affected versus very mild or normal (*11*). A difference between this situation and that reported for BBS is the apparent frequency of modification. In SMA, these families are the exception, whereas in BBS, it appears that in most cases one needs three mutant BBS genes to obtain a phenotype, and it is unclear whether BBS can develop with just two allelic mutations. Given the frequency of two-gene involvement in BBS, the ease with which linkage mapping was applied to identifying the six loci may seem surprising (*5*). One would expect to see some segregation distortion, which has been reported in SMA but not in BBS. It is perhaps fortunate that haplotype association has been used to narrow the region containing the BBS genes. It will also be of interest to know the frequency of BBS mutations in the population because a two-gene model for this disorder would predict a higher frequency of single-gene BBS mutations. In the near future, we should know whether two-gene mutations are always required in BBS, the frequency of the alleles, and how each of the genes contributes to the phenotype. It will be particularly intriguing to determine if there are gene modifiers or genetic loci that specifically predispose BBS patients to hypertension and diabetes.

The examples given so far are for recessive conditions, but phenotypic modification also occurs in dominant disorders. An example is familial adenomatous polyposis (APC), a disease characterized by numerous intestinal polyps that predispose the individual to colon cancer. In the APC^{min} mouse model of this disease, the *APC* gene is mutated but the number of polyps varies depending on the genetic background of the mouse. A semidominant modifier gene, *Mom1*, accounts for 50% of the genetic variance in polyp number (*9*). In strains with reduced polyp number, activity of the secretory phospholipase A2 (Pla2g2a) is normal. Pla2g2a is part of the prostaglandin synthesis pathway, leading to the realization that drugs affecting this pathway could be used to reduce polyp number. Although modifier genes and susceptibility genes do complicate the genetic understanding of disease, they also provide additional targets against which drugs can be directed. For example, high-throughput drug screens are currently being performed to identify compounds that activate the *SMN2* gene, which is intact in all SMA patients and is known to modify the phenotype. Can the BBS phenotype be rescued by stimulating expression of the remaining functional allele of the modifier gene? Will this approach be valuable in more common multifactorial disorders where stimulation of expression of a modifier may prevent the phenotype?

Three of the six possible genes mutated in BBS have been identified: *BBS2* encodes a protein of unknown function (*12*); *BBS6* encodes a protein with homology to TriC chaperones that form a complex of nine related proteins (*13*–*15*); and *BBS4* encodes a protein with homology to O-linked *N*-acetyl glucosamine transferase (*16*). The fact that any of five BBS loci can act as modifiers implies some form of interplay between the six genes, or more specifically, between their products. But how does this modification of penetrance work? Do the BBS gene products interact directly or affect the same biochemical pathway? The next step in understanding whether and how these proteins interact will depend on elucidation of their biochemistry. The proteins encoded by the modifier genes, in particular the BBS4 glucosamine transferase, hint that post-translational modification of other BBS proteins may be involved in the disease phenotype, but this is far from clear. BBS is an excellent model not only for more common multifactorial diseases, but also for disorders where the mode of inheritance is complex.

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PERSPECTIVES: ECOLOGY AND EVOLUTION

The *Inga*—Newcomer or Museum Antiquity?

Eldredge Bermingham and Christopher Dick

Writing in 1878 (*1*), the great biogeographer and evolutionary biologist Alfred Russel Wallace suggested that the high species diversity of the tropics could be accounted for by the greater age of tropical environments—providing more time for species to accumulate—compared with environments of temperate regions. After all, parts of lowland South America have been draped in tropical vegetation for over 100 million years (*2*), whereas the distribution of temperate forests has tracked the push and pull of glaciers. A century after Wallace, G. Ledyard Stebbins (*3*) introduced the *museum hypothesis*, providing a name for the more refined idea that "plant communities that have suffered the least disturbance during the last 50 to 100 million years…have preserved the highest proportion of archaic forms." Stebbin's view challenged the *cradle of diversity* hypothesis that had largely supplanted Wallace's early notion of the importance of time for explaining tropical species diversity. The cradle of diversity hypothesis held that the tropics are a crucible of evolution in which adaptive complexes arise owing to the biotic complexity of tropical forests. The explosive radiation of New World orchids, for example, is partly due to the group's intricate coevolutionary interactions with pollinators (*4*). The idea that high rates of tropical speciation, rather than age or reduced rates of extinction, contribute to tropical forest diversity gained added prominence with the publication of the *refugia* model in the 1960s (*5*). This model posited that allopatric divergence (that is, divergence of very similar organisms that cannot interbreed due to geographical isolation) in fragmented ice-age forests acted as a species pump, supporting the prediction that tropical species diversity is a recent event. So, the question still remains: is most tropical diversity ancient or new? To unravel the answer, Richardson and colleagues (*6*) have undertaken a molecular systematics study of the tropical tree genus *Inga*, which they report on page 2242 of this issue.

The legume genus *Inga* is composed of roughly 300 species that range from central Mexico to northern Argentina. Richardson and co-workers indicate that

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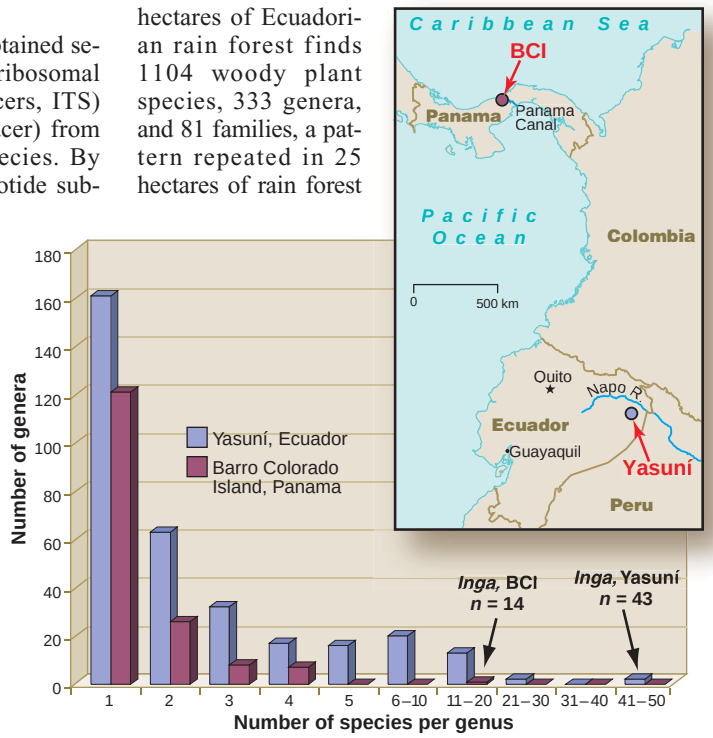
species-rich tree genera like *Inga* comprise a significant portion of the biomass and species diversity of lowland neotropical forests, and thus provide a good starting point for evaluating the age of tropical species. The basic idea behind their study is simple: If the museum hypothesis is correct and most tropical species are old, then there should be marked divergence among their DNA sequences; little sequence divergence would denote young species and would support recent speciation.

Richardson and colleagues obtained sequences of noncoding nuclear ribosomal DNA (internal transcribed spacers, ITS) and chloroplast DNA (*TrnL* spacer) from more than 10% of all *Inga* species. By comparing the number of nucleotide substitutions that have accumulated among *Inga* species to the substitution rates published for the same DNA regions in other plant taxa, the authors placed the origin of *Inga*'s explosive speciation at 1.8 to 7.2 million years ago. The difference in estimated dates of diversification reflects the variability among published rates for the chloroplast and the nuclear DNA markers. Richardson *et al.* also estimate *Inga*-specific substitution rates using the formation of the Isthmus of Panama (about 3.5 million years ago) to mark the time of divergence between South American and Central American species—they place the origin of *Inga*'s diversification between 3 and 6 million years ago. Compared with the more than 100 million years available for evolution in these forests, the radiation of *Inga* appears undeniably recent and rapid. The power of the *Inga* study, however, rests on several assumptions.

Do the DNA sequences used by Richardson and his co-workers mark time sufficiently well to indicate whether the common ancestor of these species is ancient or recent? The concept that one can use genetic divergence to tell time—the so-called molecular clock (*7*)—is debatable, although most workers in the field would concede that molecular clocks are sufficiently accurate to distinguish between young speciation events, let's say during the past 1 to 10 million years, versus older events that occurred 30 to 60 million years ago. Thus, only a curmudgeon would deny relatively recent speciation in *Inga*, given the small number of nucleotide substitutions that have accumulated among species in this genus. Nonetheless the *Inga* clock ticks somewhat irregularly and its calibration is uncertain, which raises questions regarding just how young this species group really is.

Granting *Inga* a relatively recent radiation, can we also assume that this genus faithfully represents the evolutionary history of most neotropical rain forest trees? The answer to this question is almost certainly no. A census of 25 hectares of Ecuadorian rain forest finds 1104 woody plant species, 333 genera, and 81 families, a pattern repeated in 25 hectares of rain forest in Panama, with 277 species, 174 genera, and 56 families. On these plots, *Inga* with 14 species (Panama) or 43 species (Ecuador) is an odd genus in communities with 121 (Panama) to 161 (Ecuador) genera each containing only a single species (see the figure). Indeed, the number of *genera* in the 25-hectare Ecuador plot exceeds the complete tally of tree *species* in the moist temperate forests of North America [n = 321 (*8*)]. These data support the forceful argument (*9*) that tropical regions are much richer than temperate regions not only in species, but also in numbers of genera and even families, indicating that the species richness of tropical forests has been a relatively persistent feature of Earth history.



Rain forest diversity. Histogram of the species diversity of tree genera in 25-hectare plots representing two neotropical forest sites: Barro Colorado Island (BCI) in Panama (*14*, *15*), and Yasuní in Amazonian Ecuador (*16*). The inventory includes all woody plants with a diameter at breast height ≥1.0 cm. The genus *Inga* is unusual compared with the other genera of these tropical rain forest plots as it is represented by a large number of species: 14 in BCI and 43 in Yasuní (black arrows). The data were collected by the Center for Tropical Forest Sciences in association with the Smithsonian Tropical Research Institute (BCI, Yasuní) and the Pontifica Universidad Católica del Ecuador (Yasuní).

The *Inga* report concludes that recent geological events, perhaps coupled with climatic fluctuations, have played an important part in generating tropical species diversity. The center of diversity for *Inga* lies in the Andean foothills, and evidence from epiphytic plants (*10*), birds (*11*), and small mammals (*12*) also implicates the Andes as a crucible of speciation. However, the timing of the *Inga* radiation does not provide strong support for the worn idea that Pleistocene ice ages played a grandiose part in generating tropical species diversity. Moreover, molecular dating approaches, similar to those used by Richardson *et al.*, indicate that many tropical animal species also predate the Pleistocene (*12*).

We return to Stebbins (*3*) in closing, who presciently observed that "Many, and probably most, plant communities are 'cradles' for some of their species groups and 'museums' for others." Richardson and co-workers have established that the tropical rain forest may well be a recent evolutionary cradle for *Inga*, but plant systematics permits strong inference that the museum hypothesis is alive and kicking, and that woody plant diversity in tropical lowland forests has been preserved for tens of millions of years. It is worth noting that if the explosive radiation of *Inga* does provide a snapshot of the evolutionary trajectory of many tropical plants, then extinction must pare away the species richness of genera in order to explain the taxonomic distribution of neotropical diversity. One imagines that the late Al Gentry saw all of this rather clearly when he wrote (*13*), "those of us interested in evolutionary processes have an added incentive for preserving our planet's dwindling remnants of tropical forest: We need them if we hope ever to truly understand the processes of speciation and evolution that have given rise to the diversity of life on Earth."

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PERSPECTIVES: EVOLUTION

The Ancestry of Whales

Kenneth D. Rose

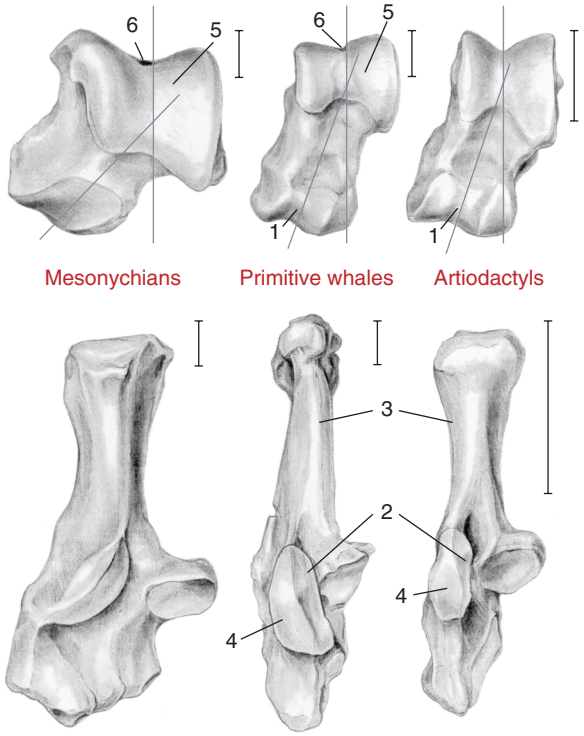
Whales are mammals that moved to the sea about 50 million years ago. Exactly how they are related to other mammals has long been one of the most vexing questions facing mammalogists and paleontologists. In the last decade, mounting evidence that whales are highly specialized ungulates (hoofed mammals) has been bolstered by the discovery of an impressive array of previously unknown fossil whales in Pakistan, India, and Egypt, which largely fill the morphological gulf between land mammals and ocean-dwelling cetaceans (whales, dolphins, and porpoises).

The move to the ocean required many adaptations to living in water, but the earliest whales still closely resembled land animals. One of the most spectacular transitional forms is the "walking whale" *Ambulocetus* from the middle Eocene (about 47 to 48 million years ago). This species had relatively well-developed limbs, paraxonic feet (where the plane of symmetry passes between the third and fourth digits), and hooflike terminal toe bones (*1*).

But fossils have failed to provide conclusive indications of the whales' closest relatives. Instead, they have sparked new controversy. Most recent morphological analyses suggest that mesonychians, an extinct group of terrestrial carnivorous ungulates, form the sister group of cetaceans (*2*, *3*). But molecular systematists maintain that cetaceans belong to the artiodactyls (even-toed ungulates such as sheep, cows, pigs, camels, deer, and hippos) and are in fact the sister group of hippopotami (*4*, *5*).

On page 2239 of this issue, Gingerich *et al.* (*6*) report important new fossil evidence—skeletons of two very primitive ancient whales with well-developed limbs from the middle Eocene of Pakistan—that goes a long way toward resolving the conflict. The fossils provide compelling morphological evidence that whales are not just related to, but descended from artiodactyls rather than mesonychians, thus bringing the morphological evidence into accord with molecular data, at least at the ordinal level.

The most important evidence comes from the shape and orientation of joint surfaces of several ankle bones in the new fossils. These specialized features, typically associated with adaptation to running, have only been observed in artiodactyls and are widely considered diagnostic of the order (see the first figure). Their presence in an animal that was probably better adapted for aquatic than terrestrial locomotion strongly suggests common heritage rather than convergent evolution.



Fossil comparison. Ankle bones of mesonychians, primitive fossil whales, and early Eocene artiodactyls; astragali above, calcanei below. Diagnostic artiodactyl traits present in early whales include a trochlea (grooved joint surface) for the navicular bone (1), modified shape and orientation of articular surfaces between the astragalus and calcaneus [(2) also present on underside of astragalus, not visible here; see supplemental fig. 3 in (*6*)], and a narrow calcaneus with an elongate heel process (3) and a large, convex fibular articulation (4). Primitive mesonychid-like traits present in ancient whales, but not in any known artiodactyl, include a shallower tibial trochlea with more rounded trochlear ridges (5) and retention of a remnant of the astragalar foramen (6), the opening of a canal through which a nerve and vessels pass in primitive mammals. Although mesonychids also have a navicular trochlea, it is much shallower and offset from the tibial trochlea at a greater angle than in primitive whales and artiodactyls. Scale bars, 1 cm.

Ankles from primitive ancient whales have previously been reported (*7*), but the new specimens are the first that are directly associated with whale skeletons and that are well enough preserved to provide important clues to the relationship between cetaceans and artiodactyls. The specialized ankle characters mentioned above corroborate a close alliance with artiodactyls, but the new skeletons also exhibit several primitive placental traits lost in all known artiodactyls or present only in the most primitive fossil artiodactyls (see the first figure). They thus seem to superimpose artiodactyl traits on a skeletal anatomy that is in some respects more primitive than that of any known artiodactyl.

For example, the forefoot in one of the new fossils (*Rhodocetus*) is mesaxonic (the plane of symmetry passes through the large third digit). This is also the case in two of the most primitive groups of fossil artiodactyls—the early Eocene artiodactyl *Diacodexis* and some anthracotherioids (*8*, *9*)—but almost all other artiodactyls (and mesonychians) have paraxonic forefeet. In addition, the new ancient whale fossils retain a clavicle and a third trochanter on the femur, vestiges of which are found in only the most primitive

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