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REVIEW ARTICLE

The power and perils of animal models with urogenital anomalies: Handle with care

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Abstract Congenital abnormalities of the urogenital tracts form a major part of clinical practice for paediatric urologists, but their knowledge of normal and abnormal development is often limited. Advances in understanding frequently come from studying experimental findings from animal models, however, most clinicians underestimate both the power and perils of extrapolating scientific knowledge from animals. In this review, the key issues that urologists need to understand in order to link animal studies to clinical practice are discussed. Urologists must avoid the traps of anthropomorphism (assuming humans are always the same as animal models) or anthropocentrism (assuming humans are too different from animal models). This review used two common disorders: hypospadias and undescended testes.

Introduction

Many young paediatric urologists aspire to investigate the underlying causes of the common congenital anomalies that they clinically treat, such as hypospadias and cryptorchidism, by using animal models. However, like all doctors, they have spent most of their education and career focused on patients. Therefore, if paediatric urology is going to advance (and their academic career is going to flourish) they need to understand how to use animal models of normal and abnormal urogenital development. A significant barrier to using results from animal models for medicine is the very limited knowledge that many surgeons have of broad biological principles.

Two of the authors are paediatric urologists (John Hutson and Larry Baskin) and two are scientists and anatomists (Gail Risbridger and Gerald Cunha), and they have all learnt how to extrapolate from animal models to clinical practice

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the hard way. It is hoped that others might be inspired to follow a similar path, and that these thoughts about extrapolation will be useful. These words may be useful for the young paediatric urologist contemplating a career as a surgeon-scientist.

Lack of exposure to biology

During premedical studies many doctors are not exposed to a deep analysis of the mechanisms of evolution, with studies in biology, embryology and anatomy totally preoccupied with the human. This is likely to lead to them (as well as other surgeons) having had little exposure to comparative anatomy and embryology, where differences between species might either be ignored or not appreciated for the insight they might bring to the comparable human process or structure.

Ignoring species differences: anthropomorphism

Underestimating the differences between species might lead surgeons to take for granted that the results of an animal experiment can be automatically translated into a human context. For some surgeons, it is as if the mouse or rat is the same as the child. This type of thinking is more common when the science and experiment looks at lower orders of bodily structure, such as the gene, the cell and the tissue. It is less prevalent at higher orders of structure, such as gross anatomy, where the differences between species are more obvious. However, the moment one stops to think, differences are to be expected, albeit minor, at every level of structure. The recent discovery that *Hox* genes, which have been recognised to control embryonic segmentation in the fruit fly and are also regulating segmentation of the human embryo, shows the power of extrapolation from one species to another [1]. However, *Hox* genes in all mammals, including humans, are more complicated than in the fruit fly, because of replication of the primitive gene set over the eons into a large cluster of related genes with overlapping functions. This 'descent with minor variation' is a powerful example of Charles Darwin's view that all species share a common inheritance, in this case, in the specific genes involved in segmental development of the embryo (Charles Darwin, 1859). Therefore, the important message for doctors is that the biology of animals is not identical, but only slightly different from humans. These differences tend to be in quirky or idiosyncratic areas of embryology or anatomy that lead to different body shapes or functions, while the fundamental processes of embryology are likely to be comparable.

Anthropocentrism: humans are different

Some doctors bring a view to medicine that 'humans are special' and not like animals at all. This was the worldview of all doctors prior to Darwin's publication of *On the origin of Species* in 1859. At first, the notion that 'men are related to monkeys' was ridiculed, but for the last 50 years the principles of evolution have not only been accepted, but also actively taught in biology classes. However, the rise of conservative religious groups in many countries, where the Bible (or the Koran) may be interpreted literally, means that a significant number of doctors (and also paediatric surgeons) in practice today may have been shielded from the full implications of seeing the world as an evolving system. This may lead to some beliefs that 'it's just a rat experiment', and, thus, not relevant for children.

In order to bring the benefit of animal models to a child with a urogenital anomaly, the differences in development between animal models, such as the mouse or rat, and the human need to be understood. These differences need to be taken into account during translation to clinical medicine, so that it is not assumed that everything is the same. Bear in mind the problems of Galen and medieval doctors, who inherited anatomy books based on dissection of animals alone, as human dissection was forbidden. Once human cadaver dissection became acceptable, these important differences were eventually corrected. However, there is a classic error of extrapolation between animals and humans recorded for posterity in a famous drawing of a human fetus within the uterus by Leonardo da Vinci, where the fetus itself is extremely life-like, but the placenta is drawn with multiple cotyledons, like a cow, rather than like a human placenta.

Sometimes, differences between animals and humans can reveal important insights into human biology. An example of this is the asymmetry of the genitalia seen in disorders of sex development (DSD) with mixed chromosomes, where mosaicism in the sex chromosomes leads to gonadal and genital duct asymmetry, rather than an even mixture of different cells. It is more common in mixed gonadal dysgenesis (45,X/46,XY DSD) and in ovo-testicular DSD, for example, for the right side to be more masculine than the left side, with a descended testis in the right hemiscrotum and an undescended intra-abdominal left ovary, ovotestis or streak gonad [2]. From where did this asymmetry suddenly spring? A review of the evolution of sexual development immediately reveals that the asymmetry was embedded in the genome of animals all along, and is normal in all female birds, where the left gonad in the urogenital ridge forms an ovary and the Müllerian duct differentiates into a uterus, while on the right side the gonad forms an ovotestis and the right Müllerian duct regresses [3]. In humans, the asymmetry is much more subtle and usually invisible, but is revealed in DSD when the right side is more likely to be 'masculine' and the left side more 'feminine'.

To highlight the strength, as well as the limitations, of animal models of urogenital development, development of the penis and testicular descent will be described, as these two examples underlie the two most common problems in paediatric urology: hypospadias and cryptorchidism. In both of these examples, the power as well as the peril of animal models is evident.

Hypospadias

This is a common anomaly that all paediatric urologists understand well; there are three characteristic features: (i) proximal urethral opening on the undersurface of the penis