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JEB Classics

THE BIRTH OF TRANSPLANTATION IMMUNOLOGY: THE BILLINGHAM–MEDAWAR EXPERIMENTS AT BIRMINGHAM UNIVERSITY AND UNIVERSITY COLLEGE LONDON

[385]

THE TECHNIQUE OF FREE SKIN GRAFTING IN MAMMALS

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(With Plates 5–7 and One Text-figure)

1. INTRODUCTION

In recent years, skin grafting has been used for the study of a wide variety of biological problems. Some of these problems relate to the properties of skin itself —e.g. pigmentation (Billingham, 1948), hair growth, sensitivity (Hasthausen, 1948), the innate 'racial' differences between the several varieties of epidermal epithelia (Billingham & Medawar, 1948*a*, *b*, 1950) and the contributions of dermis and epidermis to the formation of chemically induced tumours (Billingham, Orr & Woodhouse, 1950). With other problems, skin has been used in preference to other tissues because it it is more accessible or easier to handle, or because it gives less ambiguous answers; among these may be mentioned tissue transplantation immunity (Gibson & Medawar, 1943; Medawar, 1944, 1945, 1946*a*, *b*, 1948*a*, *b*), the measurement of the degree of homozygosity of inbred lines (McDonald & Medawar, unpublished), and the resistance of living cells to procedures such as anaerobic cultivation (Medawar, 1947) or freezing and drying (Billingham & Medawar, 1951).

The peculiar advantages of skin for grafting purposes are, briefly, these: skin is the only tissue which may easily be grafted 'orthotopically', i.e. to an anatomically natural environment; the fate of skin grafts may be watched from day to day and their behaviour easily checked by repeated biopsy and histological examination without prejudice to the well-being of the recipient; and skin may be so grafted as to self-indicate its own survival or death by the presence or absence of epithelial outgrowth from it.

The purpose of this paper is to set forth certain procedures and principles which have emerged from the authors' experience with skin grafting in rabbits, guinea-pigs and mice. The rather special problems of grafting in cows (Anderson, Billingham, Lampkin & Medawar, 1951) and monkeys (Krohn, unpublished) will be dealt with elsewhere.

The union of a skin graft with its bed is a process of healing by 'first intention', i.e. by the direct union of immediately apposed raw surfaces, and as a general rule grafting will be successful if the graft is not too thick and if it is held by light but firm pressure upon a bacteriologically clean and adequately vascular bed until primary union is complete. The greater part of this paper is concerned with

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Santa Jeremy Ono writes about R. E. Billingham and P. B. Medawar's 1951 publication 'The technique of free skin grafting in mammals'.

There are very few scientific papers that continue to have an impact on research more than 50 years after their initial publication. A paper published in *J. Exp. Biol.* in 1951 by Rupert Billingham and Peter Medawar is one such paper. Both clinicians and scientists still turn to the paper to understand fundamental concepts in dermatology and as a primer to skin grafting in mammals. Dermatologists in training still read this classic paper, and the paper continues to be cited in contemporary scientific literature involving skin transplantation. Indeed, one still frequently encounters the phrase "*skin grafts were performed following the method of Billingham and Medawar*." The impact of the paper is also greatly amplified in that the paper facilitated the later discovery of 'actively acquired tolerance' and the definition of the principal laws of transplantation tolerance. Fittingly, this line of experimentation led to the awarding of the 1960 Nobel Prize in Physiology and Medicine to Medawar. Thus, it was in a series of classic experiments (stemming from this *J. Exp. Biol.* paper) that the field of transplantation biology was born.

This paper was written at a time when very little was known about the biology of skin grafting and when the procedure was rarely used in laboratory science. Indeed, Billingham himself indicated, "*I recall that we had misgivings about the acceptability of the manuscript for publication on the grounds that few of our contemporaries were interested in grafting or skin biology*."

The paper is a self-contained manual for distinct forms of skin transplants in a variety of laboratory animals. There are very detailed discussions and illustrations concerning the anatomy of the mammalian integument. Importantly, the paper also provides unique information on regional variation of skin within a given animal and on the process of transplant survival or rejection. Specific discussions focus on principles of wound healing post-transplantation and on Billingham and Medawar's formative thoughts on transplantation immunity. The paper is most useful in discussing frankly the pros and cons of skin grafting as a laboratory procedure. There is considerable discussion of the pitfalls encountered in skin grafting, e.g. pigmentation and hair growth, but also the advantages, e.g. accessibility and availability for biopsy.

Despite such a frank discussion of the complexities of skin transplantation, the procedures described in the *J. Exp. Biol.* paper serve as the foundation for the long-term collaborative work of Billingham and Medawar (first at Birmingham University and then University College London) in which the two initially studied problems of pigmentation and skin grafting in cattle. *Via* now famous skin grafting experiments, the two established many of the key laws of transplantation that stand intact five decades later. As one example, the discovery by Medawar that a second full-thickness allogenic skin graft taken from the same donor as the first graft is rejected in an accelerated fashion (termed the second set phenomenon) provided evidence for a sensitization phase of the immune response and the concept of immunologic memory. Today, these findings are entirely consistent with what is known about the generation and longevity of alloreactive T cells.

In experiments involving skin grafts between monozygotic and dizygotic twins,

and taking into consideration earlier work by R. D. Owen (1956), the two concluded that actively acquired transplantation tolerance of homografts could be artificially reproduced. Their surprising finding that skin grafts between fraternal twins are accepted prompted the two to hypothesize that 'foreign' blood cells persistent in each twin due to placental fusion were responsible for this transplantation tolerance. This chimaerism is indeed now known to form the basis of such tolerance and continues to be a major focus of research in transplantation biology.

The series of experiments also showed that neonatal transplantation could lead to the acceptance of skin allografts, shedding first light on what would eventually be understood as thymic education of developing T cells. Their subsequent classic studies with Leslie Brent at UCL on skin transplants in mice (Billingham et al., 1953) showed that the pre-inoculation of neonatal mice with lymphoid cells from an allogenic adult donor mouse led to permanent allograft survival, which is now known to also be the case for many other organ transplants. Finally, this set of experiments also permitted Billingham and Medawar to discover that corticosteroid hormones from the adrenal grand can delay skin graft rejection in rabbits (Billingham et al., 1951). Thus, it was shown that the previously assumed insurmountable barrier to transplantation could be overcome and also led to the subsequent discovery of graft-*versus*-host disease.

Although the work described in the 1951 *J. Exp. Biol.* paper dealt exclusively with skin transplants, many of the issues discussed in the paper were invaluable in the development of other organ transplants both in rodents and humans. With the development of progressively refined techniques of microvascular surgery, the principles of transplantation immunology discovered in the skin grafting experiments have largely been shown to be true for other solid organ transplants, e.g. kidney and heart. A key exception has been Medawar's own pioneering work on corneal transplants. In their subsequent work (much of it following this *J. Exp. Biol.* paper), Medawar, Billingham and Barker would show that the transplantation of cornea and a few other tissues would result in the prolonged, sometimes indefinite, survival of an allograft (Medawar, 1948; Billingham and Boswell, 1953; Barker and Billingham, 1977). It is now known that this state of immunologic privilege results both from unique properties of certain tissues (e.g. cornea and retina) as well as anatomical sites of engraftment. Interestingly, much of the most elegant work on the biology of immune privilege in the cornea was carried out by Wayne Streilein and colleagues (Cursiefen et al., 2004; Sugita et al., 2004; Arancibia-Carcamo et al., 2004). In our own discussions, Wayne and I spoke often of the impact this *J. Exp. Biol.* paper had on both his research and transplantation biology in general. As a student of Billingham's, Streilein is one key example of the impact this paper (and the principles contained within it) have had on this branch of research.

In conclusion, this *J. Exp. Biol.* paper set the stage for an entire series of experiments (first in the Billingham–Medawar laboratories and then throughout the world) upon which the field of transplantation biology was born. Although this paper is not the one mentioned in Medawar's Nobel Prize citation, the procedures described in the paper were essential for the Nobel Prize-winning experiments. The impact of the work has, of course, been enormous and continues to this day. Much of the current research in transplantation biology can still find its roots in the work first described in this paper.

A PDF file of the original paper can be accessed online:
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