For example, when the single cell layer of which the preimplantation embyro is composed separates into the two cell layers known as the ectoderm and mesoderm, the cells that form the mesoderm stop producing E-cadherin and make the neuronal type instead. The formation of nervous tissue from the ectoderm is also marked by a switch from E-cadherin to N-cadherin production. Takeichi concludes that the switch in cadherin expression may be essential if old cellular connections are to be broken and new ones made during organ formation in the embryo. P-cadherin is needed for making the embryonic and uterine cell connections of the placenta.

Takeichi and his colleagues have compared some of the structural characteristics, including partial amino acid sequences, of E-cadherin from mouse liver and of N-cadherin from chicken brain. The results indicate that the molecules are sufficiently related to belong to a "cadherin family." The number of family members is still unknown.

The molecule called NCAM (for neural cell adhesion molecule) is another protein that aids the formation of cellular associations, principally those involving nerve cells, during development. NCAM's cellular distribution is similar to that of N-cadherin, and NCAM-mediated interactions, like those of N-cadherin, require the molecule's presence on both partners. The two adhesion proteins are different, however.

Whereas the cadherins appear to act as classic cell-sorting molecules in the early embryo, NCAM has a more regulatory role in intercellular interactions, according to Urs Rutishauser of Case Western Reserve University School of Medicine in Cleveland. Variations in expression of the molecule help to create adhesive preferences between cells during a diverse set of developmental events, especially those involving nerve cells.

Rutishauser and his colleagues have shown, for example, that the propensity of NCAM-positive cells to adhere to one another helps guide the optic nerve from the eye to its final destination in the brain. The nerve cells, which make NCAM, grow along the outer surface of the brain, following a trail of glial cell projections known as "end feet," which also make the molecule.

In addition, NCAM participates in the formation of the synaptic connections between nerve and muscle cells and possibly in the establishment of gap junctions, which are direct molecular links between cells. "NCAM is not a part of these specialized connections," Rutishauser says, "but it helps to bring cells together so that they can form." The importance of NCAM in mediating these cellular interactions is indicated by studies showing that antibodies to the molecule alter the route taken by the optic nerve and disrupt synapse and gap junction formation.

The synthesis of NCAM, like that of the cadherins, is carefully regulated during these developmental events. The glial end feet make NCAM just as the optic nerve axons pass by. Formation of nerve-muscle synapses and of gap junctions also correlates with NCAM expression at the appropriate sites. Finding out what is regulating the expression of the genes for NCAM and the cadherins will be a major goal for the future. ■

JEAN L. MARX

Japanese Super-Sequencer Poised to Roll

"In the 21st century, we foresee that DNA-sequencing supercenters will be set up in several countries," says Akiyoshi Wada of the University of Tokyo. Such centers would be symbols of human intellectual endeavor, he adds, being biology's equivalent of "large particle accelerators, and far-reaching programs of space research."

The stepping stone to this vision of the future is Japan's current effort to establish in the very near future a "factory" that will be able to run through a million bases a day. The project was conceived 5 years ago when Japan's Science and Technology Council formed a committee specifically to study the issue of automation of DNA sequencing. Wada heads that committee.

In the 26 February issue of *Nature*, Wada outlined his country's progress on its venture, including a projected cost of between 10 and 17 cents per base sequenced. This figure would represent close to an order of magnitude improvement over current costs.

The emphasis of the Japanese approach is to automate well-established techniques rather than develop new ones. This contrasts to some extent with a lot of the research endeavor in the United States where several research groups are developing substantially new approaches to sequencing.

For instance, the sequencing in the Japanese super-sequencer will be done, for the most part at least, by using the Sanger technique. And in spite of the recent development of fluorescent labeling and laser detection techniques for identifying the bases as they are separated by gel electrophoresis, Wada says that initially the super-sequencer will rely on the established method of radioactive labeling of bases and autoradiographic identification. The reason, he says is that the old approach is cheaper. "Specific labeling of the four nucleotide bases with characteristic fluorescent dyes may be advantageous in an automated system," he acknowledges, but only "if their cost-performance becomes attractive."

The prime goal of the project is to be able to sequence a million bases a day, not to produce a fully automated sequencing system, comments Wada. To this end, the sequencing task is broken up into discrete units, each of which is being automated by one or more prominent Japanese companies. For instance, Seiko is modifying its existing sequencing machine, which is based on the Maxam-Gilbert technique and charts up one base every 14.4 seconds, to produce a machine based on the Sanger method. A prototype machine, which was developed in collaboration with scientists at the Institute of Physical and Chemical Research at Wako, Saitama, now appears capable of an output of close to 300,000 bases a day, or one base every 0.28 second. With continuous operation and with "a relatively modest improvement," this machine would readily achieve the goal of 1 million bases a day.

The radiographic detection system is being handled by Fuji Photo Film Company, which has developed an acetate-covered gel film that can be exposed and developed much more rapidly than is typically done in most molecular biology laboratories. Fuji is already capable of producing sufficient quantities of this special film to cope with a 1-million-base-a-day throughput.

The autoradiographic pattern on the films will be read by one of the automatic scanners that have already been developed independently by Hitachi Software and by Seiko. So far these scanners can read at a rate of 1.4 bases a second, which is not especially fast compared with a skilled human practitioner. However, the machine can run 24 hours without interruption, giving a total of 60,000 bases a day. An order of magnitude improvement in reading rate through better optical processing and higher grade computing is easily attainable. The current 1% error rate can be virtually eliminated by reading two identical or complementary strands.

These, then, are the various components of the system, which will be linked together, says Wada, by "skilled human operators [who] would play a crucial role in monitoring the accuracy of the results." The project is poised to move into action, he adds. "We have now reached the point in the planning at which all the elements of a mass production line exist, together with the interfaces between them." The super-sequencer is therefore expected to be up and running in about a year. ■ ROGER LEWIN