



# Origins and evolution of reproductive immunology: a personal perspective



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## ABSTRACT

This is a brief personal assessment of the origins and development of the field of reproductive immunology from the 19th century to the present day, with special reference to the founding of the *Journal of Reproductive Immunology* in 1979.

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## 1. Early beginnings

Following the generous brief afforded me by the conference organisers, this is a short and personal assessment of the origins and evolution of the field that we now know as reproductive immunology, and that have been the mainstay of my professional academic career for over 40 years. Although everyone will likely have their own views on the origins of most specialist subjects, for me the landmark studies leading to the emergence of enquiries into the immunology of reproductive processes are those pursued by the Russian biologist Ilya Mechnikov (1845–1916) and later by the Austrian biologist and physician Karl Landsteiner (1868–1943). For his work on phagocytosis, showing the engulfment and destruction of bacteria by white blood cells, Mechnikov was awarded the Nobel Prize in 1908. These findings eventually led to the recognition of Fc receptor-dependent uptake by macrophages. Landsteiner classified the ABO blood groups by identifying the presence of agglutinins, and later also identified the rhesus

factor. He was awarded the Nobel Prize in 1930. His work thus laid the foundation for arguably the most important clinical contribution that reproductive immunology has ever made, the recognition of rhesus haemolytic disease of the foetus and newborn and its treatment by injection of anti-D antibody.

## 2. Anti-sperm antibodies and infertility

Although spermatozoal immunogenicity was first recognised by Mechnikov as long ago as 1899, only very sporadic confirmatory studies were reported in widely scattered literature during the early decades of the 20th century. The relationship between antisperm antibodies and infertility was first established in domestic animals (heifers) by Bratanov et al. (1949). The detailed studies of Guy Voisin and his colleagues in the early 1950s demonstrated the experimental induction of autoimmune aspermatogenesis in guinea pigs, and the existence of several spermatozoal autoantigens. In 1959, Rumke reported the association between the presence of anti-spermatozoal antibodies and clinical infertility in human males. These early studies provided the foundation for an explosion of

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interest in the identification of the molecular structure of sperm surface antigens and their precise role in the induction of infertility in both males and females, and as potential candidates for immunocontraceptive vaccines. [Sojima et al. \(1968\)](#) were pre-eminent from an early stage in this extensive search. It is, however, a cause of disappointment that after so many decades these goals have still not been satisfactorily achieved. Much less is known about female gamete antigens and their relevance in fertility and infertility.

### 2.1. Immunology of pregnancy

A defining moment in the evolution of the field of reproductive immunology came in 1953, when [Peter Medawar](#) published the text of his invited lecture to the British Society for Experimental Biology, in which he identified the truly paradoxical nature of the immunological relationship between the pregnant mother and her antigenically foreign foetus. Although Medawar later won the Nobel Prize for his pioneering work establishing the laws of transplantation immunology, he never followed up by experimentation his insightful suggestions as to how the semi-allograft of the foetus and placenta might be able to circumvent the expected recognition and rejection reactions of the immunologically competent pregnant female. Interestingly, it was one of his Oxford graduate students, Rupert (Bill) Billingham, who was, from the next decade onwards, to make significant contributions to an understanding of this problem (see below).

My own entry into this field was in 1960, when I was offered the opportunity to begin a graduate studentship with Professor Rogers Brambell, whose group was principally involved in studying the transmission of passive immunity from mother to young, indicating that the mechanism for the selective transport of immunoglobulins resided in the presence of specific receptors for the Fc region of the molecules on the surface of the transmission site, be it neonatal gut, yolk sac or placenta, depending upon the species. My own project was in a different direction, examining the effect of genetic disparity between mother and foetus on the development and growth of the murine placenta. This led to the publication of my first paper in 1964. It was submitted to the journal *Nature*, had no reference list, and was reviewed, accepted and published in little more than three weeks. I assumed at the time that this was quite normal. How wrong I was! I then joined David Kirby in Oxford to begin a most fruitful and enjoyable collaboration, extending our studies into a variety of topics on the immunology of pregnancy, with special interest in the trophoblast. During this period in the 1960s I became acquainted with, and enjoyed the friendship of, Bill Billingham. He had by then moved to the United States and established a most successful group in Dallas, investigating, *inter alia*, the uterus as an immunologically privileged site. Together with his colleague, Alan Beer, and others, he made many important advances in several immunological aspects of reproduction, and published one of the earliest and most successful books in this field. He was unquestionably a leading figure right up to the time of his retirement. His international fame also provided me

with unexpected opportunities early on. The similarity of our surnames, together with the fact that he had previously worked in the same Oxford department as myself, and in a similar area of research, led to invitations for me to attend and participate in some conferences and symposia that were intended by the organisers to benefit from Bill's presence! He was greatly amused by this mistaken identity and most generous to me in his later recognition of these missed occasions.

### 2.2. New technologies

Throughout the 1960s and into the 1970s the techniques available to experimental immunologists were extremely limited compared with what the present day researcher expects to have at his or her disposal. This is highlighted by the following dates of the potential availability (not the time of discovery) of innovative technologies:

- Flow cytometry (FACS) – 1974/1978
- Monoclonal antibodies – 1975
- Personal computers – 1980s
- Transgenic animals (mice) – 1982
- PCR techniques – 1983
- Knock-out animals (mice) – 1989
- 2G mobile phones – 1993
- E-mail communication – 1990s

Progress depends heavily upon the tools available for investigation, and scrutiny of the papers published in the later years of the 20th century clearly reflects this relationship.

## 3. The appearance of the *Journal of Reproductive Immunology*

In 1972 I had the opportunity to move to the Medical School at the University of Bristol in order to set up a research unit for reproductive immunology. This was the first unit to be so named, as hitherto the field had been referred to as “immunology of reproduction” or the “immunobiology of reproduction”. In the late 1970s, I was approached by two major international publishing houses to establish a new journal in this emerging field. After due consideration, I agreed a contract as Editor-in-Chief with Elsevier/North-Holland. Justification for a new publication was provided in the following extract from the editorial of the 1979 launch issue of the *Journal of Reproductive Immunology*:

*“Reproductive immunology has unquestionably been one of the most rapidly expanding areas of scientific enquiry in recent years. Its multiple origins have very largely been rooted in independent basic reproductive physiology and immunology and the increasing volume of information has, perhaps not surprisingly, been disseminated in a very wide range of journals. There can be few, if any, disciplines of comparable impact that do not have a central vehicle for the publication of their research material.”*

The enthusiastic support of Alan Beer (Dallas, Texas) as Associate Editor and the recruitment of a strong,

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