Sex Determination, Differentiation and Intersexuality in Placental Mammals

R. H. F. HUNTER

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Preface

This book has been written from the perspective of a university teacher whose research has been in the field of mammalian reproductive physiology but who is also much interested by developments in animal genetics and molecular biology. Preparing the individual chapters offered an exciting opportunity for bringing these disciplines together in various ways. The result is seen primarily as a text for advanced (Honours) undergraduates in Schools of Biological Sciences, Medicine, Veterinary Medicine and Animal Science. It should also appeal to those on taught MSc courses and to PhD students interested in both developmental biology and reproductive physiology in the higher mammals.

The book was planned during my time in the Faculty of Veterinary Medicine, University of Montréal, but the administrative commitment there – together with lecturing and activities in the operating theatre – meant that a serious spell of writing had to await my return to Edinburgh. In fact, the chapters were prepared in draft between May 1991 and June 1993, and then brought up to date as far as December 1993 on the basis of the extensive journal coverage available in the University of Edinburgh libraries. A small number of 1994 references has also been included.

As to the origins of this work, they almost certainly date back to the author's post-doctoral days in Paris (1968–1970) listening to lectures on sexual differentiation by the late Professor A. Jost and observing the studies of his assistants, Drs J. Prépin and B. Vigier, on freemartin calves at the Station de Physiologie Animale, Jouy-en-Josas. In similar vein, Professor R. V. Short, FRS, gave a memorable lecture on sexual differentiation in September 1970 at an Anglo-French colloquium held in Nouzilly, just outside Tours. However, the present work was also prompted by observations at the laboratory bench and during abdominal surgery. In extensive studies on normal and abnormal fertilisation in domestic farm animals, our

species of choice was the pig because of the number of eggs shed at ovulation. The inbred females used in these surgical studies often revealed unusual gonads in the form of an ovotestis or ovary on one side and a testis on the other. Initially, such intersex animals were simply seen as a major inconvenience, interrupting a carefully planned programme of research, but in due course they became a subject of research in their own right. How could apparently genetic females generate an ovary and an ovotestis within the same animal, and what form of genetic instruction would prompt the unilateral appearance of testicular tissue? Attempts to answer these questions will be found in the chapters that follow.

Although the text examines many of the latest findings on sex determination and then sexual differentiation of the gonads and genital tract, it does not dwell on dimorphisms elsewhere in the organ systems. Except in a context of intersexuality, brain sex is not considered in any specific way nor are the resulting patterns of behaviour, nor indeed sexual dimorphisms in organs such as the liver. This is not an oversight. Despite the fascination of such material and the many new discoveries, the scope of the present volume had to be kept within reasonable limits, and a systematic treatment of these other fields will have to await a future endeavour. One other limitation concerns use of the term 'placental mammals'. In reality, the text focuses on a small number of eutherians – man, mouse and several domestic species – although there is occasional reference to marsupials (which, of course, have a placenta) where they serve to illustrate major new findings or divergences from the eutherian model.

The treatment of abnormal reproductive tissues or conditions is also limited. The objective has certainly not been to document as many bizarre conditions as possible but rather to seek the underlying genetic lesions. A molecular explanation has been offered wherever possible, although research at this level is moving so fast that the text cannot be completely up to date. Nonetheless, what comes through from the writing is of major significance – the fact that a point mutation, a single base change, can wreak such havoc. Evolution may very well thrive on mutations but the cost to individuals of our own species can be physically taxing and emotionally devastating, especially in a reproductive context.

Each chapter has been intended as an essay in its own right. This has inevitably resulted in some repetition. Nowhere is this extensive except in the final chapter, for this is presented in the form of an overview. As to a policy on references, I have tried to be reasonably comprehensive and to cite both new work and old: new for there is much excitement in arriving at molecular descriptions of diverse clinical conditions, old since it is sobering

to note the extent to which many of the more fashionable ideas in today's literature have a remarkably ancient pedigree. Finally, as to conventions, the possessive adjectival form of referring to syndromes has been maintained (e.g. Turner's) rather than adopting the American approach that omits the apostrophe 's'. The original format of describing such aneuploidy has also been adhered to (i.e. 45,XO) rather than simply 45,X. And such classical and attractive spellings as chimaera, disulphide and foetus have been preferred and used consistently throughout the text; such is an author's privilege!

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February, 1994

R.H.F. Hunter

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complete freedom whilst, at the same time, taking over much of the family home with collections of books, reprints, and manuscript material is one that cannot pass unmentioned. Nor can the endless help in checking, rechecking and editing the whole of the text, and for supporting this undertaking with good humour and affection throughout. I am immensely grateful to her.

Abbreviations

ACTH	adreno-corticotrophic hormone
AMH	anti-Müllerian hormone
AMP	adenosine 3′,5′-monophosphate
cAMP	cyclic AMP
CRF	corticotrophin releasing factor
cDNA	complementary DNA
DNA	deoxyribonucleic acid
ELISA	enzyme-linked immunoabsorbent assay
FSH	follicle stimulating hormone
GnRH	gonadotrophin releasing hormone
HMG	high mobility group (proteins)
H-Y	H-Y antigen
i.u.	international units
IVF	*in vitro* fertilisation
LH	luteinising hormone
LIF	leukaemia inhibitory factor
MIS	meiosis inducing substance
MPS	meiosis preventing substance
Mr	relative molecular mass
NCAM	neural cell adhesion molecule
ORF	open reading frame
PCR	polymerase chain reaction
PG	prostaglandin
PGC	primordial germ cell
PGE_2	prostaglandin E_2
PMDS	persistent Müllerian duct syndrome
PMSG	pregnant mare serum gonadotrophin
RNA	ribonucleic acid
mRNA	messenger ribonucleic acid
RPS4	ribosomal protein S4

TGF	transforming growth factor
TGF-β	transforming growth factor-β
Yp	short arm of the Y chromosome
Yq	long arm of the Y chromosome

Gene abbreviations

AMH	anti-Müllerian hormone gene in man
Amh	mouse homologue of *AMH*
AZF	azoospermia factor
Bkm	Banded Krait minor (banded Krait is a snake)
Hox	homeobox genes
hpg	hypogonadal mouse
Hya	male-specific histocompatability antigen
iv	situs inversus viscerum mutation in mouse
KAL	Kallmann's syndrome gene
KALIG-I	Kallmann's syndrome (interval) gene
P	polled (hornlessness) in goats
RPS4Y	ribosomal protein S4 gene on the Y chromosome
SOX	*SRY* box genes
Sox	mouse homologue of *SOX*
Spy	spermatogenesis gene
SRY	sex-determining gene of the Y chromosome in man
Sry	mouse homologue of *SRY*
Sxr	sex reversal mutation (factor) in mouse
Sxr'	an H-Y antigen-negative variant of *Sxr*
Tas	T-associated sex reversal in mouse
Tda-1	testis-determining autosomal-1 in mouse
TDF	testis-determining factor (gene) in man
Tds	testis-determining sequences in mouse
Tdy	testis-determining gene on Y chromosome in mouse
TFM	testicular feminisation in man
Tfm	mouse homologue of *TFM*
WT	Wilms' tumour gene in man
WTI	Wilms' tumour suppressor gene

Wt1	mouse homologue of *WTI*
XIST	X-inactive specific transcript
Xist	mouse homologue of *XIST*
ZFX	zinc finger gene on the X chromosome
Zfx	mouse homologue of *ZFX*
ZFY	zinc finger gene on the Y chromosome
Zfy	mouse homologue of *ZFY*

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