as Melitta Schachner of the Swiss Federal Institute of Technology in Zurich and her co-workers found in 1992 when they knocked out the P_0 gene in mice, peripheral nerves have virtually no myelin, only remnants of loose, floppy membranes poorly wrapped around some axons.

Exactly how P_0 bonds the myelin membranes together was unclear, however, and in 1992 the lab teams of Colman and x-ray crystallographer Hendrickson joined forces to try to find out by solving the protein's structure. Before the structure could be determined, however, the protein had to be crystallized, and that promised to be a stumbling block. P_0 spans the membrane of Schwann cells, the specialized cells that form myelin by wrapping themselves around the axons of peripheral neurons, and membrane-spanning proteins are virtually impossible to crystallize. So Shapiro, a graduate student with Hendrickson, crystallized just the part of P_0 that protrudes outside the cell.

Subsequent x-ray analysis of those crystals showed, Shapiro says, that they were formed of "layers of molecules on the order of 45 angstroms [Å] thick." Because that is the spacing seen between the myelin membranes in electron micrographs, he adds, "this led us to suspect that we might in fact be looking at a reproduction of the layer that forms the glue between the membranes in the extracellular space of myelin."

The analysis also revealed the structure of the individual molecules making up those 45 Å layers—and suggested how they might act as the myelin glue. The structure suggests, says Shapiro, that the P_0 molecules are anchored to the Schwann-cell membrane like balloons on strings, bunching together in groups of four called tetramers. Each tetramer interleaves with four tetramers protruding from an adjacent membrane, linking the membranes together.

But because the strings are flexible, that interaction alone would not hold the membranes at a fixed distance. That is where an additional feature of the protein apparently comes in: Protruding from the top of each protein balloon, opposite the string end, is the amino acid tryptophan, whose hydrophobic nature makes it want to bury itself in fatty cell membranes. That tryptophan may firmly anchor each tetramer into the opposite membrane. And together with the tetramer-tetramer interaction, says Colman, that would "rigidly specify the distance" between the membranes at roughly 45 Å. Structural biologist Pamela Bjorkman of the California Institute of Technology concurs: "All the distances … agree with the distances in myelin. [The structure] is quite convincing."

Knowing the structure gives researchers a window onto a group of human diseases in which myelin forms improperly in the peripheral nervous system. Among these are Charcot-Marie-Tooth disease (CMT), Dejerine-Sottas syndrome (DSS), and congenital hypomyelination (CH). These conditions produce different symptoms—ranging from paralysis at birth in the most severe cases of CH to the weakness and lack of coordination that develops in young adults with CMT—and they were originally seen as separate diseases. But in the past few years researchers have found that some cases of CMT and DSS are caused by mutations in the P_0 gene, and in the current work, Lupski's team has added one case of CH to the list. "There is a spectrum of severity," says Lupski, but the conditions in his view are essentially the same disease. And that raises the question of how mutations in the same gene can cause such disparate symptoms.

The new structure should help answer that. For example, among the mutations are several in which the amino acid cysteine replaces another amino acid in the protein. Like most of the disease-causing mutations in P_0, these mutations cause symptoms when present in only one gene copy. And in these cases the symptoms are severe—the patients become ill as children with a condition classified as DSS. Baylor's Warner says that the site of the amino acid replacement in the P_0 structure may explain why. Based on their location in the structure, the cysteines should protrude from the protein's surface, enabling them to form disulfide bonds with cysteines on other P_0 molecules, perhaps creating inappropriate aggregates of P_0 and disrupting the normal P_0 interaction.

Warner found another cysteine substitution that caused milder CMT-like symptoms. When Warner and Shapiro located this change on the structure, they found that the cysteine should point into the protein's interior, where it can't make mischief by reacting with other P_0 molecules. It might affect the protein's function in more subtle ways, or even prevent it from reaching the cell surface. And a mutation that just reduces the amount of P_0 or the effectiveness of the mutant P_0 molecules should not be as bad, says Warner, as one that actively disrupts P_0 interactions.

Such reasoning is not proof of how the cysteine mutations cause disease, but it is a significant advance, says Bruce Trapp, chair of neuroscience at the Cleveland Clinic, because it produces "testable hypotheses" about how structural changes make myelin come unglued. Researchers can determine the crystal structures of specific mutant proteins, for example, or they can express the mutant proteins in cultured cells to see how they behave. And as they learn how myelin can come apart, they may find new hints about how to repair it.

–**Marcia Barinaga**

WEATHER FORECASTING

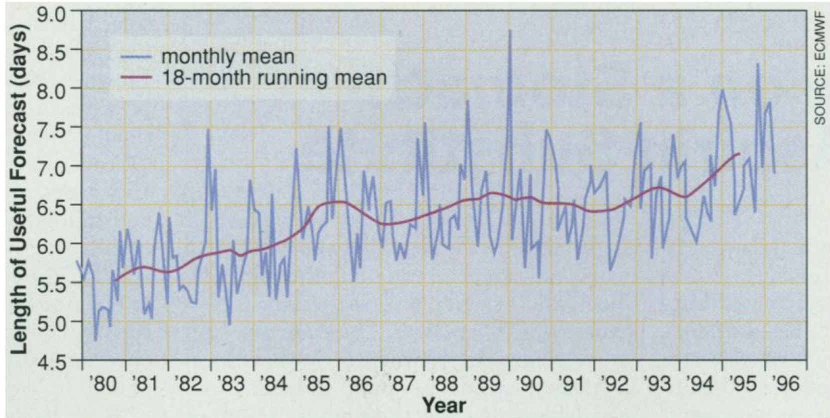
Budgets Stall But Forecasts Jump Forward

Anxious farmers and sodden picnickers may not believe it, but weather forecasts are actually getting better. By giving computer models such tweaks as a sharper picture of atmospheric properties or more realistic processes for turning water vapor into rain, meteorologists have made their forecasts much more accurate over the last 10 or 20 years; their computer models can now make useful predictions of the atmosphere's chaotic behavior up to a week in advance. Most Americans aren't reaping the full rewards of this improved forecasting skill, because official daily forecasts stop at 5 days. But in a year, the official forecasts may reflect the computational successes.

The operative word is may. The U.S. National Weather Service (NWS) plans to extend its daily forecasts to a full 7 days ahead by October 1997 and its less precise 6-to-10-day outlook out to 2 weeks. Yet this forecasting milestone, which should benefit everyone from natural-gas suppliers estimating heating needs to forest firefighters looking for relief, could be diminished by federal cost-cutting that would take human forecasters out of the picture and delay the arrival of the next powerful forecasting computer. "We have increasing pressure from the public to improve our forecasts," says James Hoke, director of the NWS's Hydrometeorological Prediction Center in Camp Springs, Maryland. "At the same time, we're being cut back significantly budgetwise. It's a difficult time."

Hard times have hit the weather service just when decades of incremental increases in forecasting skill are finally adding up to major advances. "A day-3 forecast [i.e., for the third day ahead] now is as accurate as maybe a day-1 forecast was in 1960," notes Russell Martin of the NWS's Climate Prediction Center in Camp Springs, who keeps statistics on forecasting skill. And improvements can be found at longer ranges too. Day-5 forecasts of the high- and low-pressure centers that determine weather patterns are now nearly as accurate as day-3 forecasts of 20 years ago, says Hoke. Predicting the period 6 to 10 days ahead is harder, but since that type of forecasting was begun in 1979 "we've about doubled our skill with temperature," says Martin.

Forecasters themselves can't take all the credit for this—much of the improvement is due to increasing computer size and speed, says Martin. "Being able to run bigger, more detailed computer models has been the big



Extended outlook. Forecasters' skill has increased, and meteorologists can now make useful daily forecasts up to a week ahead of time.

story," he says. All weather forecasts start with a computer model's simulation of how the world's weather will develop from the present out as far as 10 days in the future. But from the moment the model begins, its weather increasingly diverges from that in the real world. One problem is what the models leave out. While actual weather is shaped by everything from clashing fronts to the growth of microscopic droplets within clouds, computers must sum up all the weather processes in a 100-kilometer square at a single point. So inaccuracies are inevitable, but researchers have found many ways to reduce them. They have improved the model's starting picture of global weather, heightened the resolution, and created more realistic models of physical processes such as cloud droplet growth.

Another difficulty is that the atmosphere is chaotic, or extremely sensitive to small changes in starting conditions. To cope with this, the weather wizards run their models many times for a single forecast (*Science*, 23 December 1994, p. 1940). By making small changes in the starting conditions of each run, forecasters test the stability of a particular weather situation. If 20 such model runs give similar results for day 7, say, then the model may be reasonably trustworthy. But if widely differing weather patterns appear in these "ensemble" results, the forecaster can assume that the atmosphere is relatively unstable and that the model's results shouldn't be trusted entirely. "Right now we're on a long learning curve on how to use ensembles," says Joseph Tribbia of the National Center for Atmospheric Research (NCAR) in Boulder, Colorado, "but they have been quite useful. They help us understand when forecasts are likely to be very uncertain or potentially more useful."

It is these ensemble forecasts, plus the continually improving computer models, that Hoke's forecasting group plans to use to extend the official daily forecasts to days 6 and 7. But to predict each day's high and low temperatures, cloud cover, and the chance of rain, all a week ahead, the machines will need help, says Hoke. To maximize accuracy, human insight into meteorology, model weaknesses, and past analogs to current weather will be needed.

The longer range outlook—a forecast of whether temperature and precipitation will be above, below, or at normal levels 1 to 2 weeks ahead—will rely more directly on machine output, says Edward O'Lenic of the Climate Prediction Center, but humans will still play a pivotal role. For example, in experimental trials, his meteorologists took an ensemble of 17 forecasts of pressure in the high atmosphere out to 17 days, translated the results by machine into weather at the surface, folded in observations from similar situations in the past—and then decided just how "sane" the resulting machine forecast was. If the humans thought the machine had erred, they made adjustments. For week 2, the experimental forecasts have been as accurate as the official 6-to-10-day outlook, says O'Lenic, achieving a skill level of 26 on a scale on which guessing is zero and perfection is 100: "It could be beginner's luck, but it's not a bad way to start."

The human expertise these forecasts require, however, is threatened by NWS's budgetary woes. The extended daily forecasts were once scheduled for sometime in 1995, but federal budget tightening pushed them to this October. And now those fiscal woes are forcing NWS-wide staff reductions, amounting to 15% in Hoke's center. Barring a budgetary miracle, the machines will have to deliver the day 6 and 7 forecasts on their own, says Hoke, inevitably degrading forecasting skill.

Although the machines will be asked to do more, the computer component of forecasting will also suffer under current budget plans. Because of complex federal procurement procedures and also to save money, the NWS is delaying the acquisition of its next supercomputer until the first quarter of fiscal year 1999, 3 months later than planned.

And it will take all the computer power and expertise the NWS can muster to keep improving forecasts. "At some time scales, it's getting real hard to squeeze that last epsilon of improvement out of the system," says Martin. He cites the forecasting of sea-level air pressure over North America. Starting in 1968, skill at days 3, 4, and 5 rose steadily if gradually, and "days 4 and 5 are still showing an upward trend," he says, "but the day-3 forecast is plateauing a bit." Still, says NCAR's Tribbia, "we know from studies of weather predictability that we still have some room to make improvements." Those will come with better ensemble forecasting, better models, and more meteorological understanding, he says. A steady budget would help too, other forecasters add. The meteorological crystal ball may be getting clearer, but budgets remain a murky business.

–Richard A. Kerr

The Next Lap in the Forecast Race

For 17 years European and American researchers have been in a race to predict the next week's weather, propelled by the ever-increasing power of the world's fastest supercomputers. While American forecasters at the National Weather Service (NWS) focus on taking advantage of their achievements so far (see main text), researchers at the European Center for Medium-Range Weather Forecasting (ECMWF) in Reading, England, are about to surge ahead in raw forecasting power once again.

In the course of the friendly competition, the NWS and ECMWF have pushed useful forecasts made by computer models of the global atmosphere from an average limit of 5.5 days in advance to about 7 days, the Europeans often holding as much as a half-day lead over their American colleagues (*Science*, 5 October 1990, p. 30). That machine-forecasting race is now viewed as running nearly neck and neck, but "it's become clear that, although we have essentially caught up with the [ECMWF], it's not going to stay that way," says Ronald McPherson, director of the National Centers for Environmental Prediction in Camp Springs, Maryland.

Even as the NWS is having to delay the purchase of its next computer until late 1998, the ECMWF is taking delivery of a new Fujitsu VPP 700 computer that is five times faster than the NWS's current Cray C-90. Within 2 years the Fujitsu will be upgraded so that it is 25 times faster. So no matter how hard the Americans try to improve on their computer forecasts with human enhancements, the raw computer power of the Europeans is likely to prevail. Once again, the race will go to the swift. **–R.A.K.**