could group samples accurately by affected organ: for example, liver toxicity with up to 77% accuracy and kidney toxicity with up to 90% accuracy.

More significant, however, was the program's ability to crunch data taken at intervals in long-term studies. Researchers analyzed urine and serum samples at various times from the moment an animal was dosed with a toxin through its recovery. The program used probability calculations to assign the effects seen in each animal to the most likely toxin class and to identify when the compound caused the toxicity.

The analysis is "much more sophisticated" than any other screening tool now available, says Jeremy Nicholson, head of biological chemistry and COMET project director at Imperial College, because it can identify more simply biochemical changes that may cause pathology. (Nicholson has helped launch a spinoff in London to commercialize similar technology applied to medical diagnostics, called Metabometrix.)

Existing toxicology research methods can only examine toxic effects on one tissue type at a time. A gene-expression study, for example, yields data from a single time point in a single tissue. Moreover, changes in gene expression may not mean a net biological change. The body's homeostatic mechanisms may compensate by degrading or modifying gene transcripts. By contrast, "urine and plasma give the metabolic interaction of all tissues," Nicholson adds.

"Metabonomics has a big role to play in toxicology research," says Ian Blair, a professor of chemistry at the University of Pennsylvania. "Once you have a signature of toxicological response, you could use that as an assay for many things."

After the consortium published the initial results, each member developed its own database and technology in-house. Companies have been mum on details but have confirmed that they are building larger databases against which they can compare new compounds. Several companies also employ metabonomics to screen animals prior to an experiment to ensure that they are normal. Researchers say the technology could also be applied to clinical trials to correlate drug response to individual metabolism.

Drug companies aren't the only ones interested in metabolic profiling. In 2003, the U.S. National Institutes of Health awarded $35 million to a consortium of 18 institutions to identify, characterize, and quantify human cellular lipid metabolites. And recently Nicholson formed a coalition of scientists to establish standards for the field.

COMET's success has prompted several companies to join COMET II at Imperial College, says Nicholson. He's heading the project, which is scheduled to launch this month. The goal this time, however, is to create a "multiomics" platform that combines data from many sources, including gene and protein arrays, to reveal biochemical mechanisms.

That will be no easy task. Spectral data from a single urine sample contain thousands of peaks, the majority of which are unidentified metabolites. But the analytical tools to assign identities to the peaks are already emerging, says Nicholson. For example, his colleagues at Imperial College have a paper in press at *Analytical Chemistry* describing software that can combine data from NMR spectroscopy and mass spectrometry—similar yet complementary metabonomic techniques. And Nicholson says his colleagues have already developed a prototype system that integrates data from gene, protein, and metabolic profiles.

But whether the technology will actually help make drugs safer remains to be seen, says David Jacobson-Kram, head of pharmacology and toxicology at FDA's Office of New Drugs: "Technology can help to some extent, but perhaps our expectations are unrealistic." One potential application touted by the technology's supporters is to metabolically profile drug side effects. "Is there a metabolic profile characteristic of suicidal ideation?"—a side effect of several antidepressants—Jacobson-Kram asks. "That's a stretch."

Nevertheless, the field is young, Blair says, and the number of papers it is producing these days suggests it has begun a growth spurt.

–GUNJAN SINHA

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Paleontology

Tyrannosaurus rex Gets Sensitive

Its supersized smell organs have been scaled back a bit, but new studies show that the tyrant lizard's sensory apparatus was indeed fit for a king

MESA, ARIZONA—With its powerful jaws and serrated teeth, *Tyrannosaurus rex* had fearsome tools for catching and eating prey. The lumbering carnivore also had some top-of-the-line sensory equipment, paleontologists reported here last month at the 65th annual meeting of the Society of Vertebrate Paleontology (SVP).

The new insights come from studies of bony clues to the brain, ears, and eyes of *T. rex*. They suggest that the "tyrant lizard king" had an acute sense of smell—although perhaps not as acute as some recent studies had suggested—a knack for listening as well as keeping its eyes fixed on prey, and depth perception to rival modern birds of prey. To most paleontologists, it all adds up to a talented predator. "The more we look at *T. rex*, the more sophisticated it is," says Philip Currie of the University of Alberta in Edmonton, Canada.

T. rex was first unveiled and named 100 years ago by the legendary paleontologist Henry Fairfield Osborn of the American Museum of Natural History in New York City. Ever since, *T. rex* has been famous for its staggering dimensions—ranging up to 12 meters and perhaps as much as 7 tons—and its highly modified skeleton. Several of those distinctive features, such as the shrimpy arms and the bone-crushing teeth, led some researchers to propose that *T. rex* was prima-

You can't hide. *Tyrannosaurus rex*'s keen senses of smell, hearing, and vision helped it take down prey or snap up carrion.

CREDIT: JIM ZUCKERMAN/CORBIS

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rily a scavenger. That case was bolstered in 1999, when computed tomography (CT) scans revealed that the *T. rex* named Sue had enormous olfactory bulbs (*Science*, 9 June 2000, p. 1728)—a specialization that would presumably have helped it catch the scent of a dead dinosaur in the distance.

To some paleontologists, the gargantuan olfactory bulbs were difficult to swallow. One group of researchers—François Therrien of the Royal Tyrrell Museum of Palaeontology in Drumheller, Canada, and Farheen Ali and David Weishampel of the Johns Hopkins University School of Medicine in Baltimore, Maryland—decided to see what the olfactory bulbs in *Tyrannosaurus*'s closest living relatives, birds and crocodiles, could reveal about their long-gone cousin.

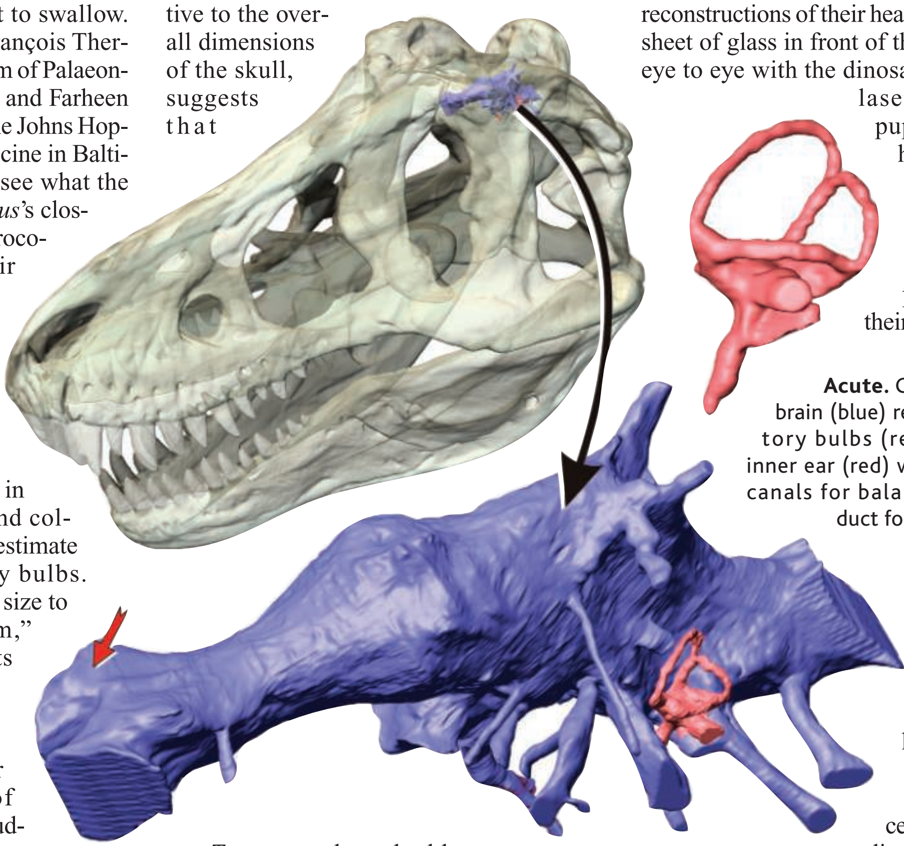
In both groups, the olfactory bulbs rest against a trough on the upper part of the braincase and are bounded toward the front of the head by a septum. By locating bony traces of this septum in *T. rex* braincases, Therrien and colleagues could more accurately estimate the position of the olfactory bulbs. "This would have limited their size to no more than that of a plum," Therrien says. Paleontologists had thought the olfactory lobes extended further forward inside the head. "I think they're probably right," says Christopher Brochu of the University of Iowa in Iowa City, who had studied Sue while at the Field Museum in Chicago.

Still, *T. rex* did very well by its nose. The relative size of the bulbs—their width compared with the width of the cerebral hemispheres—was the highest of seven dinosaurs examined, including other tyrannosaurids and smaller, more birdlike dinosaurs.

Therrien speculates that the acute sense of smell could have been used to track prey, locate putrefying carcasses, or help males patrol territory for rivals. Greg Erickson of Florida State University in Tallahassee cautions that it's not straightforward to link organ size to sensory acuity, as sense of smell is also determined by features such as the density of neurons. "We need more [comparative] studies … so we can make sense of this," he says.

In the meantime, another study described at the meeting matched Therrien's results on the size of the olfactory bulbs. Lawrence Witmer and Ryan Ridgely of Ohio University College of Osteopathic Medicine in Athens put several *T. rex* skulls into a CT scanner. By examining features preserved in the skull, including fossilized evidence of nasal tissue in front of the olfactory bulbs, Witmer found that the bulbs were roughly walnut-sized.

Witmer's study extracted clues to other sensory abilities. For example, he resolved the bones that surrounded the so-called cochlear duct of the inner ear, which helps turn sounds into nerve signals. The length of these bones, relative to the overall dimensions of the skull, suggests that *T. rex* may have had better hearing than other theropods did.



Acute. CT scans of *T. rex*'s brain (blue) reveal sizable olfactory bulbs (red arrow) and an inner ear (red) with long, delicate canals for balance and cochlear duct for hearing.

CREDIT: L. M. WITMER AND R. RIDGELY/OHIO UNIVERSITY COLLEGE OF OSTEOPATHIC MEDICINE

The inner ear can also reveal aspects of an extinct animal's posture and sense of balance (*Science*, 31 October 2003, p. 770). Thanks to the CT scans, Witmer could resolve the bony labyrinth of the inner ear with its trio of semicircular canals, oriented at right angles to one another. These once contained fine hairs that sensed the motion of fluid, helping the brain know how the body was oriented and which way it was moving. In modern creatures, the larger the loop of the semicircular canals, relative to head size, the more agile they tend to be.

T. rex turned out to have surprisingly long canals. "You might not expect a large animal to have quick movements," Witmer says. He suspects that the primary purpose of the canals was not gymnastics but helping *T. rex* keep its head and eyes fixed on prey. That's not all the canals reveal. In modern animals, the orientation of the lateral canal relative to the skull correlates with how they tend to hold their heads while alert. *T. rex* apparently kept its head dipped down about 5° to 10°. For tall animals with long snouts, such as *T. rex*, tilting the head downward can help them better see what's directly ahead.

Kent Stevens of the University of Oregon, Eugene, has come to a similar conclusion about *T. rex*'s vision, which again places it at the top of its class. He reconstructed the visual abilities of *T. rex* and six other predatory dinosaurs by working with sculpted reconstructions of their heads. After placing a sheet of glass in front of the busts, he stood eye to eye with the dinosaurs and shined a laser at each fake pupil. This allowed him to map onto the glass the entire area from which the laser glinted off the pupils, tracing their visual field.

T. rex, with its forward-facing and widely separated eye sockets, turned out to have great binocular vision and, likely, depth perception. When *T. rex* dipped its head about 10°—similar to the angle of the alert posture that Witmer estimated—it would have maximized the width of its binocular field of view at 55°, as good as that of hawks, Stevens says. That's not quite as good as those of the highly birdlike dinosaurs, such as *Troondon*, but it exceeds that of other adult tyrannosaurids. The research, which Stevens presented at an SVP meeting several years ago, is in press at the *Journal of Vertebrate Paleontology*.

To Stevens, the degree of depth perception, hearing, and sense of smell point in one direction: a top predator. In contrast, Jack Horner of the Museum of the Rockies in Bozeman, Montana, is sticking with his idea of where *T. rex* got its meals. "I think this olfactory business is very supportive of the *T. rex*–as-scavenger hypothesis." Others say it's more likely that *T. rex* wasn't a picky eater. "If it can smell a carcass a mile away, it can also smell a herd of hadrosaurs from a mile away," says James Hopson of the University of Chicago in Illinois. "I don't think it would have preferred one over the other."

–ERIK STOKSTAD