that would otherwise prevent β-amyloid from accumulating in the brain. In agreement with this possibility, Rachel Neve and her colleagues have found a relative shift in favor of the synthesis of the precursor protein with the inhibitor sequence in some affected areas of Alzheimer's brains.

In contrast, Steven Younkin of Case Western Reserve University School of Medicine and his colleagues have found the opposite, an apparent shift in favor of the synthesis of the precursor without the inhibitor sequence in Alzheimer's brains. This finding implies that the presence of the inhibitor sequence might help to prevent β-amyloid deposition by retarding the action of the proteases that release the peptide from the precursor protein.

Another unanswered question concerns the source of the β-amyloid of Alzheimer's plaques. Although most researchers think that it is a product of brain neurons, some suggest that it might be either transported into the brain in the blood or made in the linings of the blood vessels. They note that in other diseases characterized by abnormal protein deposits, the proteins come from the blood. Moreover, β-amyloid deposits occur in the blood vessels in Alzheimer's brains as well as in the brains of individuals with the Dutch cerebral hemorrhage disease.

Investigators are also looking at factors that control the expression of the gene encoding the β-amyloid precursor protein in their efforts to pin down the defect causing plaque formation in Alzheimer's brains. Some evidence suggests that the activity of the gene is higher than normal in the brain areas that degenerate, although there is not a perfect correlation between the areas of high activity and the areas of damage.

In any event, because no defects have been found in the gene for the β-amyloid precursor protein that might account for its increased expression in Alzheimer's disease, researchers have had to look for other factors that might influence expression of the gene. Two of the leading candidates are interleukin-1 and nerve growth factor.

Interleukin-1 is a protein with a wide range of activities inside and outside the immune system. It plays a key role, for example, in the induction of inflammatory responses. Dmitry Goldgaber's group at the State University of New York in Stony Brook has recently shown that interleukin-1 stimulates expression of the β-amyloid gene.

Moreover, according to Sue Griffin of the University of Arkansas School of Medicine in Little Rock, production of interleukin-1 is elevated in the brains of Alzheimer's and Down syndrome patients. "What she found was really amazing," Goldgaber says. "The number of interleukin-1–positive cells was dramatically increased in the Alzheimer's disease and Down syndrome patients."

The interleukin-1 is produced, Griffin says, by the nonneuronal glial cells of the brain, primarily by the cells of the microglia type. Indications are that the glial cells become active and begin producing interleukin-1 before the plaques and other pathological changes occur in the brains of the Alzheimer's and Down's patients. This might then be an early event in the genesis of β-amyloid deposits and plaques.

Nerve growth factor is another agent that increases expression of the β-amyloid precursor gene, according to Neve and William Mobley of the University of California, San Francisco. "It may well be that this perfectly normal gene, whose expression might be needed for neurons to grow, might be regulated by nerve growth factor," Mobley says. Researchers showed a few years ago that the growth factor is necessary for the development and survival of brain neurons, including one of the main types that degenerate in Alzheimer's disease.

The possibility that nerve growth factor stimulates synthesis of the β-amyloid precursor protein is particularly interesting in view of Cotman's suggestion that brain neurons might be attempting to grow as a way of compensating for the degeneration that occurs in Alzheimer's disease. The ironic aspect of such a situation is that it might ultimately make matters worse by leading to plaque formation.

Additional factors may also help to regulate the expression of the β-amyloid precursor gene. Beyreuther and Masters have dissected the regulatory region of the gene and found that it is complex, with the potential to respond to several different control factors. The regulatory region includes, for example, a "heat shock promoter," which would allow it to respond to increased temperature and other stresses.

If the explosion of research on β-amyloid during the past year has not solved the mystery of Alzheimer's disease, it has at least given researchers a wealth of leads to follow, almost an embarrassment of riches, Selkoe says. By defining the molecular events that lead to β-amyloid deposition in plaques, researchers may ultimately be able to work backwards and identify the primary Alzheimer's defect. ■ JEAN L. MARX

Species Questions in Modern Human Origins

The extraordinary difficulty of identifying species from fossils exacerbates the challenge of understanding human origins

A YEAR AGO *Newsweek* did a cover story on the origin of modern humans—the best selling issue of the year—which identified Africa as the Garden of Eden, 200,000 years ago. Pictured on the cover was a very modern-looking couple, black, with apple and serpent appropriately placed. "This tells you something about the recently acquired appeal of the subject," observed Christopher Stringer, of the British Museum (Natural History), London. Speaking last week at a workshop at New York University, Stringer went on to say: "But you have to remember that, black though Adam and Eve probably were, they were not *modern* Africans, as portrayed by *Newsweek*; they were the ancestors of all of us and therefore would have looked different."

That the news magazine might have been ensnared by this paleoanthropological nuance should not be surprising, given the rampant confusion among the professionals over this very same issue. "Many anthropologists simply fail to come to grips with the biological realities surrounding the origin of modern humans," says Ian Tattersall, of the American Museum of Natural History, and a workshop participant. "There is an endemic problem of how we recognize species in the fossil record, particularly the human fossil record," he told *Science*.

As Stringer and Peter Andrews, also of the BM(NH), outlined in *Science* last March (11 March, p. 1263), there are two models for modern human origins, which represent extremes on a continuum of possibilities. One, the regional continuity model, argues that modern human geographical groups (races) are the product of local evolution over a very long period of time in all parts of the Old World, essentially going back a million years when human ancestors first left Africa. The second

model, called Noah's Ark by some and Out of Africa by others, sees modern geographical groups as the result of recent evolution. Modern humans originated in Africa within the last 200,000 years, and replaced existing "human" populations as they migrated throughout the Old World.

One reason for the resurgence of interest in the question of modern human origins is the recent input of genetic evidence, particularly that of mitochondrial DNA. But what the paleoanthropologists have to deal with is fossils, specifically how to group them into meaningful patterns.

"In our *Science* article Peter and I said that the regional continuity model predicts that transitional fossils will be common," said Stringer. In a formal reply to Stringer and Andrews, Milford Wolpoff, a leading proponent of the regional continuity model, in company with seven colleagues, denied this prediction. "Nevertheless, I keep hearing Milford talking about transitional fossils, and it is what you'd expect if populations of *Homo erectus* throughout the Old World evolved in concert into modern *Homo sapiens* over a period of a million years."

The Out of Africa model predicts that transitional fossils should be restricted to Africa, and modern anatomy would abruptly replace existing anatomy elsewhere in the Old World. How does the fossil evidence look in light of these predictions?

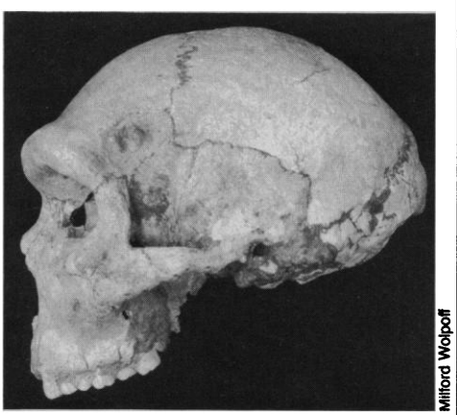
Unfortunately, even though this relatively late period of human prehistory is blessed with a significant fossil record, particularly in western Europe, there are strong differences of opinion over the interpretation of morphological variation, some of which is substantial. Where some scholars see transitional fossils, others recognize geographical variation; still others argue for evidence of hybridization, the result of interbreeding between anatomically distinct populations.

Part of that morphological variation has traditionally been associated with the supposed linear evolutionary transition through time from *Homo erectus* to archaic *Homo sapiens* to modern *Homo sapiens*. There are many legitimate objections to this simplistic scheme, not least of which is the qualifying adjective "archaic," a term not frequently appended to species names in the evolutionary histories of creatures other than *Homo sapiens*. "This is weaseling terminology, a way of avoiding the main issue," Tattersall told *Science*.

The main issue, according to Tattersall, is the recognition of more species in the human fossil record, not just through the last million years but within the slice of time from half a million to about 200,000 years ago. "I see at least four different fossil groups within this time range," says Tattersall, "that is, at least four different species." Stringer and several other participants, including Terry Harrison of New York University and Eric Delson of Lehman College, agreed in principle with Tattersall, but all were more conservative in the number of separate species that might be identified.

Fred Szalay disagreed, however. He complained that "neat cladistic analysis" might produce "neat patterns," but natural populations were not like that. Where Tattersall sees identifiably different groups of fossils as discrete species, Szalay instead sees different points on a morphological continuum, and just one, geographically widespread species.

Biologists have a difficult enough time dealing with the very idea of species, what they constitute in space and time. For paleoanthropologists, who deal only with skeletal fragments, and only fragments of the populations that once existed, the difficulties are magnified many times. Many closely related living species are differentiated more by coloration and behavior than skeletal anatomy. So what is a paleoanthropologist to do when confronted by small but significant differences in the anatomy of human fossils? Err on the side of calling it inter- rather than intra-specific variation, urges Tattersall: in other words, make them different species.



Milford Wolpoff

Petralona skull: *This 300,000-year-old fossil from Greece is seen by some scholars as an example of a transitional form, on its way to modern* Homo sapiens.

Climatic fluctuation during the past 900,000 years has been considerable, with the ebb and flow of Pleistocene ice epochs. "These are the conditions under which populations become isolated and new species arise," argued Tattersall. The establishment and persistence of new species represents too static a picture for Szalay, who envisages a fluid population structure, occasionally fragmenting, occasionally coalescing. This, said Szalay, might produce the morphological variability seen in the record. Not so, said Tattersall; such population dynamics would constrain not promote variability.

What can be learned from modern primate populations? First, as already noted, absence of major differences in bone anatomy can be misleading. "Yes, if you skin the 20 or so species of *Cercopithecus* monkeys, you'd be hard-pressed to identify different species from their bones," Harrison told *Science*.

A cautionary tale of a different sort comes from two species of baboon, *Papio anubis* and *Papio hamadryas*, which live in overlapping territories in Ethiopia. "These species interbreed quite freely," says Clifford Jolly, of New York University. "The offspring, which are fertile, are intermediate in anatomy and behavior between the parental species." If species as different as these breed and produce fertile hybrids, then the likelihood is that *Homo sapiens* and its putative siblings species, including *Homo neanderthalensis*, would also produce hybrids.

"I'm quite prepared to accept that there was some gene flow between newly arrived modern humans and existing populations," said Stringer. "But for the most part the gene flow does not appear to have been large, and in western Europe, perhaps none at all." Western Europe has the best fossil record of any part of the Old World, and shows a dramatic disappearance of Neanderthal populations coincident with the arrival of modern humans about 34,000 years ago.

A year ago a new date was obtained for modern human fossils from the site of Qafzeh, in Israel. At 92,000 years, the fossils were the oldest modern humans outside Africa. More significantly, it put modern human populations cheek by jowl with Neanderthals, a coexistence that lasted for some 50,000 years. This temporal overlap implies that Neanderthals cannot have been directly ancestral to modern Europeans, as some scholars have argued. Stringer and his colleague H. P. Schwartz, of McMaster University, are soon to publish a similar date for a second site, Es Skhul, which carries the same implications as the Qafzeh date.

It is possible, said Stringer, that modern humans appeared only intermittently in the Near East 90,000 years ago, not really coexisting with Neanderthals. "But if they did coexist over that period of time, then the likelihood is that modern humans and Neanderthals were distinct species, apparently with very little gene flow between them."

The question of modern human origins—regional continuity or Out of Africa—will obviously be illuminated by more relevant fossil finds and accurate dating. But in the absence of a proper appreciation of population biology and evolutionary theory, interpretation of fossil anatomy is likely to be faulty. ■ ROGER LEWIN