data, but I would be surprised if one could distinguish unambiguously between the linear-quadratic and the linear model. It's a judgment call," says Arthur Upton of New York University, who has the unenviable task of chairing the BEIR-V study, the NRC's reexamination of radiation risk estimates, and an ICRP study as well. Much of the BEIR committee's efforts, he says, will be devoted to just that question.

Risk estimates are also being revised in light of the new cancer mortality data among the atomic bomb survivors, which, according to Upton, "are causing total risk to appear much larger than it did a few years ago." In the past 11 years the number of excess deaths among the survivors has risen from about 100 to 300. The increase is occurring, he and others say, because the population is reaching the age when cancers typically occur. As the incidence of "normal" cancers increases with age, so, too, does the incidence of excess cancers. Japanese women who are now in their 40s and who were heavily irradiated as children are showing a marked increase in breast cancer, Upton says. The Japanese data are also showing that relative risk is greater for those who were exposed in utero or as children than it is for those exposed as adults.

When the mortality data and new dosimetry are combined, says Sinclair, radiation risks appear to be a factor of 2 or 3 higher than earlier estimates. For the young, risk could be up by a factor of 5 or 6, he suspects. And if the dose-response curve turns out to be linear, the risk estimate would rise by a factor of 2 again.

Opinion is divided, however, on whether the new dosimetry warrants a revision in radiation protection standards. Almost as soon as the new dosimetry was released, Friends of the Earth and hundreds of scientists petitioned the International Commission on Radiological Protection, which recommends protection standards for radiation workers and the public, to reduce its recommended exposures for radiation workers by a factor of 5, from 50 millisieverts to 10 millisieverts. The ICRP has deferred any decision until its risk assessment, as well as those of the NRC and the UN committees, are complete, which may be 1 or 2 years.

In the United States, the National Council on Radiation Protection will also wait until those studies are complete."We need a sound evaluation before we take such a step. You aren't going to turn the radiation protection system upside down overnight," Sinclair says. Britain, however, is expected to immediately lower its occupational standard by 70%, down to 15 millisieverts , thus breaking ranks with the ICRP. ■

LESLIE ROBERTS

Broad Attack Launched on the Nervous System

In the past few years, research on molecular and cellular phenomena has dominated the field of neurosciences and its annual meeting. But this year, organizers balanced these reports with presentations about the neurobiology of whole-animal learning and behavior. The result was an updated overview of what is known about nervous system structure and function. More than 11,000 researchers met from 16 to 21 November in New Orleans for the 17th Annual Meeting of the Society for Neuroscience to bridge the gaps between molecules and man.

Thanks for the Memory

Patty's garden is full of marigolds. "After a 5-minute delay, a patient with amnesia will only remember the key word 'marigolds' 20 to 30% of the time," says Larry Squire of the Veterans Administration Medical Center and University of California at San Diego. "And after 24 hours the patient cannot recall any part of a new passage."

It may be a common misconception that patients with amnesia only have trouble remembering past events. As Squire indicates, they have trouble learning new things. Their loss is often selective, however. Squire, Stuart Zola-Morgan, also of San Diego, and David Amaral of the Salk Institute in La Jolla recently found that patient RB had damage only to a small subdivision of the most primitive part of his cerebral cortex, but the lesion drastically affected his ability to learn.

RB developed anterograde amnesia (had difficulty forming new memories) after heart surgery and a major episode of ischemia, in which the blood supply to the brain was blocked. He recently died at the age of 57, permitting the California researchers to determine precisely what regions of his brain had been damaged by the ischemia. They correlated this information with the results of psychological tests they had administered to RB during the 5-year period from his ischemia to his death.

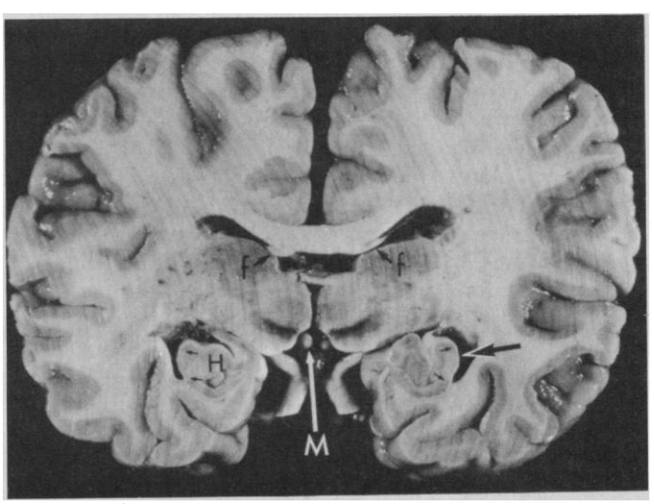
The damage to RB's brain was restricted to a small region on both sides. "We saw a complete loss, bilaterally, of the CA1 pyramidal cells of the hippocampus," said Squire at the meeting. "We postulate that this loss resulted from the toxic effects of an excitatory neurotransmitter." Other brain regions also thought to be involved in memory were normal.

Interestingly, RB could recall events from the 1940s to the late 1970s as well as or better than control subjects. He remembered public events, famous faces, and TV programs. He also recalled events from his own life without impairment. These abilities distinguish him from other patients, who have retrograde amnesia and have forgotten events backward in time from the brain injury incident. But RB had great difficulty in new learning situations. He could not recall stories, diagrams, or unrelated word pairs presented to him. In these respects, he resembled other patients with amnesia.

Despite their learning impairments, many

A section through RB's brain

Looks normal except for a loss of cells in a small region of the hippocampus (small arrows marked with H on the left and with a large arrow on the right). [*S. Zola-Morgan* et al., J. Neurosci. *6, 2950 (1986)*]



amnesic patients have some preserved abilities to learn new things, says Squire. Many can still learn complex skills like mirror writing, but cannot recall the circumstances in which they learned the skill. This kind of dichotomy has led Squire and others to propose that there are at least two distinct forms of learning—skill learning and declarative learning.

"Skill learning is embedded in procedure and is characterized by inflexibility," says Squire. In contrast, declarative learning allows a person to recall facts and episodes and depends on a person's ability to store a representation of the original experience. In other words, it relies on the integrity of the brain systems, particularly the hippocampus, most often damaged in amnesia, says Squire.

Neuropsychologists are still in the process of identifying precisely how the hippocampus contributes to learning and memory. RB clearly had brain damage that affected neural connections within the hippocampus and consequently disrupted the flow of information between the hippocampus and the neocortex. But RB's memory impairment prevented the storage of new information; it did not affect his ability to recall events that preceded his brain injury. "This suggests that the hippocampus has a time-limited role in memory," says Squire.

Alzheimer's Protein Is Also in Infant Brains

A protein previously thought to exist only in the brains of Alzheimer's disease patients or people with Down syndrome, also occurs in normal infants. Peter Davies, Benjamin Wolozin, and Angela Scicutella of the Albert Einstein School of Medicine in New York reported new data showing that protein A68 is present in the brains of fetuses at 34 weeks of gestation or older and in infants until 2 years of age. The finding itself is surprising, and it adds a dimension to controversies about A68.

A68 has a short history. Two years ago, Davies and his colleagues reported that an antibody known as Alz 50 stains protein A68 in postmortem brain tissue from Alzheimer's and Down syndrome patients but does not stain the brains of normal aged people. Last year, the New York group showed that A68 is also present in the spinal fluid of Alzheimer's patients, which Davies hopes will lead to a diagnostic test for early Alzheimer's.

"The new idea is that the A68 protein is expressed early in development and then later in a neurodegenerative disease," says Davies. There are differences between the two cases, however. First, "a 5-month-old baby has A68 staining, but only a small fraction of cells in the baby's brain are positive. Probably a thousand times more cells stain positive for A68 in the brain of an Alzheimer's patient."

A second contrast is that A68 staining occurs in different brain regions of infants as compared to Alzheimer's patients. "In Alzheimer's, layers three and five of the cortex have A68," says Wolozin. "In the infant cortex, the protein occurs deeper—in layers five and six—and also in the white matter. So it is not a match."

Questions about A68 and the Alz 50 monoclonal antibody that labels it persist. For example, Dennis Selkoe of Harvard Medical School thinks that Alz 50 recognizes an altered form of the *tau* proteins, which are associated with the so-called paired helical filaments contained in Alzheimer's tangles. "It would be wrong to say that Alz 50 is just another monoclonal antibody against *tau*," says Selkoe. "It is a very special antibody to *tau* that recognizes a form of the protein that is especially prevalent in brain tissue from Alzheimer's patients." He also acknowledges that Alz 50 may recognize a protein that is not *tau* but that has a conformation similar to that of the *tau* protein.

Davies and his colleagues have yet to determine the exact nature of the A68 protein recognized by Alz 50, but they do not believe that A68 is a *tau* protein. Last year the New York group thought that A68 might be kinase, an enzyme that adds phosphate groups to other proteins. The finding was inconsistent, however, because they could not detect kinase activity in every preparation of A68.

In his presentation at the recent neuroscience meeting, Davies said that his group now has new antibodies against the A68 protein that are more specific than Alz 50. But, like Alz 50, they also stain numerous amyloid plaques and neurofibrillary tangles in brain tissue from Alzheimer's patients. Large numbers of these structural abnormalities characterize Alzheimer's, and the fact that both stain for A68 raises several questions.

For instance, do the same nerve cells produce both plaques and tangles? Is A68 a marker for cells that are preprogrammed to develop the abnormal structures and die—in a developing brain or in a degenerating one? And how does A68 fit into the growing repertoire of information about abnormal genes for β amyloid proteins in Alzheimer's? (*Science*, 4 December, p.1352).

"These are all questions that we would like to know the answer to," says Davies. "We are hoping to get some of the answers when we sequence A68."

Peptide Turn-On for the ACh Receptor Gene

Before an animal can move, its muscles must be stimulated appropriately. In order for this to occur, there must be a sufficient number of acetylcholine (ACh) receptors on muscle cells to receive chemical messages from motor nerves. Until recently, neuroscientists knew that electrical activity in muscle cells turns the ACh receptor gene off; and they also knew that high concentrations of cyclic adenosine monophosphate (cAMP) inside the cells turns it on. They questioned whether some positive signal increases acetylcholine receptor synthesis in muscle cells; and whether electrical activity or something else triggers the production of cAMP.

"Two years ago, I had a conversation with Thomas Hökfelt," says Jean-Pierre Changeux of the Pasteur Institute in Paris. "We wondered if calcitonin gene–related peptide (CGRP), which Hökfelt had observed in the cell bodies of motor neurons, might somehow control gene expression for the acetylcholine receptor." Their new data indicate that it does. CGRP turns on the gene for the α subunit of the acetylcholine receptor and also increases intracellular cAMP concentrations.

CGRP is a 37–amino acid peptide that occurs in several parts of the nervous system, unlike its genomic neighbor—the calcium-balancing hormone calcitonin. Changeux, Hökfelt, of the Karolinkska Institute in Stockholm, and their colleagues recently identified CGRP as a positive signal for acetylcholine receptor synthesis.

Acetylcholine is the primary neurotransmitter released from the endings of motor neurons. It causes electrical activity in skeletal muscle cells and stimulates them to contract. In order to have this effect, however, acetylcholine must first bind to the two α subunits of its receptor. In 1985, Changeux and his co-workers reported that electrical activity itself turns off the gene for the synthesis of the α subunit. But muscle cells contract spontaneously, at least as they are developing in tissue culture. It was clear, therefore, that something else overrides the electrical block to acetylcholine receptor synthesis.

"CGRP can increase the number of acetylcholine receptors in cultured muscle cells even though the cells are spontaneously active," says Changeux. In his presentation at the neuroscience meeting, he reported that others have shown that CGRP is released from nerve terminals along with acetylcholine. "There are at least two signals for acetylcholine receptor gene expression coming from the motor neuron. CGRP increases

acetylcholine receptor synthesis, and acetylcholine causes electrical activity and decreases synthesis."

Simply identifying the signals that turn genes on and off is only the first step, however. In the case of the gene for the acetylcholine receptor, CGRP and electrical activity must somehow be translated into messages inside the cell, which then have a specific effect on gene expression. Changeux points out that chemical second messengers fulfill this role, and that they might be different for the on and off regulation of the acetylcholine receptor gene.

"The positive signal, CGRP, simulates the production of cyclic AMP in muscle cells," he says. "It may be one of several regulating factors that have this effect. But the negative signal, electrical activity, acts through a different second messenger pathway. It seems to stimulate the production of diacylglycerol and inositol trisphosphate and raises the intracellular calcium concentration. But we still don't know whether it is through this pathway that the acetylcholine receptor gene is turned off."

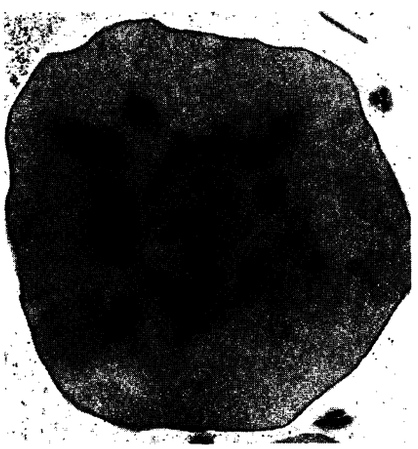
Changeux does not yet know when during development CGRP exerts its effect on the muscle cell gene genome. To date, he has focused primarily on signals that regulate the gene for the α subunit of the acetylcholine receptor. Now, he and his collaborators are beginning to study what controls the activity of the genes that code for the other subunits—β, γ, and δ. ■

DEBORAH M. BARNES

Insect Viruses Invade Biotechnology

Baculoviruses, a hitherto obscure family of insect viruses, have become an important part of the biotechnology repertoire. More than 150 laboratories are currently using this viral system for the manufacture of proteins. Most notably, investigators at MicroGeneSys, Inc., in West Haven, Connecticut, recently used a specially designed baculovirus containing the envelope protein of the AIDS virus to produce the first AIDS vaccine approved for human trials in the United States (*Science*, 28 August, p. 973).

The ability to engineer the baculovirus has important applications in agriculture as well as medicine. Natural baculoviruses have been used since the early 1970s as biological insecticides. However, in areas with serious insect infestations, the viral infection process may be too slow. Lois K. Miller and co-workers at the University of Georgia in Athens and other investigators have been engineering baculoviruses to produce powerful insect neurotoxins, which may provide a more lethal weapon against such pests as the gypsy moth.



Baculoviruses. *A polyhedral crystal within an infected caterpillar cell. Intact baculoviruses appear as rods embedded in the polyhedrin matrix.* [*C. Y. Kawanishi, EPA, Research Triangle Park, NC*]

Baculoviruses are finding a niche in biotechnology because they can be engineered to express large amounts of proteins in a relatively short period of time. To do this, scientists have focused on the gene that encodes the viral polyhedrin protein, which surrounds virus particles within the infected cell. Gale Smith, now at MicroGeneSys, and Max Summers, of Texas A&M University and Texas Agricultural Experiment Station at College Station, spearheaded studies demonstrating that the regulatory signals that are so effective in producing polyhedrin can be diverted to the production of other proteins. When a butterfly or moth cell culture is infected with a recombinant baculovirus, the foreign protein can represent as much as 20 to 50% of the total protein made.

Like other viruses, the baculovirus uses its host's synthetic machinery to reproduce. The question of whether an insect system can turn out the same product as is made by the machinery of a human cell is of great concern if baculovirus proteins are to have medical applications. A protein that is not authentic might have harmful side effects if used therapeutically or as a vaccine. In many cases biological activity, the ability to induce an immune response, and enzymatic activity of the insect-produced proteins are very similar to those of the natural products. This similarity indicates that they are close, if not identical, to the authentic proteins. Phosphates are added to some newly made proteins in baculovirus systems. In addition, peptide sequences that direct proteins to their destinations in the cell can be close enough to the original that the proteins are delivered to the organelles where they would normally be found.

However, the addition of complex carbohydrate side chains to newly made proteins may not occur with fidelity in insect cells. This could be important for proteins containing sialic acid, fucose, or galactose. The issue will not be resolved until enough proteins produced in different insect cells have been sequenced and studied in a medically relevant setting.

Ongoing research on the applications of baculoviruses is also focused on optimizing the system. The amount of protein produced depends on such factors as the particular baculovirus and insect cell and the distance of the foreign gene from the polyhedrin control sequences. Commercially, it may be advantageous to grow baculoviruses directly in live caterpillars. According to David Bishop of the Natural Environment Research Council, Institute of Virology, Oxford, United Kingdom, one caterpillar can produce enough protein for as many as one million diagnostic tests. "It's easy to keep caterpillars," says Bishop. "Feed them leaves!"

Recently, Bishop and co-workers have developed a baculovirus that can express two added genes simultaneously. This virus proliferates easily in caterpillars and broadens the potential of this system for development of diagnostic tests (such as a single blood test that might detect exposure to hepatitis or the AIDS virus) and for the production of proteins containing two different subunits.

Other systems—principally yeast, *Escherichia coli*, *Aspergillus*, and mammalian cells—are available for large-scale production of proteins, although each one has its own problems. According to Summers, "We don't know enough yet about protein structure to predict which system will produce a particular recombinant protein that most closely resembles the original one." Which proteins will become part of the domain of the baculovirus system remains to be seen. ■ BARBARA R. JASNY

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