fewer experiments," says William A. Goddard III, director of the Materials and Molecular Simulation Center at Caltech's Beckman Institute. Reducing overhead is just one benefit, adds Herman Finkbeiner, manager of GE's chemical/biological research laboratory. "We want more wild ideas tried out on computers," he says.

Finkbeiner and other industrial chemists are following a computational trail blazed by the pharmaceutical industry, the first to run with the computational ball starting about 10 years ago. Drug developers routinely compute hundreds of variants on a molecular theme, rotate them any which way in space, and probe their interactions with a specific receptor, biochemical, or pathogen, remarks Donald Boyd, a research scientist at Eli Lilly. The computerless alternative, which characterized the field for all but its most recent history, was to synthesize and test real molecules, an extremely costly and inefficient process. Even now, there's no getting around synthesizing and testing actual compounds; no drug yet on the market was invented solely by a computer, says Mark A. Murcko, a molecular modeler at Vertex Pharmaceuticals Inc. in Cambridge, Massachusetts. But any streamlining of the time and expense of developing a marketable drug—one estimate puts the average at 12 years and $125 million—can yield big payoffs.

Hot numbers. The potential gains are turning computational chemistry itself into a hot item commercially. In 1990, according to the 1992 Aberdeen Group report, the "overall market for computational-chemistry hardware, software, service, database, and other sales was $530 million," up from $330 million in 1988. "We conservatively project the market to increase to $2 billion by 1996," continues the report. To supply the expanding job market, the field has even spawned its own recruiting agency: Molecular Solutions in St. Louis.

All this ferment is a bit unsettling to some chemists, who fear the ascendancy of chemistry-by-computer could spawn generations of chemists who lack hands-on experience with chemicals and reaction. When theoretical chemist Roald Hoffman of Cornell University wants to get a real feel for a molecule, for example, he builds a three-dimensional model so he can hold it in his hands and run his fingers around its contours. "There's no better way" to understand chemical structure, he says. And he worries that the visual appeal of molecular modeling programs could end up wooing researchers away from this tactile route to chemical intuition.

The boom in computational methods makes it inevitable that, well-grounded or not, those fears will get a thorough testing. By Murcko's reckoning, the computational chemistry wave is just coming in. "Maybe 1% of computational chemistry's potential has been tapped."

–Ivan Amato

MEETING BRIEFS

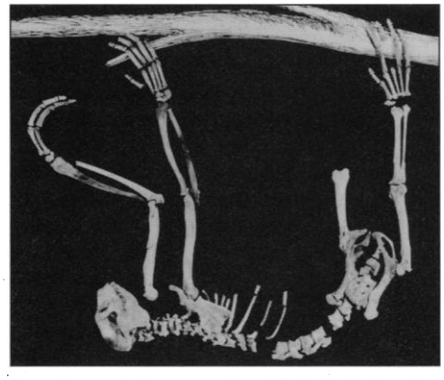
Anthropologists Bet on Their Latest Data in Las Vegas

Anthropologists need luck on their side when they search for key fossils or study monkeys in the wild, but their work can still hit the jackpot. That was clear at the 61st annual meeting of the American Association of Physical Anthropology, which brought more than 800 anthropologists to Las Vegas in early April. Among the reports was one on new fossils of early hominids in Ethiopia and another on extinct giant sloth lemurs in Madagascar.

Extinct Lemurs in Madagascar

Last July, anthropologists Elwyn Simons of Duke University and Laurie Godfrey of the University of Massachusetts were deep inside the dank Cave of the Lone Barefoot Stranger in northern Madagascar, busily wrapping up bone fragments after a hard day's work, when a student in another part of the cave yelled out: "You better come over here." They found Ted Roese, now a graduate student at the University of Iowa, standing beside a muddy pool of water with a grin on his face and a large skull, still dripping, in his hand. "What do you think it is?" he asked.

Even in the dark, Godfrey and Simons knew the answer immediately: It was an extinct species of giant sloth lemur they had recently named *Babakotia radofilai*. "We said,



Hanging out. A composite of *Babakotia* fossils.

'That's it,'" Godfrey told the audience in Las Vegas. And their excitement built as they drained the pool and found a nearly complete skeleton of the creature. Their excitement was well founded: The discovery is causing anthropologists to revise their notions of how lemurs evolved. And that's important because the work could shed light on primate evolution since lemurs preserve some features that were found in the earliest primates—creatures that were ancestral to both lemurs and the primate branch that includes humans, apes, and monkeys.

What's more, the lemurs give anthropologists a glimpse of an alternate world that might have evolved if apes and monkeys had never come onto the scene. Since monkeys never made it to Madagascar, they weren't able to crowd out lemurs, which flourished there as a result. "Probably in Madagascar there was an amazing radiation in lemurs that took place millions of years ago to develop and produce all kinds of strange end products," says Simons.

Indeed, Madagascar has proved to be an extremely rich source of lemur fossils. The first fossils of giant sloth lemurs were discovered at the turn of the century, although anthropologists did not search for more until the mid-1980s. That's when Simons joined forces with researchers from the University of Antananarivo in Madagascar to explore the so-called Crocodile Caves, a warren of underground caverns that extends 100 kilometers through a limestone range called Ankarana Mountain. Right from the start, Simons' team found thousands of bones of extinct lemurs, culminating in 1988 in the discovery of the fragments of a jaw from what proved to be the first example of a new genus and species. The researchers called the species *Babakotia radofilai* in honor of French mathematician and spelunker Jean Radofilao, who mapped the caves.

But it wasn't until after Roese's discovery last summer that they began to appreciate just how different this primate species is. It's "one of the most strangely adapted creatures that ever lived," says Simons. Unlike living lemurs, which are agile leapers and sometimes as small as mice, *Babakotia* was as big as a baboon and probably slow moving. Indeed, its fossils suggest that it acted more like a sloth, spending much of its time hanging upside down in trees.

The team proposes that the *Babakotia*'s skull and upper limbs suggest that is related to a family of living lemurs known as the Indri—and that is challenging the notion that the Indri's dramatic ability to leap was a primitive condition for all primates. Now the team thinks that the Indri's agility and the *Babakotia*'s slothfulness were more recent adaptations.

Babakotia also is giving anthropologists a glimpse of a past where lemurs came in all sorts of shapes and sizes and exhibited a far greater range of bizarre behavior than they do today. "We still don't know the whole story of what took place," Simons says. But the wealth of lemur fossils in Madagascar should help fill in the gaps.

New Fossils Found In Ethiopia

For most of the 1980s, anthropologists were banned from doing field work in Ethiopia because the government was rewriting laws on antiquities, including fossils. But in 1990 foreigners were allowed to return, and now they're finding fossils that are sure to help flesh out a crucial period of prehuman evolution, according to anthropologist Berhane Asfaw, director of the National Museums of Ethiopia.

Asfaw announced in Las Vegas that researchers in the Middle Awash area, a lowland zone north of Addis Ababa that is part of the Awash River drainage, had found fossils of at least three species of hominids (the family containing humans and their extinct ancestors) that lived between 400,000 and 4 million years ago. Although the discoveries are so recent that the researchers haven't yet fully analyzed them, hominid fossils from these time periods are so rare that the specimens are sure to help produce a better picture of what early hominids were like—and how they evolved and were related to one another.

The most dazzling of the finds is a hominid mandible discovered by a team led by Asfaw and University of California anthropologists Desmond Clark and Tim White at a site known as Maka in the Middle Awash. Asfaw said this jawbone belonged to a hominid that lived 3 million to 4 million years ago, which would likely make it an example of *Australopithecus afarensis*, the species that includes the partial skeleton known as "Lucy," and is the oldest known ancestor of modern humans. The same researchers also did well at two other Middle Awash sites. At Bodo, they found a humerus from a hominid who lived about 400,000 to 500,000 years ago, probably an example of archaic *Homo sapiens*. And at Gameda, they found a mandible from a hominid who lived 2 million to 3 million years ago, although the dates on that site are preliminary.

And the discoveries don't stop there. To the north in Hadar, anthropologists Donald Johanson and William Kimbel of the Institute of Human Origins in Berkeley found what Asfaw says are "beautiful hominids"—although Kimbel declined to discuss the find, saying he just returned from the field. All this prompted Asfaw to conclude that "despite other problems in the country, we keep moving: We have discovered more hominids."

–Ann Gibbons

CRYSTALLOGRAPHY

New Methods Make Mid-Sized Molecules Easier to Solve

In large families, the oldest child and the youngest often get most of their parents' attention, while the middle children seemingly get lost in the crowd. Until lately, such has been the fate of the in-between molecules—the ones having between 200 and 500 atoms—when x-ray crystallographers set about determining three-dimensional structures. The researchers have been able to devise techniques for solving the molecular structures of both the larger and smaller molecules, but the mid-sized molecules have proved tough to decode. Now, two research teams, each using an entirely different strategy—one chemical, the other mathematical—have come up with methods for solving mid-sized structures that should make the job far easier and faster than it used to be.

MEDICAL FOUNDATION OF BUFFALO, INC.

Advancing direct methods. Herbert Hauptman.

And that will come as welcome news to biochemists and drug designers. Many in-betweeners have important physiological roles. They include, for example, small proteins, such as the hormone insulin and the blood-pressure regulator angiotensin, as well as many antibiotics. Having detailed structural information about these molecules should not only give researchers a better understanding of how they work, but might also help in the design of more effective antibiotics or of drugs that either mimic or block a protein's effects. "The starting point of rational drug design," says crystallographer Bart deVoss of Genentech Inc. in south San Francisco, "is getting a protein structure to work with."

What the two groups have had to overcome for the mid-sized molecules is the "phase problem," a bugaboo for all crystallographic analyses, but especially intractable for structures of intermediate size. To determine a structure, a beam of x-rays is directed at a crystal of the material under investigation. The substance will scatter some of the x-rays, forming a diffraction pattern that can be detected on a photographic plate as an array of spots of varying intensities. Exactly how the crystal scatters the x-rays depends on how its atoms are arranged, and the goal is to work back from the diffraction pattern to calculate the structure.

Unfortunately, there's a problem. To calculate the structure, crystallographers use a mathematical relation called a Fourier transform to derive a wave of electron density for each spot in the diffraction pattern. They then use the waves to reconstruct the electron density pattern—and thus the arrangement of atoms—in the crystal itself. But while crystallographers can easily get the amplitude of each wave from the intensities of the diffraction pattern spots, they have a much tougher time getting the phases of the waves, that is, the positions of the wave crests and troughs relative to one another. And without the phase information, the researchers can't solve the crystal structure.

For small compounds, with fewer than 200 atoms, crystallographers get around this phase problem with so-called direct mathematical methods that enable them to cull the phase information from the diffraction data. And for large compounds, such as proteins, they get around it by inserting atoms of a heavy metal, such as mercury or uranium, into specific sites in the protein molecule. The easily recognizable metal diffraction pattern then serves as a sort of landmark for determining the phases of the x-rays diffracted by the protein crystal.

But neither method has worked well with the mid-range compounds. Their structures are so small that it's hard to insert heavy metals into them without causing unacceptable amounts of distortion, but they're nonetheless too complicated to be readily solvable by the standard mathematical approach. Take for example the antibiotic gramicidin A, which is a dimer consisting of two identical 15-amino acid peptides. David Langs of the Medical Foundation of Buffalo Inc. and his colleagues managed to solve the gramicidin A structure with traditional direct methods. But it was a struggle, requiring 10 years. And several other groups grappled unsuccessfully with the problem over the years. That's where the new work, done independently by biophysicist Jeremy Berg and his postdoc Laura Zawadzke of Johns Hopkins University, and by Herbert Hauptman of the Medical Foundation of Buffalo Inc. and his colleagues, should help.

The Johns Hopkins group was the one that took the chemical approach to solving the structure of mid-sized proteins. Proteins are, of course, made by hooking together