To Bde or Not to Bde: Sex and the Bdelloid Rotifer

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Most species eventually end up having sex, but not the bdelloids, and in pondering what lies beyond what we can see in evolution, there's the rub.

Nothing gets the public's attention more than sex, but it is the *absence* of sex that gets noticed by biologists. This is not (necessarily) because scientists are hormonally dull, but because sexual reproduction is one of the most fundamental properties of plants, animals, and even micro-organisms. A sizeable body of theory explains why this apparent self-sacrifice—tying your reproductive fate to another organism's and only giving your offspring half your genome—would evolve.

The most common argument for the evolution of sex is that it recombines existing variation to provide species with greater genotypic variety that can respond to changing environments.[1] There are variations on the theme,[2,3] such as to protect against parasites or harmful mutations, but they all tread the thin line between group selection (*shh!*) in which something costly evolves because it's good for the species in the long run, and classical darwinian selection where all that counts is competitive advantage of individuals in the here-and-now. If I'm doing OK in that battle, it's a mystery why compulsive ardor gives the charge to entrust half my offspring's genetic fate to any mate no matter how sweet. I don't care if such a sacrifice might mathematically be good for my species, a fractious lot

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without the foresight to know what its future needs might be.

There's no denying the widespread distribution of sexual reproduction in all the major king- and queen-doms of life. Sex must have such important evolutionary value that we might expect its mechanism to be frozen in place by stringent selection. But that is anything but the case. Perhaps it's madness for me to try to capture nature's vast sexual array by describing a few examples, but bear with me because there's method in it, because sex has lessons to teach us about evolution in general.

THE SEXUAL CHARIVARI: A MOTLEY TROUPE

The parade of sexual variation is impressive across the biosphere (for a review, see[4]). Just among our closest relatives, the primates, think of the variation in size difference between male and female gorillas (and some ancestral hominid species), or the palette of form and color of facial fur and sexual swelling, or behavioral and pheromone signaling, in getting primates together.

More broadly, mammals generally share the familiar *heterogamic* sex determination, with X and Y chromosomes in males and XX females. The Y-linked *SRY* gene determines male embryonic differentiation, but only in association with autosomal (non sex-linked) modifying genes, like *DMRT1* on human chromosome 9. This genetic way—*our* way—of making ends meet is sometimes portrayed as *the* way, but in fact that's not even so in all mammals.

Mice have the same kind of XX-XY sex determination we do, but at least

one close relative, the vole *Ellobius lutescens,* has no *SRY* gene and both sexes have only a single X chromosome.[5] The "missing" effect may be achieved by chemical modification, known as imprinting, of key regions of the other chromosomes, but the mechanism is unknown. Of course, nothing's really missing, unless we set ourselves up as the standard, because these voles are doing perfectly well!

Like ice cream, heterogamy is a treat with many flavors even among closely related species. Birds have reversed the mammalian system, with ZW females and ZZ males, and their sex-determining gene is not *SRY*, but the aforementioned *DMRT1*. And even closer to mammals is the duckbilled platypus (*Ornithorhyncus anatinus,* Figure 1A), a monotreme with an unusual if not bizarre version that has recently been reported.[6] Duckbills have 52 chromosomes, 21 that are paired and 10 that are paired in females but *unpaired* in males, who have five different Y chromosomes (single copy in males, absent in females) and five X chromosomes (one each in males, two in females). In male meiosis (sperm formation), these 10 elements link together into a single chain structure, with alternating X and Y elements (Figure 1B). This happens because a history of rearrangement has put closely related (homologous) chromosomal segments onto different chromosomes. Their homology (sequence similarity) lets them align (vertical elements of Figure 1B), while the non-homologous parts of these same chromosomes can't align (horizontal elements), resulting in a multi-chromosome chain. Remarkably, these alternating elements then segregate in a way that somehow leads sperm to end up with just the five X or five Y elements. In addition, the male doesn't seem to have an *SRY* gene. A plausible history of translocation has
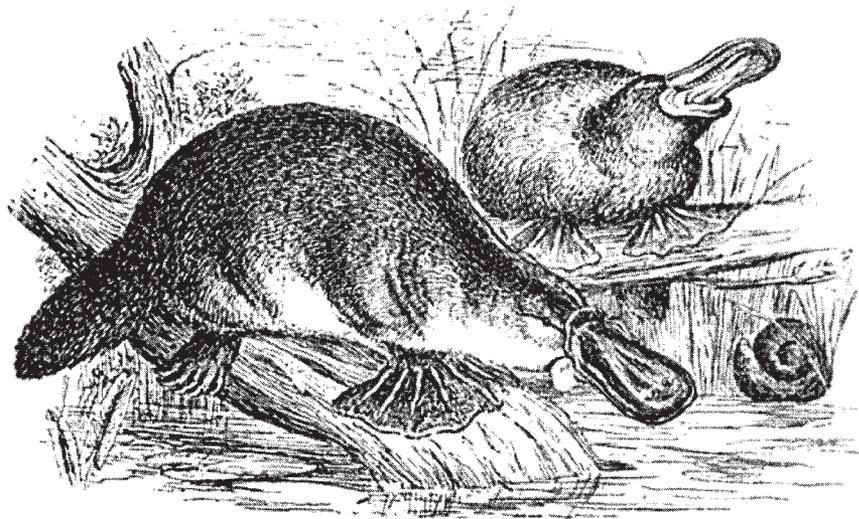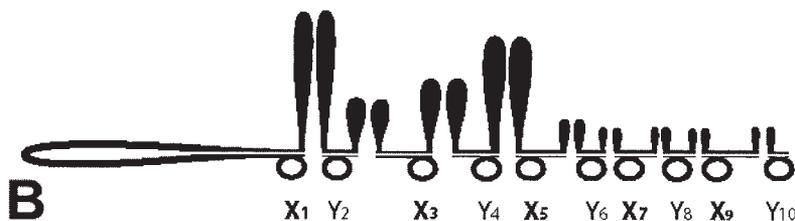
Figure 1. Pair by pair, each in its own way. A. Duckbill platypus. By Louisa Meredith, 1812–1895. Reprinted with permission from the Tasmaniana Library, State Library of Tasmania. B. Chromosomal chain in males. Regions homologous between separate unpaired chromosomes in males are shown as darkened vertical segments. Their homology leads to their joining into a single structure early in meiosis. Non-homologous regions of these chromosomes can't pair, and are shown as horizontal segments. Centromeres are indicated by circles. The chromosomes are identified by numbers across the bottom. The odd-numbered X-like chromosomes are paired in females but single in males, the even-numbered Y-like chromosomes are found only in one copy in males and absent in females. (See[6,7])

been suggested, to reconstitute the ancestor of these remnants of past life.[6]

In fact, comparative analysis shows that there has been a lot of translocation (scrambling) of sex-related genes during vertebrate evolution. The largest of the platypus X chromosomes (X_1 in Figure 1B) bears homology to the human X, while platypus X_5 resembles birds' Z including their putative sex-determining gene *DMRT1*. Thus the modern platypus may retain an indication of the ancestral branch point between mammalian and bird systems.[7]

Heterogamic sex raises a genetic dosage problem. The general physiology of cells in males and females of a species is the same integrated system that involves proteins coded by genes all over the genome. Chemical reactions are often concentration-dependent. This can cause problems if male mammals produced only half of the level of X-linked proteins that XX females produce. Instead, there is dosage compensation in mammals, in which each female cell randomly inactivates one of its two X chromosomes, leaving only a single active one just as is found in males. The uncompensated Y chromosome determines sex. The platypus has essentially the same genome and physiology as mammals, but some of the genes on its several sex chromosomes are autosomal in mammals. This means that

for species like platypuses to hook up properly, their histories of gene rearrangements must have been accompanied by an evolutionary tinkering with dosage compensation mechanisms.

Indeed, endocrinologically, mammals are not so different from reptiles, but reptiles have *environmental* sex determination, which is the likely ancestral condition of terrestrial tetrapods including ourselves, and which persists to this day in some reptiles. While still in the egg, the embryo develops into a male or female depending on the temperature outside the egg (which the mother doesn't incubate). In turtles, females form above a species-specific temperature and males below it, but this is reversed in lizards, and male crocodiles form only within a narrow intermediate temperature range.[8] One can view this kind of system as evolutionarily vulnerable, and it has been speculated that thermosexuality was responsible for the extinction of dinosaurs when the Long Cold Shadow cast by the Big Meteor suddenly (and sullenly) unisexed them, leaving the boudoir to species with a more highly regulated chromosomal sex mechanism who were lurking behind the drapes.[8] Their vulnerability may be overstated, however, because thermosexual species managed to get done what they had to do for hundreds of millions of years—and some are still at it today. And fish are doing very well (except when we catch them all) even though in some species individuals can change their sex to respond to external conditions.

Insects use a variety of explicitly dosage-dependent mechanisms to produce sexes. *Drosophila* has an XX-XY chromosomal system, and Y-linked genes are needed for fertility, but male morphology is produced by the relative dosage levels of X-linked genes and genes on the other chromosome. However, not even all flies use the same system, and social insects have their own varieties. Queen bees can lay unfertilized haploid eggs that become males, or they can lay fertilized eggs. These become sterile female workers or fertile queens depending on how they are fed, for example whether they are given "royal jelly," as larvae. It's no surprise that there are
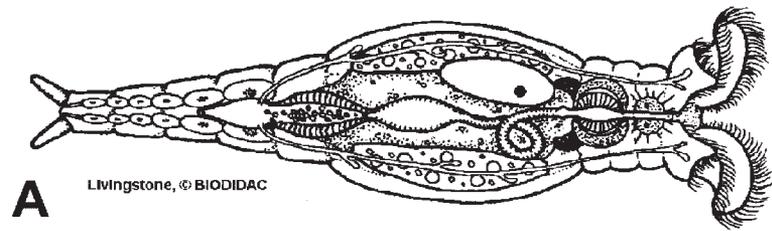
A
Livingstone, © BIODIDAC

Figure 2. Bdelloid rotifer, by itself (A) Anatomy (Drawing by Ivy Livingstone reproduced with permission from Biodidac.bio.uottawa.ca). (B) Sequence relationships among copies of the same gene (Alleles **A, α**) in three related species (1, 2, 3). Left, if the species are asexual, the **A** and **α** alleles each independently have a tree of sequence relationships that reflects the time and pattern of species divergence; right, within sexual species recombination keeps the alleles **A** and **α** similar within each species, but they jointly represent the history of species divergence (courtesy A. Buchanan).

B
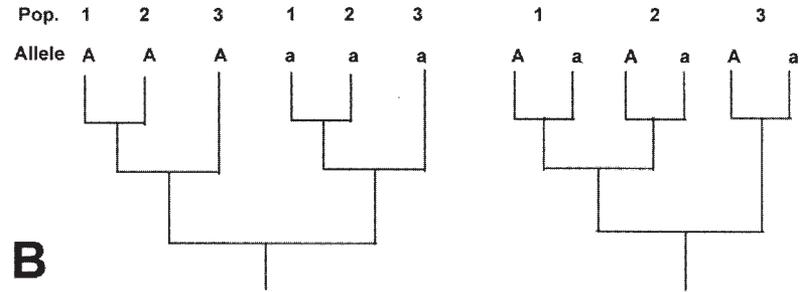
variants of this system, or that some close relatives of bees and ants, the isopteran termites, use "standard" sex determination. And, as found here and there in the animal world, some insects like some aphids reproduce parthogenetically some of the time (no mating, just diploid formation of new offspring in the mother).

Yet farther afield among animals is the nematode *Cenorhabditis elegans*. This lab favorite only produces males and hermaphrodites. And plants have all sorts of sex mechanisms, including self-fertilizing hermaphrodites (both sexes in same plant), self-excluding species, and a fantastical array of details. Many plants can't even do it on their own without help: their sexual apparatus includes a very specialized sex organ called a "bee."

Unlike most animals, plants do not sequester a germ line, and every meristem (stem end) can differentiate into flowers. Sponges and slime molds don't have a sequestered germ line either. So why was it so important for us to evolve one?

Even single-celled organisms that reproduce by asexual cell division most of the time have sex under some environmental conditions. However, the reproductive mechanisms are totally different. Bacteria exchange genes in cellular organelles (plasmids) that can transfer even between species and bacteria also exchange plamids with so-called F-elements; F+ and F− cells conjugate and genes transfer from the former to the latter. This isn't exactly sexual reproduction because after conjugating both cells can reproduce, and bacteria are haploid so they do not produce haploid gametes that fuse to form a diploid zygote. But it's certainly a related gene-pooling mechanism.

Fungi can exist in haploid or diploid states, and can undergo mating, but not even all fungi dance to the same tune. Mating type in brewer's and baker's yeast is determined by a single short chromosomal region called *MAT*, when one of two DNA sequence cassettes (called **a** or α) from elsewhere on the chromosome is activated by being copied and physically inserted into the *MAT* location. But the corn fungus, *Ustilago madis*, has two unrelated mating-related chromosome regions, one containing pheromone genes, the other regulatory genes, and each region has two states (alleles **a** or α). Two regions with two states makes a four-state system, but mating only occurs between cells that differ in both regions. In a related human parasite *Cryptococcus neoformans* that affects AIDS patients, there is only one *MAT* region, but it is quite large and contains both the pheromone and regulatory genes, that have been translocated into the location, yielding two mating-type alleles, *MAT***a** and *MAT*α. But this two-state system does not use a cassette-replacement system as found in yeasts.

So who cares about fungi except bakers and brewers? A comparison of *MAT* regions in three closely related fungi suggests that the current *C. neoformans* system was produced during three different historical stages of gene rearrangement.[9] Some plants may have had a similar history, and comparable arrangements of interspersed genes characterize the mammalian Y-based sex-determining chromosome, in which four blocks of genes seem to have been put there at different times, again suggesting that chromosome reassembly is one basic means of sex-determining evolution.[9]

TO THINE OWN SELF BE TRUE

Finally, this tale of devious plots brings us to our star performer, the solitary brooding bdelloid rotifers (Figure 2A; bdelloid is pronounced as it is spelled—if you are able—and is from the Greek meaning "leech-like"). These widespread, small freshwater organisms are among the few known species that never play the mating game. They reproduce parthenogenetically, making diploid eggs through mitosis.

This deviant behavior goes so much against prevailing theory that considerable effort has been made to find

genetic sequence patterns that show that bdelloids really *have* been asexual for a long time (Figure 2B).[10–12] In asexual diploid species, both copies of each gene are passed from a parent to its own offspring only—there are no spousal exchanges. As a result, the two copies of a gene found in an individual today have evolved independently, accumulating mutational variation since the burial of sexual reproduction in their ancestry. If you compare the two sequences of a gene within each species, to the same genes among related species, the sequence patterns of each allele should *separately* reflect the history of divergence among the species (Figure 2B, left). By contrast, alleles within a sexual species are more closely related to each other, because of recombination, than they are to their homologues in related species; thus, your two copies of *DMRT1* are more like each other than either is to a chimp's (Figure 2B, right). This kind of comparison shows that bdelloids have indeed been on a 40 million year soliloquy—strange indeed, given the supposed advantages of sexual recombination.

CHANGING THE STAMP OF NATURE

Since sexual traits are directly related to reproductive fitness, we might expect selection to minimize their variation, entrenching a mechanism once it's established. But we've just seen that sexual traits are as variable as other traits, so how could evolution have caused the countless jumps from one mechanism to another, without falling into a grave that lasts 'til doomsday?

This question can be addressed conceptually using Sewall Wright's 1932 notion of an adaptive landscape (the contour map in Figure 3).[13,14] Although it can't be taken too literally from a formal theoretical viewpoint,[15,16] after 70 years this figurative metaphor still retains its heuristic value. The height of the surface at any point on a "space" of genotypes reflects the fitness value of the phenotype resulting from that genotype. Gradual darwinian selection can only nudge genotype frequencies incrementally towards the most immediately beneficial form—the nearest
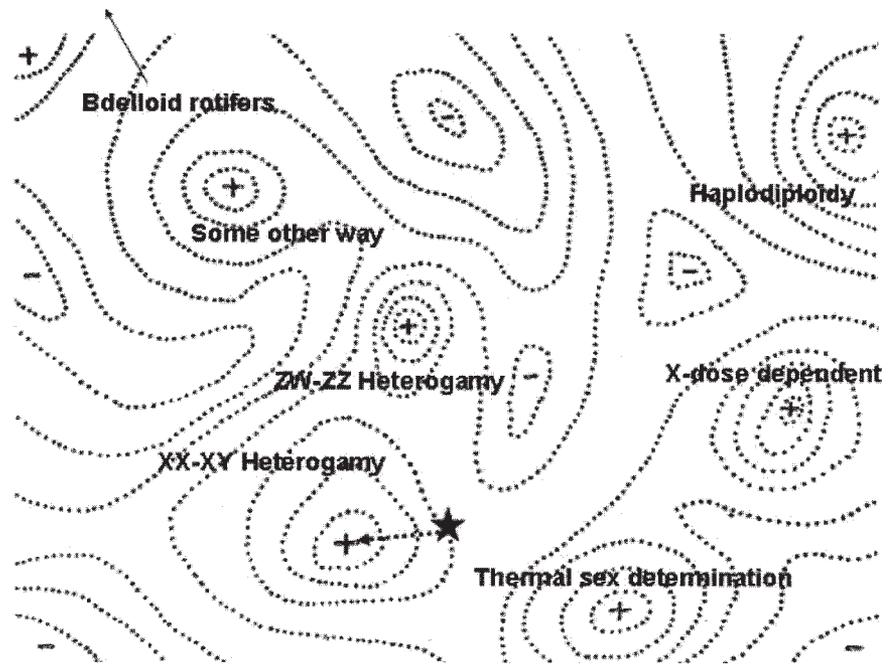

Figure 3. Sewall Wright's traditional adaptive landscape (contour plot)[13] with different sex-determining mechanisms schematically added. The dotted arrow shows that from the current position (star) gradual selection can only move a species up towards the nearest peak (XX-XY heterogamy in this example). +'s indicate peak tops, and −'s the valleys.

peak on the adaptive landscape—because that's the only direction in which slight (non-disastrous) changes in genotype will improve fitness. Selection has no way to go around a nearby peak to find higher peaks elsewhere. In Figure 3 the star schematically reflects a point from which selection would move a population towards the XX-XY heterogamy peak, but could not "find" ZW-ZZ or any other peak. Unless environments changed, the state is frozen. But how can environments cause one genetic way to have sex to switch to another very different orientation?

Wright suggested that the way to get to different peaks involves *chance:* genetic drift in small local populations could produce unusual genotypes whose phenotypes might jump past a local peak to land near another peak, whence to be moved by selection. This seems a leap of fidelity given the stringency with which selection might preserve a given sexual arrangement, but there may be another way to view the role of chance in adaptive evolution.[4,17,18] The genetic basis of a trait can change even when the trait is conserved by strong natural selection, by

phenogenetic drift:[4,19] even when there is selection, different genotypes can produce phenotypes that are equally fit, and hence will drift neutrally with respect to each other in the face of selection, as shown intuitively by the modification of the adaptive scenario in Figure 4. The trait under selection is "sexual reproduction," and its fitness peak is sharp, but the population could evolve variation in the underlying genetic mechanism so long as the new genotypes stay somewhere on the sexual reproduction peak. Species could form on different slopes of the same peak. There are many good-enough ways to have sex.

One such possible pathway is a recent speculation that mammalian sex chromosomes may have evolved their degenerate state initially by an epigenetic (non sequence-based) means, the kind of chemical chromosomal modification called imprinting that produces X-inactivation for dosage compensation today.[20]

In this interpretation of the role of happenstance in adaptive evolution, the diversity of sexual mechanisms is not remarkable and indeed is consistent with the evolution of other traits.

That's good, because that's what we observe in nature.

In the *Origin of Species,* Darwin noted something that is indirectly related to this idea, and involves his idea of sexual selection, in which one sex chooses among potential mates—the coy female choosing the best among passionate jousting males. Darwin said that characters associated with sexual selection that hence manifest sexual dimorphism within species, also distinguish closely related species and thus help demonstrate their common origin—perhaps as their ancestors meandered around the slopes. Chromosomal changes may initially lead to reproductive incompatibility, but clearly they don't always do so because chromosome structure routinely differs even between closely related species like humans and chimpanzees, and such changes might even help produce mating barriers that facilitate speciation.[21,22]

For these reasons we shouldn't be surprised at the amount of slippage in so important a trait as sexual reproduction. The bdelloid rotifers show that it's even possible for this trait occasionally to wander broodingly through the valleys past the nightwatch of selection.

THE PLAY'S THE THING

Today, sexual behavior and sexual orientation are the subjects of great societal controversy. Debate ranges over what's right and wrong, natural and unnatural. Genetics gets into the act because of the controversy over whether genetic research can determine if we are what we are because of what we inherit—such as the search for the "gay" gene—or because of our experiences. Much of this argumentation comes from a simple deterministic and dichotomous XX-XY view of sex and gender. Life may be a battle between "the" sexes, and both sex and gender are bimodally distributed, but even within species sexual acts and gender behavior are far from dichotomous. They are quantitative traits whose distributions overlap. This is not just true of facultative species like thermally induced reptiles. It's true of mammals, including human and non-human primates as well. Even chromosomal sex-determinants have quantitative aspects including contri-
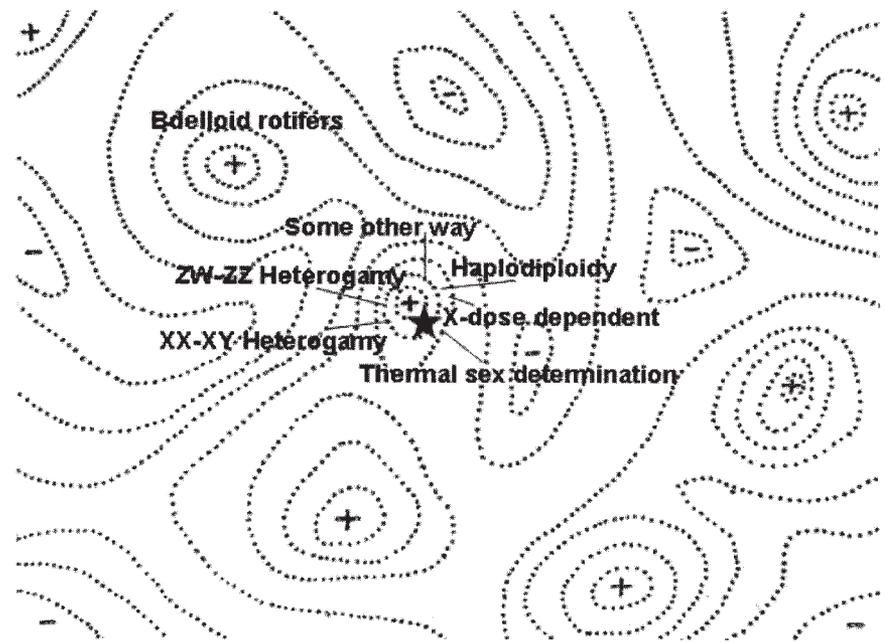

Figure 4. An alternative view of the adaptive surface, based on phenogenetic drift. The sexual reproduction peak is high and hard to move away from, but so long as the basic trait is conserved, the underlying mechanism doesn't matter much to fitness and can change by drift or other factors. Here, the star shows the location of some particular species.

butions from autosomal genes like *DMRT1,* or complete or partial sex-chromosome variants, like variants of X0 females (Turner syndrome), XXY males (Klinefelter), and many others—some of whom are fertile.

This is not a parochial or a moralistic view based on our own society's ambiguous genders, sexual preference patterns, and the like. There's nothing either good or bad, but thinking makes it so, and the ethnological literature clearly shows that cultures around the globe accept overlapping sex and gender patterns, variants, and ambiguities, and the same is even true of other animals that have been observed closely enough. Sexual reproduction is not just plumbing and anatomy, features which themselves vary considerably, as has recently been described in detail.[23] It's as much between the ears as between the legs. Largely in the mind, sexual reproduction begins with recognition, chemical attraction, visual, vocal, or other behavioral ritual, and display traits like primate face- and genital coloration patterns. Courting and family patterns likewise vary. There is ample normal, perfectly fertile variation in both the piping and the prancing, as

has recently been described in great detail. This variation is the face-paint for phenogenetic drift and the working material for sub-plots to change on the sexual stage, under a main plot that persists.

The diversity of mechanisms for sexual reproduction says much about the fluid nature of evolution itself, and convincingly so, because sexual reproduction is prior and primary to adaptive evolution in general. If anything is tightly constrained by selection, sex should be it. That makes it all the more remarkable that an experience so much on our minds and so central to whether we are to be or not to be, would be totally absent from the life of a bdelloid rotifer, unless . . . to sleep, perchance to dream, a distant, atavistic dream?

NOTES

I welcome comments on this column: kenweiss@psu.edu. I have a feedback and supplemental material page at http://www.anthro.psu.edu/weiss lab/index.html. I thank Anne Buchanan, Jeff Kurland, and John Fleagle for critically reading this manuscript.

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