age lies somewhere between Ras and Raf-1. "Ras is basically backed up, sitting there in the active state with nowhere to go," says Onyx Pharmaceuticals' Frank McCormick.

Although researchers have yet to pin down the mechanism of this blockage, the fact that it occurs, inhibiting the Ras pathway, is consistent with cyclic AMP's known ability to depress the growth of the cell types that these five groups used: certain strains of fibroblasts (found in connective tissue), fat cells, and smooth muscle cells. But while this first wave of papers consistently shows an inhibitory effect of cyclic AMP on the Ras pathway, cyclic AMP's growth stimulation in other cell types raises the question of whether it might increase the Ras pathway's activity in other circumstances. The answer appears to be yes.

At least two groups (who have not yet gotten their papers into the journals), have results indicating that in the neuron-like PC12 cells, elevated cyclic AMP concentrations stimulate MAP kinase activity. One group includes Emmanuel van Obberghen, Morten Frödin, and Pascal Peraldi of the INSERM lab at the Medical School in Nice, France, who presented their data at the FASEB meeting in July and who have a paper in press at the *Journal of Biological Chemistry*. The other work comes from Jeremy Tavaré's team at the University of Bristol in England. Although their results might seem to contradict the others, they don't. In fact, says van Obberghen, "the nice thing is that the biology makes perfect sense."

In contrast to the cells studied by the initial five groups, in which cyclic AMP antagonizes growth factor action, in PC12 cells it has the same effect as nerve growth factor—stimulating neuronal differentiation. And since nerve growth factor works through the MAP kinases, it's logical to think cyclic AMP would also do so, although the explanation for cyclic AMP's different effect in PC12 cells is still unclear. As McCormick points out, however, the new results should help researchers solve the mystery by telling them where to look for the biochemical events that account for the difference.

The rapidly accumulating results leave no doubt that crosstalk is taking place between cyclic AMP and the Ras pathway. Nevertheless, everyone agrees that the full significance of the findings remains to be determined. Signaling pathway expert Philip Cohen of the University of Dundee, Scotland, calls the results "quite interesting," but he adds that "we don't know what the mechanism is, or what it means physiologically. It's very early days indeed."

As Cohen's remarks suggest, one very desirable additional piece of information would be the mechanism by which cyclic AMP affects the Ras pathway. The Sturgill group's work points to one possibility—at least for the inhibitory effects. Cyclic AMP exerts many of its effects in the cell by activating another regulatory kinase, protein kinase A (PKA). Sturgill and his colleagues have evidence suggesting that PKA phosphorylation of Raf-1 may be what causes the blockage in the Ras pathway. Consistent with this suggestion is the finding by John Lawrence's group at Washington University School of Medicine that cyclic AMP's inhibitory effect requires an active PKA.

Beyond answering fundamental questions about pathway crosstalk, the work also has the potential for clinical application. "I think it has very broad significance," says the University of Washington's Graves. "It's the first physiological example of inhibition of the [Ras] pathway." And that's of great potential import because it might be possible to use the information to devise ways of inhibiting the abnormal cell growth of those cancers in which the Ras pathway is overactive by stimulating cyclic AMP production in tumor cells or finding drugs that mimic its effects on the MAP kinases. Atherosclerosis, a major contributor to heart attacks and stroke, might be another target, since the Washington group saw the inhibitory effect in smooth muscle cells, whose abnormal proliferation in the artery walls may lead to the formation of atherosclerotic plaques.

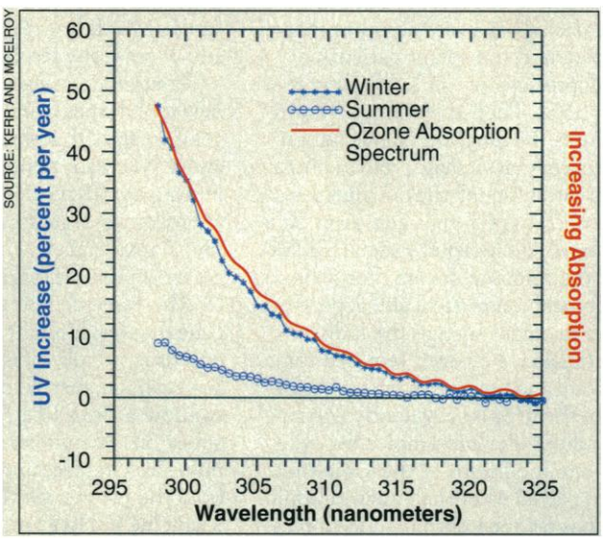
Particularly encouraging from the point of view of drug development is the specificity of cyclic AMP's inhibitory effects. "The important thing," Johnson says, "is that it inhibits one component—uncoupling Ras from Raf—but other upstream functions can remain intact." That may mean that cancer drugs based on mimicking cyclic AMP's action will have fewer side effects than do those currently in use. If so, then Johnson's predicted bandwagon should soon be getting up a pretty good head of steam.

–Jean Marx

ATMOSPHERIC SCIENCE

Filling a Hole in the Ozone Argument

Most researchers are expecting an increase in harmful ultraviolet radiation over the coming years, as the protective stratospheric ozone layer thins, eroded by manmade chlorine compounds. That's the reason stock in sunscreen makers looks like such a good bet at the moment. Yet a small, vocal group of dissenters insists this scenario has a hole as big as the "ozone hole" that forms every year over Antarctica: In spite of years of ozone loss, the only site that shows a long-term increase in sunburning rays is Antarctica itself. Indeed, a 1988 study even found a slight *decrease* in harmful ultraviolet rays at eight U.S. sites between 1974 and 1985.



Telltale match. Ultraviolet light has increased most at the wavelengths most strongly absorbed by ozone *(red)*.

A paper in this issue of *Science* may help close this gap in the ozone argument. On page 1032, James Kerr and Thomas McElroy of Canada's Atmospheric Environment Service show that at a carefully monitored site in Toronto, wintertime levels of ultraviolet-B (UV-B) radiation—the skin-damaging wavelengths that ozone ordinarily soaks up—increased more than 5% every year from 1989 to 1993, as ozone levels dropped. "It's the closing of the loop," says Kerr.

John Frederick of the University of Chicago, who studies ultraviolet light near the Antarctic ozone hole, agrees. "It's important that this result get in the literature," he says, since skeptics have argued that air pollution and clouds, by absorbing ultraviolet light, may negate the effects of ozone loss, making it less urgent to protect the ozone layer. "There's been too much loose talk," he adds. But the result may not end the debate, since critics argue that the Canadian results could stem from unusual atmospheric conditions.

One reason all sides are taking the new results seriously is the care that Kerr and McElroy took to ensure that any UV-B changes recorded over time reflect a real trend, and not simply a drift in the sensitivity of the instrument. In developing the instrument, says Kerr, he and McElroy took "a fair bit of care to stabilize the electronics" that detect the light. They also recalibrated it every month or so by testing its response to a battery of standard lamps.

Because of those precautions, other UV researchers are convinced that Kerr and McElroy's readings, taken once or twice an hour every day for the past 4 years, reveal a real increase. "I'm very impressed with the measurement," says John DeLuisi of the National Oceanic and Atmospheric Administration's Air Resources Laboratory in Boulder.

The researchers were also able to show that the UV-B increase was due to ozone loss and not, say, to clearer skies or less low-level air pollution. Because clouds, haze, and sulfate particles from power plants block radiation across the entire UV-B band while ozone leaves its mark only at the shortest wavelengths, making that link requires an instrument that can discriminate between different UV-B wavelengths.

Unlike earlier instruments, which deliver a single intensity reading for the whole UV-B band, from 290 to 330 nanometers, the Canadian device splits the UV-B radiation into component wavelengths and tracks their intensity individually. At 324 nanometers, where ozone should have little effect, Kerr and McElroy found no changes in intensity. But at 300 nanometers—closer to the peak of ozone absorption—UV-B intensity shot up, with summertime intensities increasing by 7% each year and wintertime intensities jumping by 35%.

Kerr and McElroy hasten to point out that the 300-nanometer increase, striking as it is, won't turn Toronto into a skin-cancer capital. Wintertime UV-B is very weak to start with, they note, and future increases may not be as steep. The period of their measurements included, among other things, the eruption of Mt. Pinatubo, which helped to push 1993 ozone levels over the mid-latitutes to their lowest point ever (*Science*, 23 April, p. 490).

Those unusual conditions, however, are one reason why Kerr and McElroy's result may not convert the doubters. S. Fred Singer, for example, a former chief scientist of the Department of Transportation who says he is "skeptical about the need to take hasty action to protect the ozone layer," sees nothing in these findings to change his opinion. Singer says that assuming Kerr and McElroy's UV-B increase is real, the ozone losses and the UV-B rise might have resulted from an unusual combination of natural causes, including the volcano. Four years of measurements, he contends, isn't enough to establish a trend.

Both sides do agree on a way to resolve this debate: longer-term data on UV-B trends. Canada has had a network of UV monitoring stations running since last year, with the Toronto site as its nucleus, but the United States is only now planning a comparable network. After Kerr and McElroy's finding, says Frederick, "I hope someone in the United States has the sense to be embarrassed that we haven't done something similar."

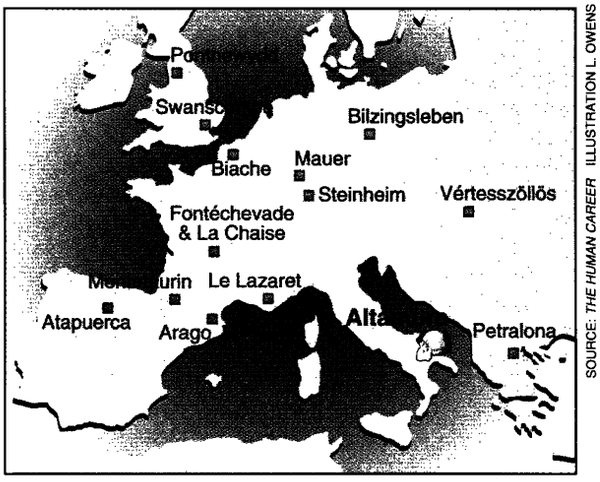
–Tim Appenzeller

PALEOANTHROPOLOGY

Possible Neandertal Ancestor Found

Peering out from its limestone tomb and pinioned by stalagmites growing from its body, a face from the distant past gazed for the first time on the modern world last month. The face is attached to a partly visible skeleton trapped in a cave in southeastern Italy, and a team of Italian scientists has tentatively identified the individual as a pre-Neandertal, possibly 400,000 years old. If they are correct, it would be the most complete skeleton ever found from this period in Europe, otherwise represented by some skulls and small fossil fragments, and it may finally shed some light on the origin of the Neandertals.

Neandertal expert Bernard Vandermeersch of the University of Bordeaux, who has seen photographs of the bones, says it appears to be a major discovery. "We've never seen a complete skeleton," he says. "Skulls, yes, quite a few. Bones, yes, plenty. But you are never quite sure, when you put them together, that they belong to the same individual. We've never seen the actual relation of the skull to post-cranial bones."



SOURCE: *THE HUMAN CAREER* ILLUSTRATION L. OWENS

Few and far between. The Altamura skeleton joins scattered fossils from the period preceding the Neandertals.

Spelunkers, intrigued by air coming from a hole in the ground, stumbled on the skeleton in the cave-wormed hills near the town of Altamura on 7 October. They lowered themselves down, and as they progressed some 60 meters along an underground corridor, they found the skeleton, partly covered by cauliflower-like formations of calcium carbonate and stalagmites. Anthropologist Vittorio Pesce Delfino of the University of Bari, some 40 kilometers north of the site, examined the specimen soon after. He says the skeleton is that of an individual 160 to 165 centimeters tall. It lies on its back, with the skull partly turned to the left. A fork-shaped stalagmite covers the base of the skull. Part of the face is apparent, including the eye orbits and all of the frontal region.

It's the characteristics of the face that give scientists clues to the skeleton's age and its evolutionary status somewhere between Neandertals and an earlier hominid, *Homo erectus*. According to Eligio Vacca, an archeologist from the University of Bari, the face has pronounced ridges over the eye sockets, which are Neandertal features, but "the morphology of the ridges, that of the vault of the skull, and the maximum facial width are not fully Neandertal." Since the first fossil evidence for *erectus* appeared in Europe about 500,000 years ago, and the first Neandertals appear about 130,000 years ago, the transitional features of the Altamura fossil put it somewhere in between those dates. Appearances can be deceiving, of course, and most researchers are waiting for more precise geeologic dating before accepting the fossil's transitional status.

But it's the bones below the neck that have created excitement in the research community. The period preceding the Neandertals in Europe is particularly murky, and anthropologists hope that a more complete skeleton, such as the Altamura find, will provide them with a better understanding of the evolutionary progression from *erectus* to Neandertals. The existing hominid fossils from this period vary enough that some scientists argue they must have belonged to at least two species, one of which led to Neandertals—and then a dead end—while another, separate species eventually became *Homo sapiens sapiens*. But others claim these fossil variations are relatively insignificant, and the hominids all belong to one lineage that gave rise to Neandertals.

The Altamura skeleton, says paleoanthropologist Christopher Stringer of the Natural History Museum in London, "may be a key finding for the little known transitional period and may help resolve the controversy." Of course, nothing is going to be settled until the fossil is released from its calcium sheath and examined completely, and that will be a slow and delicate process since it's hard to determine where the covering ends and the bones begin. In the meantime, Italian carabinieri stand guard over the remains of what may or may not be a Neandertal ancestor.

–Alexander Dorozynski

Alexander Dorozynski is a science writer in Paris.