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PERSPECTIVES

Centenary of Haldane's 'rule': why male sterility may be normal, not 'idiopathic'

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Abstract. While the term 'idiopathic' may be applied correctly to many diseases of unknown origin, its broad application to undiagnosed cases of human male infertility is unwarranted. Infertility can be a nonpathological expression of the action of Nature's normal quality-control mechanisms. We now celebrate the centenary of Haldane's famous 'rule' paper that has clarified much uncertainty. Furthermore, there are similarities between two 'seed organs' that audition and then export, either T cells (thymus), or germ cells (gonad). Nature sets high bars both for generating T-cell repertoires and for gamete entry into the next generation. Extrapolations from thymus studies suggest that germ cells are severely scrutinized for incompatibilities at both protein and nucleic acid levels, and many perish. Scrutiny continues through fertilization to embryos, which may abort, sometimes with couples unaware. The auditioning continuum is something that the inchoate forms we once were had to progress through. Even post-partum and into adulthood, it continues. Defining a point when Nature relaxes and 'life' can be considered as having begun, is not easy. Those who medicalize the normal with inappropriate terminology may reinforce certain attitudes on the morality, ethics, and legality of induced abortion.

Keywords. auditioning continuum; infertility; quality control mechanisms; planned parenthood; Roe versus Wade; seed organs.

> *Idiopathic is a word we medical men use to conceal our ignorance of the cause of disease. Idiopathic diseases are those that have come of themselves, that is, without ascertainable cause.*
>
> *Essays in Pastoral Medicine*, ÓMalley and Walsh (1906)

Introduction

Literally interpreted from the ancient Greek, 'idiopathic' means 'a disease of its own' that is distinct from known diseases. While dictionary definitions may vary, most patients when checking their physician's use of the term likely get the impression that their complaint, although undiagnosed, remains a pathology—an abnormal state that, hopefully, future medical research will remedy. On the other hand, the negative of idiopathic—'nonidiopathic'—means that their pathology is known and hence may be checked online or in a textbook.

For most medical complaints this general understanding is correct. Nevertheless, regarding idiopathic: 'it is well known that the same terms may be interpreted differently by clinicians and patients, causing miscommunication,' and hence some may come to believe that it "is 'all in their head', which is not conducive to a good doctor–patient relationship" (Tirlapur *et al.* 2013). Beyond this, especially for complaints relating to fertility, miscommunication may be of wide-ranging societal import. The idea that infertility should always be viewed as pathological is biologically incorrect. This has ramifications that involve the issue of when a 'life' can be considered to have its beginning—a matter of much concern to those debating abortion rights legislation (Pilpel 1969).

Sometimes 'beginnings' are nebulous. When stage-curtains part, the play 'begins,' but the play itself requires much prior activity. Some may even lament that a play did not really start until the second act. And for formal purposes, a sod-turning ceremony may mark the beginning of a

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construction project, but this follows many months of planning. Some may believe that completing the foundations marks the beginning. When viewed from a biological perspective, when a life 'begins' can seem equally nebulous. This is not helped when, through inappropriate terminology, physicians assign pathology where it does not exist.

'Natural' is a value-loaded term. When we see the film of a lion stalking, pursuing, and devouring it prey, we shrug—well, that's nature 'red in tooth and claw'. What is 'natural' is good. The 'unnatural' is bad. Most cases of male infertility (60%) are deemed 'idiopathic' (Laan *et al.* 2021). Given the usual understanding of the term, male patients presenting with a condition so designated, will tend to consider themselves somehow unnatural. For some infertile males, their condition will not be viewed as within the scope of normal biological expectation. They will be worried. This 'unnatural' mindset—perhaps due to unwarranted medicalization of the natural—may have influenced attitudes on the morality, ethics and legality of induced abortions, with possible societal consequences. While the essential normality of biological abortion is well recognized (the 'Wood–Boklage–Holman hypothesis'; Rice 2018), the underlying science is not. Assuming some knowledge of meiosis, I here review the underlying biology as illustrated by Haldane's rule and the 'auditioning' of germ cells for transfer to future generations.

Centenary of Haldane's rule

Patiently guided by the geneticist William Bateson, J. B. S. Haldane produced his eponymous 'rule' paper on the sterility of hybrid offspring (Haldane 1922; Cock and Forsdyke 2022). Over the century it has gathered many citations (Clarivate lists 1318; Google lists 1889). The paper has greatly assisted our understanding of speciation—a seemingly arcane topic that may not find a place in busy medical curricula. Yet, speciation—the divergence of a single species into two, reproductively isolated, species—is one of a range of normal responses to environmental pressures. Albeit infrequently completed, various mechanisms for speciation have been retained in all biological organisms as they have evolved since the origin of planetary life some three and a half billion years ago.

Understanding Haldane's rule requires a complex temporal separation of generations—grandparents, parents, children—with clear distinctions between the roles of each. This difficulty also makes it an unlikely item to include in medical curricula. As with other species, the genomes (DNAs) of human individuals normally vary. Although deemed 'idiopathic', a failed cross between two individuals that may not *themselves* vary, may be a *natural* consequence of variation between the parents of one of them—the grandparents of any children they might produce. The grandparental chromosomes that meiotically pair within gonadal germ cells of one individual may fail to pair, or pair incorrectly, and gametogenesis is interrupted. That individual is sterile.

Prior to meiosis, *all* chromosomes in human female germ cells have a partner (one derived from her mother and one derived from her father). This includes the two sex chromosomes (X and X). However, Nature has arranged that the two sex chromosomes in male germ cells (X and Y) already have some degree of mispairing (Ma *et al.* 2022). When grandparental genomes vary widely, this X–Y mispairing should *add* to the general meiotic mispairing tendency of the 22 autosomal chromosomes in the male gonad of their sons (Forsdyke 2000). This is a simple explanation for Haldane's empirical observation that male sterility occurs more frequently than female sterility. For other possible explanations see Charlesworth (2017). The 'rule' applies generally to whichever sex happens to be the heterogametic sex (male in the human species; Haldane 1922).

Thus, when partial sterility is evident, it usually affects offspring of the XX sex less than of the XY sex—girls are less affected than boys. It occurs when a grandparental couple happens to be more differentiated from each other in their genomes than usual. This differentiation is a *natural* process that, *in extremis*, can extend to their genomes being so different that their crossing is unproductive in that the child they produce is sterile. It cannot be a parent—so no grandchildren are produced. Thus, the line ends and the stage is set for a speciation event that requires that two lines be 'reproductively isolated' from each other (so facilitating natural selection).

However, when the differentiation has not gone that far, then grandparental genomes can pair normally at meiosis in the gonads of a child, and some grandchildren can be produced. But the generation of a fertile *male* child requires, in addition to the pairing of the nonsex chromosomes, the pairing of a X and a Y chromosome. These chromosomes already have some degree of differentiation. On the other hand, the pairing of two parental X chromosomes to generate a fertile female, would not have this extra difficulty to overcome (Forsdyke 2000).

The auditioning continuum

Haldane's rule is an example of Nature's demand for perfection. Although its explanation has long been contentious (Charlesworth 2017), the case for chromosomal incompatibilities (Forsdyke 2000) has grown stronger over the century (Forsdyke 2001, 2017, 2018, 2019a, 2019b, 2021). Since *each* gamete is the *unique* result of the recombinational shuffling of grandparental genomes, gametes can be viewed as competing (auditioning) for passage into the next generation. Nature sets a high bar for approval. She scrutinizes developing germ cells for incompatibilities, and few may survive to tell the tale (Forsdyke 2020).

While a couple may be reassured that their problem does not reflect an underlying known pathology—it is labelled

'idiopathic' (Laan *et al.* 2021)—their perceived problem remains. If on further investigation no underlying pathology emerges, then, in the hope that recombinational shuffling will surmount Nature's obstacles (i.e., sterility is partial), an infertile couple may continue attempting to produce children. Otherwise, to the extent that the problem is *collective*, and each individual partner is normal, then, although generating a fresh set of problems, they may need alternative partners to produce children. There is then the potential for two independent lines to develop (i.e., speciation).

Nature's scrutiny continues through fertilization to zygotes that develop as embryos, which Nature may abort, sometimes with couples unaware (Rice 2018). This hybrid unviability—often found to result from incompatibilities between individual genes (not entire chromosomes)—was also encompassed by Haldane. The auditioning continuum is something that the inchoate forms we once were, needed to progress through. Even post-partum and into adulthood, it continues. We remain hybrids throughout our lives and gene products that influence later stages may manifest incompatibilities at those times. If this occurs during the reproductive years, then fewer offspring may be produced. There is little evidence for a clear definable point when Nature relaxes.

Evidence that Nature's scrutiny is carried out at both nucleic acid and protein levels comes from comparison of germ cells with cells in an organ that engages in another form of auditioning, the thymus (Forsdyke 2020). Thymus and gonad are both mutant breeding 'seed organs'. Male germ cells, each distinguished by its genomic uniqueness, can be viewed as auditioning in gonads before being exported, *external* to the body, to seek an ovum. On the other hand, T cells (lymphocytes), each distinguished by unique genes encoding immunological specificity, can be viewed as auditioning in the thymus before being exported, *internal* to the body (which a cell then patrols seeking foreign antigens). Proposed mechanisms of lymphocyte auditioning have extensive experimental support (Forsdyke 2022)—much less so for mechanisms of germ cell auditioning (Forsdyke 2000). Nevertheless, in view of several similarities between processes in the two seed organs, a comparison appears valid, so assisting the present discussion of germ cell auditioning.

The quality-control mechanisms begin with either local (thymus) or general (gonad) genome-level diversity generating processes (mutation and recombination), which create *individual* cellular phenotypes. Each cell then proceeds through selective gauntlets to optimize either the organism's immune repertoire (thymus), or its gamete repertoire (gonad). Intriguingly, *both* processes require the 'promiscuous' expression of numerous genes, many of which are *not* normally required for the function of the corresponding organ. Such expression requires the autoimmune regulator (*Aire*) gene. The natural mutation or experimental deletion of *Aire* impedes function in *both* organs, with associated diseases (Zou *et al.* 2021; Kaiser *et al.* 2022). Each process is part of a continuum, so making it difficult to pin-point their beginnings.

Roe versus Wade

Views on the morality, ethics, and legality of terminating pregnancy touch on many issues (e.g., human rights, population control, eugenics, religion) that are of worldwide interest. These are now coming into increased focus in the USA where a many decades old court decision—that of Roe versus Wade—is being reconsidered. While legal strictures are of comparatively recent origins (Pilpel 1969), they now threaten to tear that society apart. Pressures for abortion rights led to a 1973 US Supreme Court opinion (Blackmun 1973) that overruled many federal and state abortion laws governing a woman's right to medical abortion. Continuing arguments relating to this case have centered around the premise that destroying a human life is wrong. In turn, this has centered around the premise that human life begins when gametes meet. Yet, diffidence was expressed by Justice Blackmun in the initial Court opinion: 'We need not resolve the difficult question of when life begins. When those trained in the respective disciplines of medicine, philosophy, and theology are unable to arrive at any consensus, the judiciary, at this point in the development of man's knowledge, is not in a position to speculate as to the answer'. A half century later, as discussed here, an incomplete understanding of the underlying biology, possibly nourished by loose medical terminology, still remains to be corrected. It is doubtful that there is a uniform, clearly definable time point, when Nature can be considered to have relaxed, so permitting unfettered lives to begin. Those who medicalize the normal with inappropriate terminology (Tirlapur *et al.* 2013; Laan *et al.* 2021) may be reinforcing incorrect attitudes, with profound societal implications.

Conclusions

Planned parenthood is something that, in their own ways, both Nature and prospective parents engage in, and which physicians advise on. A better understanding of Nature's role might help avoid incorrect usages of terms such as 'idiopathic', which may confuse rather than inform. The easiest *legally* definable points for designating the beginning of a life process are fertilization (gamete meets gamete) and parturition (the baby physically separates from its mother). However, *biologically* the process appears as a continuum with no such easy definition. Lengthy gonadal vetting prior to fertilization can impair continuation of a lineage, with the potential to facilitate speciation. By accurately recognizing termination at various stages in the process as natural and routine, preoccupation with fertilization as life's starting point would be reduced and hopefully also any stigma associated with natural or induced

abortion after fertilization. Haldane (1922) lit the way, so continuing what was to become a long association with the *Journal of Genetics* (Rao 2017).

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Queen's University hosts my evolutionary biology and immunology webpages.

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