CLINICAL SURGERY INTERNATIONAL

VOL. 3

Tissue Transplantation

EDITED BY

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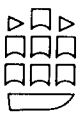

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Preface

Transplantation has come of age. Renal transplantation is now the treatment of choice for end-stage renal failure, and corneal grafting is so widely practised and successful that it is often forgotten that it is a tissue allograft, albeit a rather special one. Some success has been achieved with cardiac and liver transplantation, while the possibility of successful pancreatic transplantation appears not too distant. An increasing knowledge of the problems of transplantation of other tissues, for example the lung and musculoskeletal tissues, enables one to see their clinical application in the future.

However the overriding problem to be solved in the transplantation of any tissue (with possibly the exception of the cornea) is the immune response of the host to the foreign histocompatibility antigens in the grafted tissue (the rejection reaction), and its suppression. If relatively safe suppression of rejection could be achieved then virtually any tissue or organ could be transplanted, for on the whole the technical problems of transplantation of organs and tissues have been solved (or soon would be).

Has there been progress in our knowledge of the rejection reaction and our ability to suppress it by either better tissue matching or better immunosuppression? Unquestionably yes, for we do know more about the mechanism of rejection, and as we look at progress in matching for HLA-DR, the recognition of the transfusion effect in renal transplantation and the advent of cyclosporin A and total lymphoid irradiation as newer methods of immunosuppression, it is apparent that the whole field of transplantation biology is on the move. Perhaps even the clinical Holy Grail of transplantation, namely specific immunosuppression, in which the immune response of the recipient is suppressed only against the foreign graft (and which can be induced in certain experimental models) will be achieved in our lifetime.

In this volume the contributors, all leading authorities in their field, have presented the current state of knowledge and practice in the subject to which I have asked them to address themselves. I hope that the final product succinctly reviews the state of the art, which readers not only with a specialist interest in transplantation but also those with a general interest in medicine and surgery, will find of value. For familiarity with the current state of transplantation can no longer be the province of the specialist surgeon or physician. All practising surgeons and physicians should be aware of developments in this field, for increasingly patients

and their relatives want to know whether transplantation has any part to play in the management of their illness, and indeed it may well have in many instances in the near future.

Oxford, 1982 P.J.M.

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1 A history of transplantation

DAVID HAMILTON

The early history of transplantation is linked with the earliest attempts at plastic surgery. Leaving aside the magical claims for transplantation of organs found in Chinese history and the slightly better authenticated story of the total leg replacement by the saints Cosmas and Damian, the modern era started with the classic work of the Bologna surgeon Gaspare Tagliacozzi (1545–1599), *De Curtorum Chirurgia per Insitionem* (1597) – (The Surgery of Mutilation by Grafting). In it he described what was later to be called the forearm flap, attaching a skin flap from the forearm to the nose, severing its original connections some weeks later. These methods had been derived from those of Italian empirics, notably the Brancas in Sicily, who had in turn followed the ancient Indian plastic surgical methods recorded in the Sushruta manuscripts. Tagliacozzi never described the use of allograft skin or of the use of a live donor attached to the recipient, for not only did he feel that such a donation would be physically impossible, but he also seemed to reject the idea of allografts because of the 'force and power' of the individual. It was to be 400 years before 'this force and power' was to be acknowledged as a major biological phenomenon, and rejection of tissue allografts accepted as the rule rather than the exception. During the decline in the status of surgery during the 17th century, Tagliacozzi's original text was ignored, while fanciful stories of his use of nose allografts from slaves were put about and his sensible plastic surgery was satirised.

The revival

It was the work of John Hunter that heralded the revival of interest in skin grafting and transplantation. His claims for success with ovarian and testicular grafts between unrelated animals have not been confirmed, nor has his experimental work which seemed to justify clinical tooth transplants. But his experimental approach heralded the modern era of surgery and he was the first to use the term 'transplant'. Interestingly, his transplant terminology also used 'scion' for the graft, and it is likely that his use of a botanical

Fig. 1.1 Patient with forearm flap to lip as practised by Tagliacozzi. Reproduced with permission of the publishers, Hoepli, Milan and New York.

term reveals that these early workers regarded human transplants as ruled by the same laws as grafting in the plant kingdom, namely that tissue of widely different origins could unite, and that firm adhesion alone was required for success.

Tagliacozzi's neglected work was revived in the early 19th century as a result of better scholarship, which revealed his original work as he himself had described it, rather than allowing the myths surrounding his work to continue. In addition, the British colonial expansion in India led to the rediscovery there of the ancient plastic surgical methods which were still practised by surgical empirics. Cautiously the forehead flaps were reintroduced in the west, first by the British military surgeon Joseph Constantine Carpue (1764–1846), and quickly thereafter by others. A few claims were also made at this time for

Fig. 1.2 The first patient of Carpue with a forehead flap replacing a destroyed nose. Reproduced by courtesy of the Wellcome Trustees.

success with full–thickness autografts, both in human and in experimental animals, notably by Giuseppe Baronio (1759–1811) in Milan. But there were also many failures to get thick grafts to take. It was not until 1869 that the crucial factor in the success of human skin grafting was discovered, namely that the skin graft had to be thin. It is not known whether Jacques Louis Reverdin (1842–1929), then a young house-surgeon, empirically derived his method of using thin pinch grafts – 'lambeaux cutanes' – or whether the young man had heard of the new histological work on graft healing by Paul Bert in 1863 which showed that the ingrowth of new host vessels was required for graft nutrition. There was a major clinical need for such skin grafting in the mid-19th century, since the commonest cause of admission to the surgical wards was for 'common ulcers' of the leg, a non-varicose condition probably

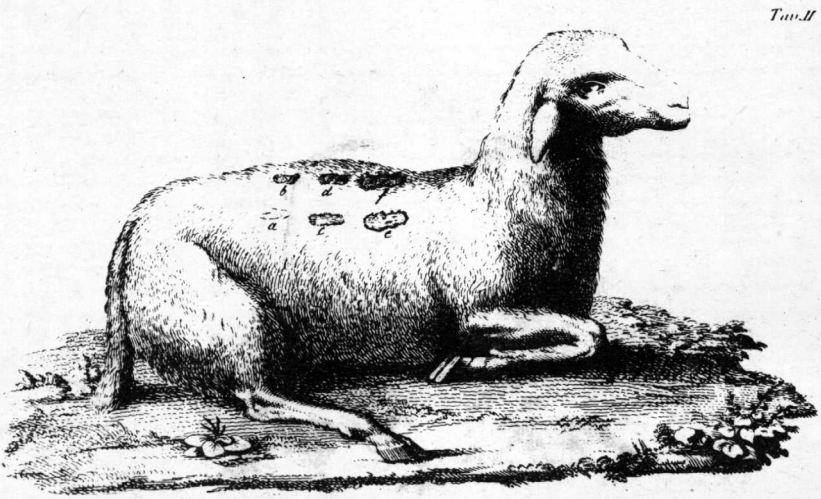

Fig. 1.3 Baronio's successful full thickness autografts in a sheep. Reproduced by courtesy of the Wellcome Trustees.

resulting from nutritional deficiency. There were also many unhealed burns and syphilitic ulcers to be treated.

The allograft era

The use of the new grafting methods spread and they were improved by C. Thiersch's method of removing split-thickness grafts described in 1886. But, almost in homage to the Tagliacozzi legend of the slave donors, or perhaps because of success with plant grafting, there followed a period of widespread use of allograft skin and fragments of organs. While a few surgeons and scientists declared that only autografts succeeded, the consensus was that allografts and even xenografts might work. Even Reverdin had reported success with xenograft skin.

In explaining how these claims could be made, there can be a degree of innocent self-deception in judging the success of skin grafting. Any skin graft leaves a pad of collagen when it rejects, and this may be mistaken for a successful graft. Epithelialisation can also occur under a rejecting graft by ingrowth from the sides, and this new skin can be confused with successful grafting. Added to these spurious successes must have been the encouragement coming from reports of undoubted success with allograft bone by William MacEwen in 1881 and successful corneal grafting by Edward Zirm in 1905. It is hardly surprising that there followed claims for success with gland grafting.

Prior to the mid-19th century, surgeons could only be concerned with the treatment of trauma and of external tumours and ulcers. But by the late 19th century, surgery could be more adventurous as a result of the introduction of anaesthesia and antiseptics. Surgeons could now contemplate treatment for the newly described diseases and deficiencies in the unexplored interior of the

Fig. 1.4 Professor Gosselin with his assistants in Paris in 1870. Reverdin is seated on his right. Reproduced with permission of the publishers, Aarau, Switzerland.

body. For example, endocrinology was advancing with particular speed. Study of the glands of the body had some striking successes. J.L. Reverdin made his second great contribution to medical science by noticing that after the first total thyroidectomies for goitre, a myxoedematous state appeared and Theodor Kocher and others were to reason that the gland should only be partially removed. They also discovered that a thyroid extract would reverse the states of myxoedema and cretinism. Kocher, who gained a Nobel Prize in 1909 for his work, also advocated allotransplants of thyroid for myxoedema, but extract therapy proved to be more convenient.

Other workers argued, reasonably, that the same approach must succeed in other glandular deficiencies, and Brown-Séquard himself, in the twilight of his career, announced his extraction of a rejuvenating substance from guinea pig testicles. This extract, and many others from other glands, thereafter had a place in orthodox therapy – 'organotherapy' – until the early 20th century. At this point, though the success of some extracts, like thyroid powder, was undoubted, the use of testicular extracts was discredited, and instead there was a vogue for testicular grafting. The original pioneers of this had orthodox posts and careers, but others who achieved fame, like Serge Voronoff (1866–1951) while they had an orthodox early career (Voronoff wrote the entry on 'Rejuvenation' in the 1926 *Encyclopaedia Britannica*) did not return later to the establishment fold when the discovery of testosterone and the demonstration of its lack of sexual or other stimulation, discredited the entire approach. Other gland transplanters started outside the orthodox ranks entirely, and the greatest of these was the Kansas goat-gland surgeon, John R. Brinkley, who made a fortune using donor tissue from odourless local goats.

The modern era

1. Carrel and vascular surgery

The confusing allograft era slowly came to an end. Though scientists like G. Schöne in 1912 and Erich Lexer of Jena in 1914 clearly stated that rejection of allografts was inevitable and the Danish scientist C.O. Jensen in 1903 even suggested that this rejection was an immunological event, claims for allograft survival continued. Plausible reports of skin graft success continued to appear, crediting the survival to matching of donor and recipient for their blood groups or because human neonatal foreskin allografts were used. But, starting in the early 20th century, there were new results from novel transplanting methods which contrasted sharply with the uncertainties of skin grafting and the claims for effects with tissue slice or fragment implantation. This advance was the result of new surgical methods which allowed experimental transplantation of organs.

Alexis Carrel (1873–1944), the ambitious French émigré, worked after his arrival in America with the inventive but self-effacing Charles C. Guthrie in the Hull Physiological Laboratory of the University of Chicago to devise reliable methods of suturing blood vessels. As a result they were able to carry out a remarkable series of experimental organ transplants. Though they were primarily, and understandably, only concerned with perfecting the surgical technique, they also did many allografts, usually of kidneys, and noted that these failed eventually, findings confirmed and extended by the Mayo Clinic group, notably Williamson and Ibuka. Guthrie, who was aware of the growing knowledge of immunology and of how the body rid itself of invading bacteria, remarked prophetically that if transplantation was to succeed, then 'the principles of immunology which had had such success elsewhere, might be applied with benefit to transplantation'. Guthrie, who had eventually to protest at Carrel's failure to acknowledge his contribution, did not share in Carrel's Nobel Prize of 1912. Carrel moved to the Rockefeller Institute for Medical Research in 1906 where, in spite of the presence of the transplant scientist J.B. Murphy, he turned instead to devising methods of tissue culture. But during this time he devised a workable organ perfusion apparatus to preserve the heart.

2. The mechanisms of rejection

World War II had profound effects on science and accelerated progress in the understanding of kidney disease and tissue transplantation. The war produced new clinical problems, such as massive burns and new forms of renal failure, problems for which existing therapies were ineffective. The fearful burns on the faces and hands of British fighter pilots caused concern, and in civilian life the acute renal failure seen in those buried under bombed buildings puzzled the interested physicians. They also saw for the first time acute renal failure as a result of mismatched blood transfusion, as well as the obstruction of ureters by crystals from the new sulphonamide drugs.

Of crucial significance to the future of kidney transplantation was the independent development, by W.J. Kolff in Holland and N. Alwall in Sweden, of the first artificial kidney machines to be used regularly. The later use of

this method of treatment was an important factor in allowing kidney transplantation to succeed. The war effort in America also directed efforts towards the final synthesis of steroid hormones and a war accident, in which mustard gas exploded, gave the clue that the nitrogen mustard compounds had antimitotic properties. These two drugs, plus the knowledge of the biological effects of radiation also resulting from the war, were to make successful transplantation possible later.

In Britain during World War II the necessary collectivism meant a new degree of government intervention and this central direction strengthened the Medical Research Council in its support of research necessary for the war effort e.g. studies on the 'crush syndrome', fluid balance, antibiotics and burns. The plans for an MRC Burns Unit at Oxford came to nothing and instead it was set up in Glasgow, which already had, in the Royal Infirmary, special wards dealing with the large number of local civilian burns. Peter B. Medawar, who had already helped the MRC with an investigation of the toxicity of tannic acid, an older method of treating burns, became interested in the problem of skin grafting as a result of seeing a seriously burned pilot in an Oxford Hospital. His request to the MRC for funds for a two-month study period in Glasgow was granted. There, he and Thomas Gibson carried out the simple experiment which showed that a 'second set' of skin grafts from a parent to a burned child were rejected more quickly than the first set. They reported this work in 1943. For Gibson, the plastic surgeon, it was final proof that allografts were of no immediate clinical use: for Medawar it was evidence that allograft rejection was a major, unexplained, immunological mechanism. Back in Oxford, he repeated these basic observations in rabbits, and termed

Fig. 1.5 Participants at the 1954 Ciba Foundation symposium on Preservation and Transplantation of Normal Tissues. Reproduced by courtesy of the Ciba Foundation Archives.