Review article

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Erroneous theories of sex determination

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SUMMARY Throughout the major part of history, theories of sex determination had to be formulated in the absence of knowledge of ova and spermatozoa. The most persistent theory postulated that males are associated with the right parental side and females with the left side. At the end of the 19th century, sex was thought to be determined by nutrition. Recent findings regarding bilateral asymmetry in human hermaphrodites and of temperature dependent sex determination in reptiles may restore a small degree of credibility to certain theories predating the discovery of sex chromosomes.

Since the discovery of sex chromosomes occurred at the beginning of the 20th century, all ideas before this time fall into the category of 'prescientific'. Prescientific ideas are not necessarily wrong, any more than ideas developed during the scientific era are invariably right. In 1912, when H J Muller was a student at Cornell Medical College, he wrote a paper entitled 'Erroneous assumptions regarding genes', which at the time he was unable to publish. This is hardly surprising, for in this paper Muller complained about "certain needless assumptions regarding sex" and criticised the genetic formulae proposed by his teacher, T H Morgan, to explain sex determination in *Drosophila*. Part of this paper was later included in an article 'Some genetic aspects of sex'.¹

The present account will confine itself to theories of pre-20th century vintage. By the 19th century the number of theories to explain the determination of sex had been estimated at about 500. In a famous passage by Geddes and Thomson² we read that: "The number of speculations as to the nature of sex has been well-nigh doubled since Drelincourt, in the last century, brought together two hundred and sixty-two 'groundless hypotheses', and since Blumenbach quaintly remarked that nothing was more certain than that Drelincourt's own theory formed the two hundred and sixty-third. Subsequent investigators have, of course, long ago added Blumenbach's 'Bildungstrieb' to the list".

In view of the magnitude of the subject, the present list will of necessity be selective.

The elusive basis of reproduction

Like all reproductive processes, sex determination is ultimately based on the behaviour of cells, and the trouble with cells is that they are small and invisible in the absence of special instruments and techniques. It follows that before the advent of the compound microscope, theories of reproduction suffered from an almost insurmountable handicap. While the eggs of birds and of diverse other creatures were known since the beginning of civilization, the mammalian egg was not discovered until 1827.³ The discovery of spermatozoa occurred one and a half centuries earlier, when for the first time microscopes were made that could magnify up to 270 times.^{4 5} The best microscopes were made by Antony van Leeuwenhoek, a Dutch draper, and it was he who sent the first communication of the existence of spermatc animalcules to The Royal Society.^{4 6 7} It now became apparent that the mysterious substance, semen, was populated by a multitude of seemingly eel-like little animals. Van Leeuwenhoek provided illustrations of spermatc animalcules from man and dog. Hughes⁸ comments that: "It is still mysterious how a drawing no less inexact than this, at a magnification of over 2000 diameters, could have been made at that time. Certainly no better appeared for a century and a half".

Once discovered, the seminal animalcules gave

rise to a long-lasting controversy concerning their origin, structure, and function.⁴ They might be artefacts, such as any observer with a good microscope could concoct, and what Leeuwenhoek regarded as tailed worms might only have been an agitated portion of the viscous semen; alternatively they might be the result of putrefaction. Even if they really existed, this would be no reason to associate them with any essential process in generation; for instance they might prevent the semen from clotting. Furthermore, the notion that animalcules played an active role in the process of generation ran counter to the accepted idea of the time, which was that animals originated from eggs.

William Harvey, renowned for his discovery of the circulation of the blood, was also a pioneer investigator into the process of generation. Harvey was physician to Charles I, a position which allowed him to dissect the red and fallow deer shot in the royal parks. It now appears, though, that this choice of species was unfortunate, both because ovulation in deer is delayed until a month after the rutting season⁹ and because the early embryo is more difficult to see than that of the rabbit.¹⁰ At any rate, Harvey failed to detect any connection between the female "testes" (ovaries) and the process of reproduction, but he nevertheless maintained that "all animals whatsoever, even viviparous ones, nay man himself, are all engendered from an egg".¹¹ His treatise on *The generation of animals* was published in 1651 in four editions, of which two contained a frontispiece showing Jupiter holding in his hand an egg, from which emerged all manner of animals including man. On the shell of the egg are engraved the words *ex ovo omnia*. Cole⁴ records a history of the misquotations of these words. It must be remembered also, as pointed out by Punnett,¹² that to Harvey the word ovum meant something different from the modern usage of the term, namely a small mass of undifferentiated matter, which became gradually fashioned into the form of the species from which it was derived. Eggs of birds, pupae of insects, and early human embryos are all ova. Steno, in 1667, proposed that the female testes corresponded to the ovaries of egg-laying animals⁴ and this proposition received strong support from the experimental investigations of the Dutch physician, R de Graaf, which Cole⁴ describes as follows.

"De Graaf published his great work on the female organs of generation in 1672. He dissected rabbits at varying intervals from half an hour onwards after coition, and partially succeeded in tracing the 'eggs', which he maintained existed already formed in the ovary, from the ovary down the Fallopian tube to the uterus—thus establishing the suggestion of Wharton. He found that the number of cicatrices or

empty follicles in the ovary corresponded generally with the number of eggs in the uterus, and he was therefore able to demonstrate that the generative process was associated with changes occurring in the ovary, which is consequently essential to generation. Thus he discovered that the 'eggs' of the mammal originated in the ovary and developed in the uterus—a conclusion which was not at first completely established, and obviously required for its confirmation very exact and skilful observation. De Graaf describes the 'ovarian vesicles', since named after him, or hydatid vesicles as they were in his time often called, which had already been seen by Vesalius and many other anatomists, and called 'ova' by van Horne in 1668. The latter name was given them because of their resemblance to the ovarian eggs of birds. De Graaf holds that ova are to be found in the ovaria or female testicles in all animals, such as mammals, birds, fish, and even in mules, whether oviparous or viviparous . . . The ovary and eggs of birds are directly comparable with those of mammals . . . It must be emphasised that, although de Graaf recognized that the 'ovum' in the oviduct was much smaller than the ovarian follicles, he never saw the mammalian ovum . . ." Nevertheless, as a result of de Graaf's microscopical investigations, the Aristotelian doctrine, which held that the female reproductive organs produced menstrual blood and that the embryo was formed from the male semen (see below), was laid to rest.

The new doctrine, moreover, lent itself to a little fanciful exaggeration. According to the theory of emboîtement, or encasement, the development of the ovum was merely an unfolding, or *evolutio*, of what had always been there from the day of Creation. Eve's ovary contained in miniature all humans ever to be born. Although deviating from the teachings of Aristotle, this was a doctrine of which the leaders of the Church could approve. An influential work in this connection was Mallebranche's *De la recherche de la vérité*, published in 1674, from which Punnett¹² quotes the following extract.

"That all the bodies of Men and Beasts, which shall be born or produc'd till the end of the World, were possibly created from the Beginning of it: I would say, That the Females of the original Creatures were for ought we know, created together, with all those of the same species which have been, or shall be, begotten or procreated whilst the world stands."

The ovists' position, however, was threatened by the discovery of the spermatozoa. Van Leeuwenhoek claimed that the animalcules provide the entire material contribution to the embryos, the egg serving only as nourishment. In support of

this he quoted the results of a breeding experiment in rabbits, in which a grey male and a white female had only grey offspring.⁴ Not only did the animalculists have a technical advantage because Leeuwenhoek's observation could be confirmed by anyone who had a microscope, while those of de Graaf on ova required a high degree of skill,¹⁰ but animalculism allied with encasement theory could transfer the creation of all humans from Eve to Adam.

Hartsoeker¹³ was the first author to illustrate a fetus inside an animalcule, although he did not claim that this was any more than supposition. He added that this new view of generation may be pushed further and that each of the male animalcules encloses within itself an infinity of other animals of the same species, both male and female. This was the first time that it had been proposed that the members of a series enclosed in the first individual were not all the same sex.⁴ In later years, Hartsoeker abandoned the theory of encasement and of preformation in general; and those who adhered to it, whether animalculists or ovists, simply ignored the difficulty of having two sexes encapsulated in either series.⁴

The following extract from a footnote in the abridged version of the *Philosophical Transactions of the Royal Society*¹⁴ describes the state of knowledge, or lack of it, concerning the animalcules at the beginning of the 19th century.

"The discovery of the spermatic animalcules has always been considered as one of the most extraordinary which the microscope is capable of exhibiting . . . and though the Leeuwenhoekian theory of generation be now exploded, yet the existence of such legions of animated beings affords a wide field for philosophical speculation . . ."

Von Baer, the discoverer of the mammalian ovum, regarded the animalcules as parasites of the semen akin to Infusoria, and he perpetuated this view by naming them Spermatozoa.⁴ In the following decade, Schleiden¹⁵ in Jena and Schwann¹⁶ in Berlin enunciated the cell theory. Schwann concluded that the egg is a cell.¹⁶ The riddle of the spermatozoon was solved by Albert Kölliker,¹⁷ a Swiss citizen from Zurich, who examined all manner of marine creatures with his microscope by the coast of the North Sea. He concluded that spermatozoa were not independent animals but products of cells in the testis that needed to come into contact with the egg for successful reproduction. The coming together of two cell nuclei in fertilisation was first observed in 1875.¹⁸ In the same period, chromosomes were described, but the sex chromosomes are a discovery of the 20th century.¹⁹ The mode of action of sex chromo-

somes remains a subject of conjecture and controversy today.

A recipe for having sons

The desire to solve practical problems generally precedes an understanding of the underlying scientific basis. An 18th century French anatomist who wrote under the pseudonym of Procope Couteau achieved lasting fame as the author of a book *The art of having boys* of which the first edition appeared in 1748.²⁰ Procope thought that the male semen is filtered through the testicles and the female semen through the ovaries; and since these organs occur in pairs, does it not stand to reason that they also determine the sex of the species? Moreover, one testis tends to be a little larger than the other, which increases the suspicion that one testis functions in producing males and the other females; the same argument applies to ovaries. On this hypothesis it is indeed easy to have either boys or girls according to choice, since all that is necessary is to remove the testis or ovary connected with the sex that is not wanted.

The author admits that there may be persons who do not want to use the method on themselves, even though it is probably no more painful than having a tooth extracted. Besides, the operation is routinely practised on dogs and horses and it is rarely fatal. For timid souls, there was a less drastic, although also less effective, method. Here the author addresses himself to the ladies. Although a man cannot control from which testis the semen originates, a woman can direct it to the ovary of her choice. All she has to do is to lie on the correct side and let gravity do the rest.

On the question of which ovary or testis predisposes to which sex, the author is strangely reticent. Nevertheless it would seem that the book sold well, for it went into at least four editions.

The effect of nutrition

Towards the end of the following century, the idea that the sex of the offspring is determined by the testes or ovaries of its parents appears to have been largely abandoned. E B Wilson, who was soon to take on the leading role in the discovery of the sex chromosomes, and to whom indeed we owe the term 'sex chromosomes',²¹ wrote in the first edition of *The cell in development and inheritance*²² that "the determination of sex is not by inheritance, but by the combined effect of external conditions". The most decisive of the external conditions was thought to be food and therefore in the last analysis the determination of sex appeared to be a problem of

nutrition. Düsing²³ states categorically that in humans maternal nutrition influences the sex of the embryo during the first three months of gestation. A poor nutrition results in males and better nutrition in females. The higher birth weight of boys may seem a problem but can be related to the greater rate of stillbirths. Since boys grow faster, they require more nourishment but in fact develop under unfavourable conditions. The effect of temperature was thought to be less important than that of nutrition. Düsing and others noted that more boys were born during the winter months and the same seemed to be true of horses. Of course, not the time of birth but the time when sex was determined would be important in this respect. It was also thought that temperature may exert its effect indirectly via nutrition, which at that time would have been subject to very marked seasonal variation. Düsing²³ admits, however, that in higher animals, the nutrition of embryos exerts only a small effect, since sex ratios vary only by a few percent. Geddes and Thomson² cite an important experiment made by Girou, who divided a flock of 300 ewes into equal parts, of which one half were extremely well fed and served by two young rams, while the others were poorly fed and served by two mature rams. The proportions of ewe lambs born were 60 and 40% respectively.

In lower animals, the results described were more striking. In an experiment carried out by Yung,² tadpoles left to themselves developed on average into 57% females. When the tadpoles were fed with beef, the proportion of females rose to 78%, while feeding with fish resulted in 81% of females. Finally, when the specially nutritious flesh of frogs was supplied, 92% of the tadpoles developed into females.

Similarly striking results were obtained by Mrs Treat²⁴ on butterflies. When larvae of *Papilio asterias* were reared on a plentiful food supply, the large majority developed into females while nearly all poorly fed larvae turned into males. Two other species of butterfly gave similar results.

Then there is the example of aphids. "During the summer months, with favourable temperature and abundant food, the aphides produce parthenogenetically generation after generation of females. The advent of autumn, however, with its attendant cold and scarcity of food, brings about the birth of males, and the consequent recurrence of strictly sexual reproduction. In the artificial environment of a greenhouse, equivalent to a perpetual summer of warmth and food, the parthenogenetic succession of females has been observed for four years . . ."²

Summarising the available evidence, Geddes and Thomson concluded that, although it must be

recognised that a number of factors cooperate in the determination of sex, the most important of these is nutrition, operating upon parent, sex elements, embryo, and in some cases larvae. Adverse conditions, particularly of nutrition, but also of temperature and age, tend to produce males while favourable conditions are likely to result in females.²

The reason for this consensus of opinion may at least partly be seen in a mixup in the minds of natural scientists in the late 19th century between germ cells, whose nature had only recently been discovered, and the organisms producing them. "The less nutritive, and therefore smaller, hungrier, and mobile organisms we call male; the more nutritive, usually more quiescent organism we call female. The small starving male cells seeks out the well-nourished female cell for purposes of conjugation".²

Ancient ideas about sexual development

The idea of a small, starving male would have been totally incomprehensible to the ancient Greeks. Galen, in the 2nd century AD, sums up the classical position as follows.^{25 26}

"Now just as mankind is the most perfect of all animals, so within mankind the man is more perfect than the woman, and the reason for his perfection is his excess of heat, for heat is Nature's primary instrument. Hence in those animals that have less of it, her workmanship is necessarily more imperfect, and so it is no wonder that the female is less perfect than the male by as much as she is colder than he."

Nevertheless, the imperfect female has her usefulness. "Indeed, you ought not to think that our Creator would purposely make half the whole race imperfect and, as it were, mutilated, unless there was to be some great advantage in such a mutilation."^{25 26}

The idea that males are hotter than females is attributed to the Greek philosopher Empedocles, who also had the idea that organisms are made up of different proportions of the four elements, fire, water, air, and earth, which have the qualities of hot, cold, wet, and dry respectively.²⁷ This concept forms the basis of Aristotle's idea of sex determination, which is illustrated in fig 1. The male is characterised by an abundance of the superior element, fire, and the qualities hot and dry, while the female has an abundance of water and is therefore rather cold and wet.^{26 28}

The fieriness of the male and the coldness of the female determine their respective roles in reproduction (fig 2). By virtue of the extra heat that characterises the male, he is able to process his food intake into the ultimate residue, namely white,

FIG 1 The difference between males and females according to Aristotle. Males have an excess of heat and dryness, females of cold and wetness. From Gordon,²⁶ redrawn by A J Lee.

FIG 2 Male and female roles in reproduction according to Aristotle. By means of their superior heat, males produce the perfectly processed, concentrated semen. Females produce only partially processed menstrual blood. From Gordon,²⁶ redrawn by A J Lee.

concentrated semen. Since the female lacks heat, she can achieve only an imperfect concoction, which is evident in the relatively voluminous, red menstrual blood (Aristotle). The half-cooked menstrual blood Aristotle regarded as the material substance of the embryo, to which the semen provided form and movement, rather as a potter forms a lump of clay.^{26 28}

The superiority of males over females is matched by the superiority of the right over the left side, and by assuming that the right side of the body is hotter than the left, a consistent theory of sex determination is arrived at: males are associated with the right side, females with the left.^{27 29} Details may differ. Parmenides seems to have thought that the sex of the child is determined by its position on the right or left side in its mother's womb: males are on the right, females on the left,²⁹ whereas Anaxagoras thought that the father was responsible for the sex of his offspring, semen from the right side becoming male and from the left side female.^{28 29} Aristotle criticised both theories, since he had evidence that twins of different sex can be found on the same side of the womb and that males with only one testis can father both male and female offspring. However, the left-right theory of sex determination withstood such factual details and in fact survived for more than 2000 years. After becoming part of medieval medicine, it was transmitted as part of the 'Hippocratic teachings' until recent times.²⁷ In 1895, a paper published in a gynaecological journal quoted recent reports on the subject of the different sexual potentials of right and left ovaries and suggested that it was time that the idea was properly tested.³⁰

During the course of centuries and millennia, there was ample time for the right-left theory of sex determination to become simplified, popularised, and applied in diverse methods of predicting and selecting the sex of the offspring.³¹ An Alexandrian manuscript of the 1st century AD contains the statement that if after service the bull dismounts from the cow on the right side, this will result in a bull calf, while dismounting on the left side leads to the conception of a heifer calf; this statement is illustrated in a 16th century woodcut (fig 3), which clearly shows the conception of a bull.

The method can of course be adapted to human sex selection; for instance, to have a son, it is advisable to get out of bed with the right foot. In case this sounds too simple, a 16th century Venetian tract lists eight requirements for the production of male offspring: first, warmth and second, quantity of seed, both because the male sex is the more perfect being; third, complete purity of the woman regarding her monthly purification, since any aqueous liquid would weaken the efficacy of the semen; fourth, origin of the semen from the right testis, since this is warmer, thicker, and better concocted; fifth, ejaculation of the semen into the right half of the uterus; sixth, warm condition of the female 'semen'; seventh, northern winds, since these, by a kind of counter-action, warm and strengthen the body; eighth, optimum ages of the parents.³¹

FIG 3 A 16th century woodcut illustrating a statement from an Alexandrian manuscript of the 1st century AD stating that if a bull descends from the right side of the cow, conception will result in a bull calf, while descending from the left side will result in a heifer calf. From Meisenheimer,³¹ redrawn by A J Lee.

Conclusions

While it is remarkable that the theory associating right body side with maleness and left body side with femaleness has been so consistently adopted and has lasted so long, it is surely equally remarkable that recent findings indicate that when the theory is divested of its more extravagant trimmings, it is found to contain an element of truth. In human hermaphrodites, ovaries are preferentially situated on the left and testicular tissue, either in testes or ovotestes, on the right side.³² The finding that mammalian fetal testes grow faster than ovaries³³ echoes the ancient view that males are hotter than females, and the idea that the right side is hotter than the left finds some support in the fact that in human fetuses, right gonads grow faster than those on the left.³³ Last, the discovery of temperature dependent sex determination in reptiles^{34 35} will surely bring some measure of validation to the theory—current a hundred years ago and perhaps swept away too hastily by the advent of chromosomes and of genetics—that sex is environmentally determined. Although we now know that sex is not determined by nutrition in man and other mammals, it is also apparent that chromosomal sex determining mechanisms are not universal even in higher vertebrates.

We may conclude that while there are many erroneous theories of sex determination, not all of them are groundless.

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