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Dinner at Baby's: Werewolves, Dinosaur Jaws, Hen's Teeth, and Horse Toes

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Occasionally traits arise that appear to be atavistic throwbacks to the remote past. How can this make evolutionary sense?

As we get older we have a tendency to become nostalgic and think back on old times. We've recently seen a surge of nostalgia for the 1950s; among the remarkable comebacks are the new old diners, like Baby's here in State College (Figure 1). These new-old wonders proffer burgers and shakes like they used to be in the good old days. The decades of change in the competitive fast-food industry seem not to matter at all. The old taste is back! Even Patsy Cline and Elvis are still singing the same songs in the background.

There is a similar phenomenon in biology. Nobody accepts Ernst Haeckel's famous recapitulation argument that, as embryos, we literally go through the adult stages of our ancestors. Nonetheless, many seem to think the evolutionary past can rise again. Can it?

"A CIRCUMSTANCE WELL WORTHY OF ATTENTION"

One of the key facts in Darwin's "long argument" for evolution were atavisms—"throwbacks"—to evolutionary earlier states. In *Descent of Man,* he argued that these reversions were "well worthy of attention." Such traits are easier to explain as reflecting historical connections than by creationist arguments (for a popular treatment, see[1]). Many such traits occur naturally, but recently some surprising examples have arisen out of experiments in developmental biology.

NATURAL "ATAVISMS"

The occasional presentation of extreme hairyness in humans is an example of a naturally occurring "atavism." Our primate ancestors were fully furred, and when a variant allele or new mutation arises that causes a person to be very hairy, he or she may understandably be seen as ape-like. Such human atavisms, because we tend to think of ourselves as advanced and gentile, are often popularly portrayed as haunts of a brutish past, as in the "abominably hairy" atavism Red Eye of Jack London's book *Before Adam* who "was a monster in all ways." In our attention-hungry society this has even been likened to werewolves.[2]

Another common reversion discussed by Darwin is supernumerary nipples (polythelia). The "milk line" is well known in mammals. It runs along the thorax and abdomen on both sides of the midline. Different species have

Figure 1. Dinner at Baby's (State College, PA).

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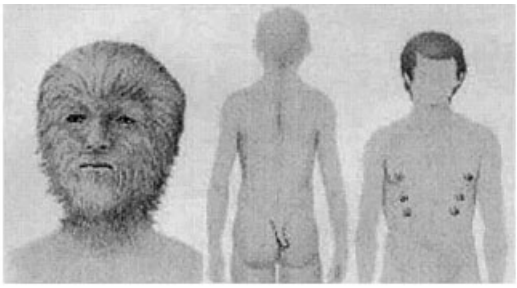

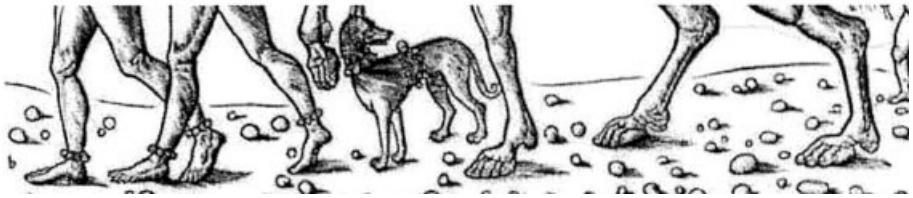

Figure 2. Atavisms. (A) Werewolves, and other "atavisms." Source: http://www.e-pub.org.br/cm/n09/fastfacts/atavismo_i.htm from "Evolution: Zufall oder Sinn?" Bild der Wissenschaft, 4: 114-126, 1979 (B) Horses's toes (which are the horse, which Caesar?). Source: Modified from Bettman Archive.

differing numbers of nipples located along this line, and this, as Darwin noted, can vary naturally and be heritable.

The evolution of digits has long been of interest to anthropologists.[3] Julius Caesar's horse is said to have had toes (as have the horses of Napoleon and Alexander the Great). Whether seeing these thundering toes in battle terrorized the barbarians we can only speculate, but the fossil record shows that horses haven't had toes since *Merychippus* during the upper Miocene (and *they* were already reduced and probably bore little or no weight).[4]

Another classic is the occasional appearance of rudimentary hindlimbs in whales.[5] Whale legs and horse toes are related to Darwin's notion of vestigial traits, because vestiges of the horse's original toes are present in the form of splint bones in the legs of all modern horses, and many whales retain bones or cartilage related to hindlimbs hidden beneath their incredible mass.

EXPERIMENTAL ATAVISMS

Hen's Teeth

Teeth develop through a process of tissue *induction* between two embryonic tissues in the developing jaw (Figure 3B). The overlying dental lamina is an epithelial layer. Underneath it is a *mesenchyme* largely composed of neural crest cells that have physically migrated to the jaws from the early neural tube.[6] The epithelium differentiates into ameloblasts that produce enamel, while the mesenchyme becomes odontoblasts that produce dentine. When these two tissues come in contact early in embryonic development, the information for initiating dental patterning resides in the epithelial layer, which activates the mesenchyme, and the two then interact during tooth morphogenesis.

Kollar and Fisher[7] wondered whether teeth could be induced in birds. They grafted chick embryonic jaw epithelium to mouse dental mesenchyme, and found the development of what appeared to be teeth (Figure 4). This famous "hen's tooth" experiment was questioned because it seemed implausible that chick epithelium could be re-awakened to make teeth tens of millions of years after chick ancestors had any choppers to chop with. The tooth seems to contain enamel, but chicks appear not to have the required gene (amelogenin), and it was molariform, but chicks don't have molars in their family tree (We assume as an artifact that it looked more like a human than a mouse molar.)

The standard explanation was that this was really a mouse tooth because the grafted mesenchyme was contaminated with mouse epithelium. But the experiments have been replicated[8,9] in many ways generating tooth-like structures, but without enamel. Wang et al.[9] reversed the combination (mouse epithelium and chick mesenchyme) and showed molecularly that the mesenchyme in fact expresses chick, not mouse, genes. There is still much to be learned about the crosstalk between these two tissues required for tooth development as suggested by the seemingly contradictory results of two recent papers. Chen et al.[10] show that pathways involved in tooth development are conserved and can be turned on in chick mesenchyme by the addition of a single signaling factor (Bmp4) to the *chick* epithelium. However, the chick epithelium is perfectly capable of initiating tooth-like formation when chick neural crest is replaced by neural crest from a mouse.[11]

Dinosaur Jaws

It is exciting to perform an experiment for one reason, and discover something totally unexpected. You scurry to the nearest textbook to find out what has occurred. If you were working on a detailed biomedical problem, but discovered something of evolutionary interest—like an atavistic trait—it would make a quote-worthy thing to jazz up a paper.

This kind of surprise has resulted from transgenic mouse experiments, and a particularly interesting case involves mutations engineered to inactivate a gene believed to be involved with jaw and tooth development. Two components made up the jaws of mammalian ancestors, Meckel's cartilage in the lower jaw, and the palato-

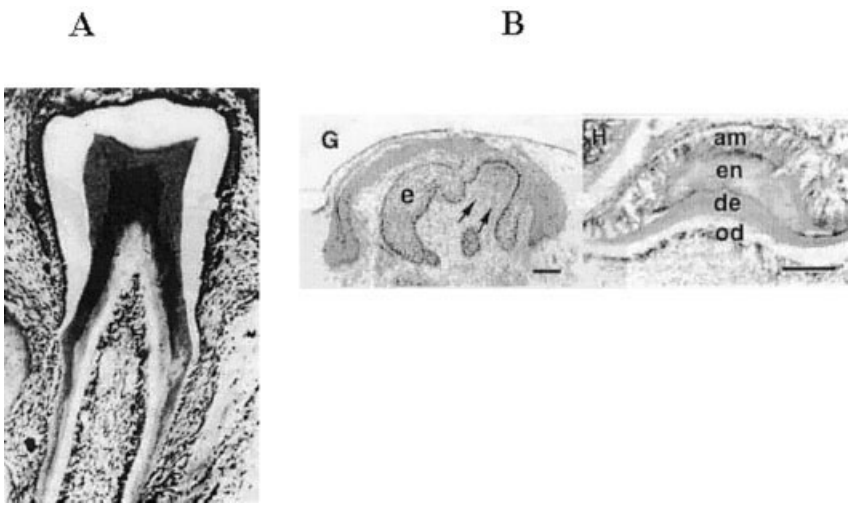

Figure 3. Hen's tooth (A) original and (B) a confirmation showing the morphology and corresponding different dental tissues. Mouse dental mesenchyme grown in culture in combination with chick "dental" epithelium. am, ameloblasts; en, enamel; de, dentine; od, odontoblasts. G and H are from the original panel notation. In G, e indicates area of invaginating mouse epithelium; arrows indicate chick mesenchyme. (A: Reprinted with permission from Kollar and Fisher[7]) B. Wang et al.[9] (Reprinted with permission, copyright 1998 Developmental Dynamics, Wiley.)

quadrate cartilage in the upper (Figure 4A). The palatoquadrate has been severely reduced during mammalian evolution with an anterior surviving remnant, the alisphenoid, that forms part of the braincase, and a posterior surviving remnant that is the incus ossicle of our middle-ear (Figure 4B). The *Dlx-2* DNA regulatory gene is expressed early in jaw development. When *Dlx-2* was experimentally inactivated in a mouse, the abnormally developing jaws possessed anomalous cartilage[12] (Figure 4C). The investigators suggested that this cartilage was homologous to the ancestral palatoquadrate, as if ancient dinosaur jaw development had been recreated. Similar atavistic explanations have been offered for anomalous cartilage in experimental results inactivating the *Hoxa2, MHox, Otx2,* and retinoic acid receptor genes.

In fact, this probably reflects misunderstandings of the path of evolution and a simplistic notion of atavisms.[13] The cartilage formed in these mutants bears no real resemblance to the ancestral condition, and thus fails a key criterion for identifying atavisms.[5] Comparing the results of the *Dlx-2* knockout with the appearance of the actual palatoquadrate cartilage shows too vague a resemblance of these structures to substantiate claims of homology, much less the atavistic recreation of an ancestral organized trait.

The assignment of homology often implies similar developmental origin of structures, but gene phylogeny and expression by David Stock, working in our lab, showed that *Dlx-2* existed and was expressed in embryonic jaws long before reptiles came on the scene. The ancestral jaw developed *with,* not without that gene, so its experimental deletion could hardly duplicate ancestral processes in dinosaur jaws. Smith and Schneider offer the more plausible explanation that cartilage formation relies on a threshold level of cell condensation in development. Experimental disruption of early jaw development could lead to the piling up of migrating cranial neural crest cells in uncharacteristic locations, leading to anomalous local cartilage formation. Consistent with this is that the experimental animals had numerous other craniofacial developmental anomalies.

GENETIC EXPLANATIONS

What Probably Isn't

A general principle of evolution is expressed by Dollo's[14] famous rule that "an organism is unable to return, even partially, to a previous stage already realized in the ranks of its ancestors." Marshall et al.[15] addressed this from a genetic point of view, showing by plausibility calculations that accumulating mutations are likely to destroy genes not maintained by selection by around 10 million years. Subtle coordination and interaction among genes are probably the first to go, but eventually unused genes simply mutate into oblivion.

Why can't such a gene be restored by reverse mutation? With few exceptions (olfactory receptors being one possible example), the probability that reverse mutation could restore the complex function of a gene is somewhere between impossible and unbelievable. A gene long silent (as between a chicken and it's former teeth) cannot be resuscitated. Avian amelogenin appears to be but a memory.

Sometimes a given complex trait *does* recur independently in related lineages, as for example, complex eyes, or immature stages in various amphibian or sea urchin larvae.[16,17] Traits of similar general form may be rather simple to initiate but these recurrences are probably not identical at the gene level. And because they occur among evolutionary lineages, rather than within a lineage over time, we would not normally call them atavistic throwbacks to a former state.

What Probably Is

At any given time, traits can come and go across generations. Recessive traits are familiar examples. But blue eyes are not an interesting atavistic throwback even if both of one's parents had brown eyes but at least one grandparent had blue ones. This is variation still circulating in the population even if rare or masked in some individuals. Similarly with polydactyly: it is only a kind of statistical typology to say that horses have hooves rather than toes.

Sewall Wright[18] and others made formal breeding studies of existing digit variation in guinea pigs early in the 20th century. Wright showed evidence for genetic causation, as well as random effects among and within inbred strains. Interestingly, because other South American Caviidae have

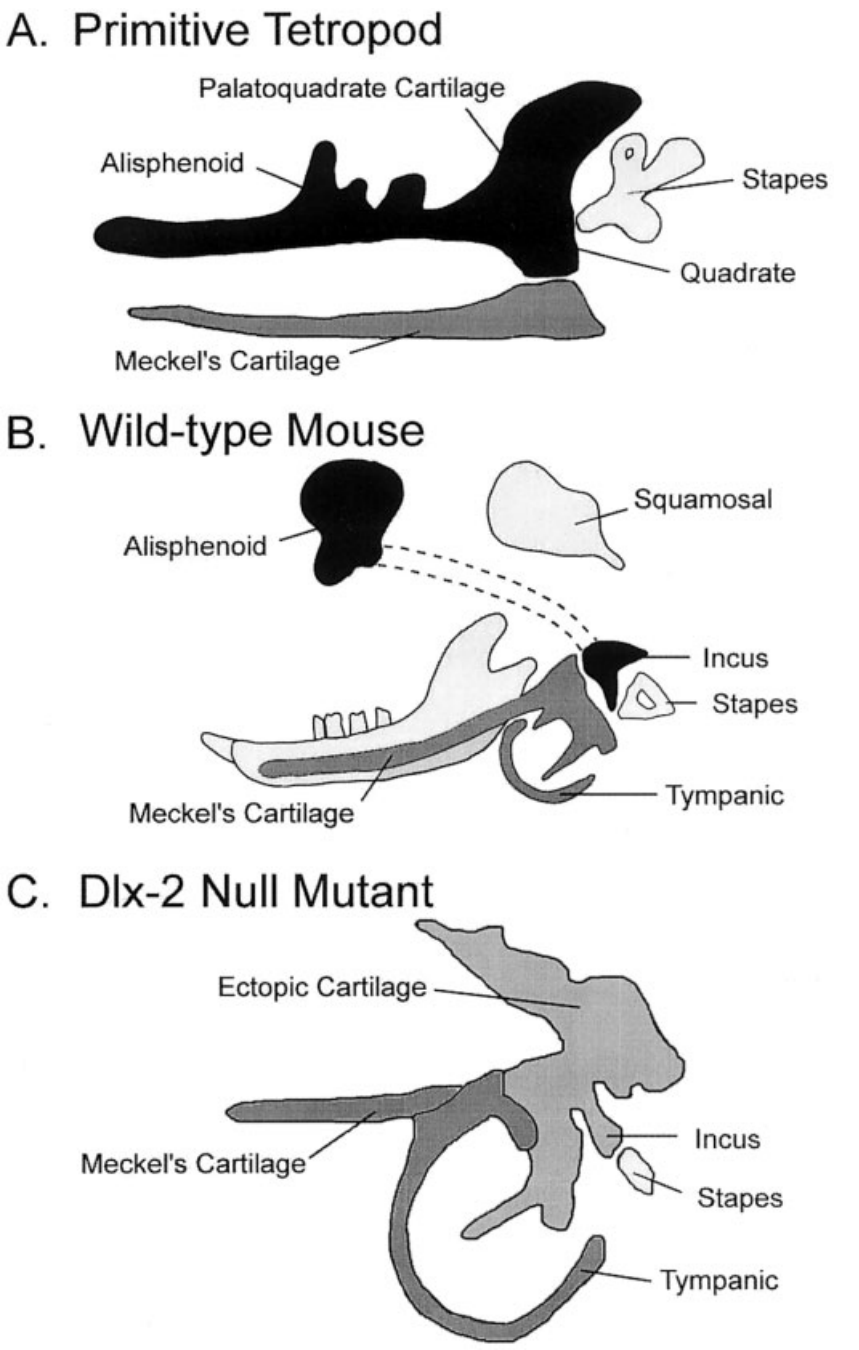

Figure 4. Dinosaur jaw "atavisms" that aren't really. (A) Primitive tetropod jaw, (B) normal mouse and (C) *Dlx-2* knockout "atavism." (Black, upper first arch elements or palatoquadrate cartilage; dark grey, lower first arch element, or Meckel's cartilage; light grey, (ectopic cartilage.) (Source: Smith and Schneider[13] with permission).

thumbs, big and little toes, Wright referred to their occurrence in guinea pigs as atavistic, despite the degree of natural variation he observed. He noted that the genetic basis of these recurrences was probably different in different strains, and attributed this to polygenic threshold causation. With polygenic causation, the same trait arises in many different genotypes, implying that the same genetic basis of these toes in guinea pigs and other Cavids past or present is unlikely. It's similarly unlikely that the genetic basis of Caesar's horse was the same as the toes on ancestral horses.

Similar arguments apply to supernumerary nipples, variation in dental formulas including transitory dental rudiments in the diastema of developing mouse jaws which have been described as representing "missing" teeth, and the occasional presence of "tails" in humans. Given their rather common natural occurrence, if these are atavistic throwbacks, they are not throwing very far back.

Then How Do Horses Get Toes and Hens Get Teeth?

A lot has been written about these same traits, often in terms of developmental genetic "thresholds" and conserved developmental "programs," but this amounts to little more than hand waving. However, we can make genetic sense of it. Most examples of atavisms are in traits produced by periodic patterning processes, a point famously stressed by William Bateson.[19] These serially homologous structures are produced by generic developmental processes that involve signaling-factor molecules that diffuse between cells in a particular developing tissue. The relative local concentration of these molecules affects gene expression in the cells, resulting in the production of epithelial placodes, tissue-layer invagination, branching, and periodically spaced growth and inhibition zones where members of a series (e.g., a tooth) develop.[3,6]

The same genes are used to pattern many structures, including the classic "atavism-prone" traits like limbs, mammary glands, teeth, vertebrae, and hair. The genes that make teeth in primates are still around biting and kicking in hens. A tooth is developmentally also a hair, feather, scale, or nipple. For example, the close relationship of teeth and hair is shown by the interesting effect of mis-expressing the regulatory gene *Lef-1* in mice, which leads to tooth development in the lip furrow or hair development among developing teeth. (Is that woolly morning-after mouth a remembrance of times past?) Natural as well as experimental alteration of these developmental processes can produce variation in the number, size, and other characteristics of the ele-

ments in the structures they pattern—sometimes resulting in variation that resembles traits from distant earlier ages.[20] The genetic pathway that could turn the splint bones in horses into actual toes still exists in the horse's remaining digit. Many genes are involved in these processes, but they may actually be simpler than the polygenic control envisioned by Wright.

Hen's teeth aren't really teeth, because some of the patterning instructions and the enhancers needed to integrate the pathway *in one of its contexts* are gone. The chick epithelial layer has lost these capabilities, and mouse mesenchyme can't induce them, but mouse epithelium has the Start instructions and can invoke the responses in chick mesenchyme. It is instructive that the missing amelogenin gene that is used only in the production of enamel was not protected from obliteration by pleiotropy.

In most cases, only some aspects of the process have been anomalously expressed, and atavistic changes are usually not completely normal. Thus the hen's tooth has no enamel, and supernumerary nipples usually are only imperfectly formed and do not or cannot function normally in humans.

BUT THERE AREN'T ANY CENTAURS

We can imagine all sorts of assemblages of characters. One example might be the Centaurs of classical mythology. These half-horse half-human creatures have not actually been seen recently, but we have evolutionary reasons to assert that they, like unicorns and mermaids, aren't real. It would be impossible, based on everything we know, for the genetic and developmental organization required to make a human torso *also* to make a horse's aft. The forelimb and hindlimb of mammals develop using at least some of the same genes, and there is a genetically based correlation in the form of the two limbs. The divergence between primate and horse genomes happened so long ago that too much independent evolution has occurred in each genome for one to be a part of or function with the other. In this sense, unicorns might just be conceivable, but Centaurs and mermaids, sadly not. By contrast, at least in the past, hens had teeth, and horses had toes, so hen-like and horse-like genomes once were compatible with teeth and toes.

Still, from a gene-regulation, developmental point of view, the verisimilitude of atavism *does* indicate a connection to the past, though it's not an awakening of long dormant developmental programs. Recent developmental genetics has been showing how deeply conserved developmental processes really are. Developmentally, hen's teeth are truly tooth-like. But they are not truly teeth. Evolution doesn't generally reverse itself, but the past does seem to weave in and out of complex traits, in that elements of the mechanisms producing those traits do seem to be conserved in interesting ways. The atavism story is subtle and we're now getting a genetic understanding of why we see what we see.

Thus, from what we know Dollo will rule. Genetic engineers might produce chickens with teeth, but they won't be real atavisms. It's like that with retro diners, too. They have a nostalgic appearance and Patsy Cline may be singing the same songs in the background, but most everything else in these diners has changed, and we're "So wrong," if we think we can really be "Back in Baby's arms."

NOTES

We would welcome comments on this column: kmw4@psu.edu. CrotchetyComments are maintained on: http://www.anthro.psu.edu/weiss_lab/index.html. We thank Anne Buchanan, Kathleen Smith, and John Fleagle for critically reading this manuscript.

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