Chapter 4
The First Limb Transplants with Cyclosporine

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4.1 Introduction

Cyclosporine was first described in 1976 as a fungal metabolite and found to have remarkable immunosuppressive properties both experimentally and clinically.\(^1\) It was several years later that at the University of California, Irvine, College of Medicine, Drs. Kirby Black (Research Director for the Plastic Surgery Division within the Department of Surgery) and Charles W. Hewitt (Director of Research for the Division of Urology within the Department of Surgery) found themselves next door to one another, each directing the research efforts of their respective divisions. Dr. Black’s interests at the time were in developing models of ischemia reperfusion injury and flap studies in the field of Plastic Surgery and Dr. Hewitt’s primary interests were in studying transplant rejection and mechanisms of tolerance induction, as the Division of Urology was the division that was primarily responsible for kidney transplantation at the University of California, Irvine.

Dr. Black’s ischemia-reperfusion model involved amputation and replantation of a rat hindlimb, and the mechanisms of ischemia-reperfusion injury by reattachment of these preserved amputated limbs under various conditions. In specific, the effects of temperature on tissue survival were evaluated with the use of a refrigerated environmental chamber located in Dr. Hewitt’s lab. A discussion concerning these experiments ensued between Hewitt and Black and ultimately an investigative partnership was formed, along with a very meaningful friendship. Each investigator became interested in the other investigator’s research, and further discussions ensued.

4.2 The Questions

From the model developed for replantation of the amputated limbs and the results of organ graft prolongation came a mutual realization that it would be very interesting to test additional mechanisms related to transplantation using the hindlimb model. Thus, the two investigators eventually decided to investigate...
the answer for a fairly unique question, namely, could this model be used to study limb transplantation and some of the developments found successful in prolonging organ transplantation? It was hypothesized that these new and unique types of transplants, integumentary musculoskeletal transplants, would have particular usefulness in plastic and reconstructive surgery applications and indications. In specific, these composite tissue allografts or substructures thereof would be useful for reconstructing full-thickness soft tissue defects such as those encountered in victims of severe burn injury or other traumas or after tumor extirpation, in addition to possible restoration of muscle function for recessive myopathies. Therefore, a bond was formed, initially as an alliance between a transplantation immunology laboratory and a plastic surgery microvascular surgical laboratory, which later blended and integrated the two investigator’s interests into one focus of pursuit over the next 20 years, and which represented the pioneering efforts for these investigators in the field of composite tissue transplantation.

4.3 Materials and Methods

All were not successful in the early years. For a year and a half, these investigators used every proven technique that was successfully developed in the kidney transplant model and applied it to the rat hindlimb composite tissue transplant model. There were only minor successes, with perhaps a few days here and there of prolonged graft survival. Although cyclosporine-induced prolongation of skin graft survival in mice was obtained for about 20 days in earlier years and muscle allograft transplantation in rats was feasible with cyclosporine, it became readily apparent that this particular allograft entire limb transplantation model was indeed a difficult one in which to achieve graft prolongation and success. The failures became frustrating and several discussions resulted concerning dropping the whole idea of composite tissue transplantation, as it just did not seem feasible in view of the results that were obtained. It was during this time that this new immunosuppressive compound came onto the scene; however, its reputation was rather uncertain. Cyclosporine’s promise was in debate, due to concerns of its reported toxicities. In regard to wound healing, however, no detrimental effects specifically related to cyclosporine administration had been observed. Indeed the considerable problems in wound healing were undoubtedly related to the continuous use of steroids. Thus cyclosporine, a steroid sparing drug, gave an advantage.

In Dr. Black and Hewitt’s laboratory it was a drug that was initially viewed as not very promising. However, once the two investigators realized that failures were common with respect to prolonging limb transplant survival, the attitude changed and the two were willing to try new and promising interventions and drug therapies to improve their results.