real world; this power, which feeds art, could be an invitation to fraud. In a 1961 issue of the New England Journal of Medicine, the "real world" of transplantation was described by F McFarland Burnet (Nobel Laureate, 1960) in sombre terms "... much thought has been given to ways by which tissues or organs not genetically and antigenically identical with the patient might be made to survive and function in the alien environment. On the whole the present outlook is highly unfavourable to success... [24]".

Yet, there already was a place for legitimate dreams. Once it was established that rejection was an immune reaction, strategies had begun to evolve to weaken the recipient immune system. By 1950–51, total body irradiation [25] and adrenal cortical steroids [26, 27] had been shown in the experimental laboratory to delay skin rejection. The immunosuppressive effect was either minor if the animals survived, or lethal to the recipient if the grafts were spared.

Although there appeared to be no margin of safety, the surgeon Joseph Murray demonstrated for the first time at the Peter Bent Brigham Hospital in January 1959 that human renal transplantation was feasible, following sublethal total body irradiation (TBI) of a fraternal twin recipient [28]. The success with TBI

could not be duplicated at the Boston centre, but five more examples of long survival (two with unrelated kidney donors) were reported from Paris during the next 3 years on the services of René Küss [29] and Jean Hamburger [30].

Three years later (April, 1962), it was shown that the same result could be accomplished pharmacologically, using chronic therapy with azathioprine [31]. This advance was preceded by extensive studies in dogs by the Englishman Sir Roy Calne [32]. Although the clinical results with azathioprine alone were no better than with total body irradiation, the fog of pessimism surrounding clinical organ transplantation lifted dramatically in 1962 when azathioprine was systematically combined with dose-manoeuvrable prednisone at the University of Colorado [33]. Rejection that developed despite azathioprine treatment could be reversed surprisingly easily with high doses of the prednisone. More importantly, the subsequent need for maintenance immunosuppression with both drugs frequently declined.

The same characteristic cycle of immunologic confrontation and resolution was soon observed with the liver [34], ultimately with all other transplanted whole organs, and over the next 3 decades with each of the increasingly potent new baseline drugs substituted for azathioprine. Recognition, reversal, and the progressively easier control of rejection was the base upon which the new and increasingly practical multidisciplinary specialty of transplantation was constructed. Thirty years and a revolution in immunology elapsed before the meaning of the mysterious change in host/graft relationship that began in the first few weeks after transplantation was resolved.

This was made possible by a study of the still-surviving early Colorado kidney and liver recipients who by then were as long as 30 years post-transplantation [35, 36]. Donor leukocytes of bone marrow origin (including pluripotent stem cells), which are part of the structure of all organ grafts (the so-called "passenger leukocytes"), had migrated from the transplanted organs and could still be found in small numbers in the recipient skin, heart, lymph nodes, blood, and elsewhere. It is only now becoming clear how changes in the organ and the host caused by the migration and persistence of these donor cells allow "allograft acceptance" [37].

How could the activities so long ago of the persons named here from France, England and the United States have had such an impact on medicine and science, particularly in a modern era in which individuals are increasingly viewed as mere cogs in a multidisciplinary machine? By obliterating the artificial distinction between art and science perhaps they were able to exercise the imagination and creativity of the artist. Their expressions of individuality allowed them to see and create things far beyond the reach of the comfortable Philistines who criticized their efforts at the time.

In his book, "The Sleepwalkers", Arthur Kœstler wrote: "... 'Progress' can by definition never go wrong; [Darwinian] evolution constantly does; and so does the evolution of ideas, including those of 'exact science'. New ideas are thrown up spontaneously like mutations; the vast majority of them are useless crank theories, the equivalent of biological freaks without survival-value" [38]. Viewed from the vantage point of 1998, the ideas of the French surgeons of a half century ago, and Carrel long before then, were anything but freaks. They were part of the primordium for the birth of organ transplantation.

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