the *per* gene product, Young and his colleagues decided to see whether the *per* gene is present in other species. They identified similar sequences in DNA from humans, mice, and chickens and discovered that it is an unusual repetitive DNA sequence, coding for alternating serines and glycines or threonines and glycines. However, Konopka notes, these similarities are quite limited. It is not as though most of the *per* gene sequence is found intact in vertebrates. For that reason, he remarks, "it's still a possibility that the homologous sequences don't have anything to do with rhythms. We still don't know what part of the *per* locus is responsible for the rhythms."

But the finding of the repetitive sequences "was surprising," says Young, who had suspected, along with others, that the *per* gene might control an ion channel in cell membranes. There were models of how biological clocks might be made to oscillate that involved controlling the opening and closing of ion channels. But these repeating amino acid sequences in the *per* gene product did not look like part of an ion channel protein. On the other hand, says Hall, perhaps ion channels are not what they are assumed to be either. "Two ion channels have been sequenced out of 20 or more—and I emphasize *or more*. God knows what this ultimately means."

But the *per* gene product looked so different from the ion channels that are known that Young and, independently, Rosbash, asked what that kind of amino acid sequence might code for. To their surprise, they found that similar sequences are in proteoglycans. These are mysterious proteins that are poorly understood. They appear outside the cell and have been found in extracellular matrices such as cartilage, for example. Other proteoglycans are believed to be cell adhesion molecules. Proteoglycans are loaded with carbohydrate, "which gets them on the outside of cells," says Young. "We're kind of fuzzy on what to do with something like that. This protein doesn't look like an integral membrane protein so the ion channel model looks less likely. Perhaps we're dealing with a molecule that governs interactions of groups of cells which in turn form a clock."

No one, in all the speculations, had ever suspected that the clock might be controlled by molecules lying outside or between cells. "I expect that whatever we find out now will be all new," says Young. "But we will have to examine the structure and distribution of a rare protein in vivo, so we certainly will have to do some real hard work."

—GINA KOLATA

Additional Reading

1. W. A. Zehring *et al.*, "P-element transformation with *period* locus DNA restores rhythmicity to mutant, arrhythmic *Drosophila melanogaster*," *Cell* **39**, 369 (1984).
2. H. S. Shin, T. A. Bargiello, B. T. Clark, F. R. Jackson, M. W. Young, "An unusual coding sequence from a *Drosophila* clock is conserved in vertebrates," *Nature (London)* **317**, 445 (1985).

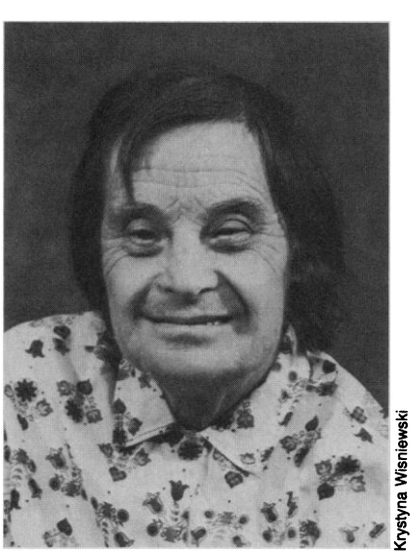
Down Syndrome–Alzheimer's Linked

Down syndrome adults get Alzheimer-like changes in their brains and many become demented, leading researchers to ask about the connection

Recent studies of people with Down syndrome and patients with Alzheimer's disease are revealing previously unexpected similarities between the two that may be important to the understanding of each of them. Adults with Down syndrome get a form of dementia that looks very much like Alzheimer's disease, and their brains, on autopsy, have Alzheimer-like lesions. And Down syndrome adults tend to get Alzheimer-type changes in their brains when they are still young—by age 30, the typical plaques and tangles are there.

These studies are possible because, gradually, over the past decade, a population of older Down syndrome patients has accumulated. People with Down syndrome used to die in childhood, but now, as a result of post-World War II antibiotic treatments, the switch to home care rather than institutional care, and heart surgery to correct the congenital defects that afflict 40 to 50 percent of Down syndrome babies, as many as 80 percent of these individuals are living to age 50 or more.

The relationship between Down syndrome and Alzheimer's disease tantalized neurologists. Why should these adults get Alzheimer's disease, and at such young ages? Is there something coded by the genes of the extra chromosome 21 inherited by Down syndrome patients that causes Alzheimer's disease? If so, could that substance be isolated and the seemingly inexorable development of Alzheimer's disease blocked? Within the past few years, several research groups have begun to systematically attack this problem by conducting the sort of longitudinal and morphological studies that are tedious but likely to provide answers. "It's 90 percent perspiration and only 10 percent inspiration," remarks Melvyn Ball, who directs the dementia study of the University of Western Ontario. The results, so far, are surprising.

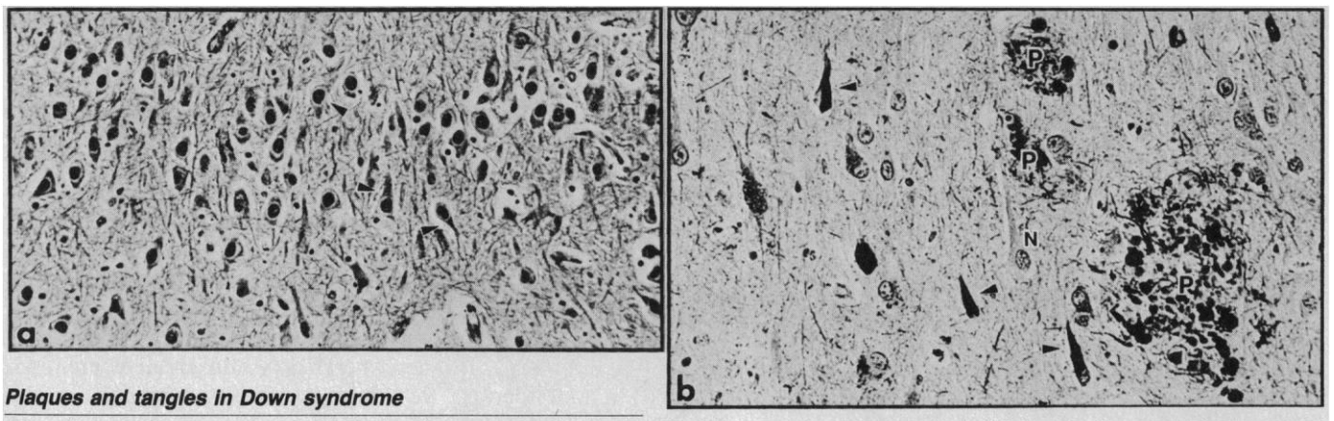


Krystyna Wisniewski

Down syndrome and Alzheimer's disease

A 55-year old woman who regressed from a 6- or 7-year old mental level to a state in which she cannot speak or comprehend language, is disoriented, and is incontinent.

At a meeting held in New York on 14 and 15 November sponsored by the National Down Syndrome Society, investigators reported that previous anecdotal statements that virtually all Down syndrome adults get Alzheimer's disease if they live long enough are not correct. It is true that all Down syndrome adults over age 30 get brain lesions that are typical of Alzheimer's disease. These are the neuritic plaques, the spherical areas in the gray matter of the brain in which nerve cell ends are degenerating, and neurofibrillary tangles, the strand-like clusters of filamentous protein in the body of nerve cells of the brain. But,



Plaques and tangles in Down syndrome

Virtually every Down syndrome adult who lives past age 30 develops brain lesions that are typical of Alzheimer's disease. Only a minority, however, become demented. On the left (a) is brain tissue from a normal adult. The neurons are marked with arrows. On the right (b) is brain tissue from an adult with Down syndrome. Neurons with neurofibrillary tangles are marked with arrows, plaques are marked with P's, and normal neurons are marked with N's. [Source: National Down Syndrome Society]

contrary to the conventional wisdom, only about 25 to 40 percent of Down syndrome adults actually become demented. Since there is a difference between being mentally retarded and being demented—demented persons lose their memories and lose the ability to care for themselves, for example—it is possible to document dementia in persons with Down syndrome.

Researchers differ on how to interpret these findings. Some, including Charles Epstein of the University of California in San Francisco conclude that "the pathology may be necessary but not sufficient for dementia." Others, including Stanley Rapoport of the National Institute of Aging suggest instead that there is a threshold effect. Rapoport proposes that a primary process causes the plaques and tangles and also causes dementia. The plaques and tangles, he says, may be a necessary and sufficient accompaniment of dementia, but there must be a critical number of them before a person actually is demented.

The resemblances between the brains of deceased Down syndrome individuals and those of Alzheimer's patients can be striking. Using techniques developed for the study of brains of Alzheimer patients, Ball found that the brains of Down syndrome adults are "every bit as severely afflicted." In both cases, the brain tissue contains extensive plaques and tangles—lesions that appear to be concentrated in the hippocampus the area of the brain that plays a selective role in learning and memory. Patients with a damaged hippocampus, "cannot put things together effectively," says Lynn Nadel, a psychologist at the University of Arizona. "They can learn to ride a bike, for example, but they will not remember where or when they learned to ride."

Ball's initial studies documenting plaques and tangles were of five Down syndrome adults aged 21 to 62 when they died. They had lived their lives in institutions, and their mental status was not well documented. It was believed, however, that they were not demented. Yet all had Alzheimer-type brain lesions. Their brains, in fact, were no different than those of several other Down syndrome adults who were demented. Ball says he also has examined the brains of several patients who were clinically diagnosed as having Alzheimer's disease yet who had no plaques and tangles.

On the other hand, Ball recently examined the brain of a 48-year-old man who had had Down syndrome and who had been demented for 3 years before he died. The lesions in the man's brain, says Ball, "were the most severe that I have ever seen." The man had a particularly pronounced loss of neurons in his hippocampus. Ball speculates that when a Down syndrome adult, who has fewer neurons than normal anyway, gets Alzheimer's disease, which is characterized by a loss of hippocampal neurons as well as plaques and tangles, the dementia can progress rapidly. This may be why Alzheimer's disease shows up in such young Down syndrome adults. But the relation of plaques and tangles to the dementia is not clear to Ball. "Some people are convinced that plaques and tangles are the explanation for the symptoms of Alzheimer's disease," he remarks. "Our group is not sure."

Krystyna Wisniewski, chief of the neuropathology laboratory at New York State's Institute for Basic Research in Developmental Disabilities on Staten Island, examined the brains of 100 Down syndrome adults who died in institutions for chronic care. Half of these individuals were over age 30 and half were younger when they died. Forty-nine of the older Down syndrome patients had plaques and tangles in their brains and seven of the younger individuals did. But only 15 of the Down syndrome patients had been demented.

Wisniewski's findings indicate that plaques and tangles may be more or less inevitable in older Down syndrome individuals, but dementia certainly is not. Wisniewski reports that she has examined 60- and 70-year-old Down syndrome adults whose minds "are crystal clear." Yet, she notes, there is a correlation in her study between the numbers of plaques and tangles and the likelihood that the person was demented. Like Rapoport, she postulates a threshold effect.

The best way to get at the question of the relation between Down syndrome and Alzheimer's disease is to do long-term prospective studies—to follow Down syndrome patients for years and record what happens to them clinically and psychologically. If what Down syndrome individuals develop actually is identical to Alzheimer's disease, examination at autopsy should provide new insight into Alzheimer's disease also.

Wisniewski is conducting a prospective study as are Rapoport and Mark Shapiro of the National Institute of Aging. So far, Shapiro and Rapoport are finding that Down syndrome individuals invariably experience declining mental abilities as they age. The investigators have studied 14 Down syndrome individuals who are younger than age 35 and six who are older than age 35. The younger adults did better on tests of attention, visual memory, and intelligence than did the older individuals. Yet only three of the six older subjects were demented.

These recent observations leave researchers with many questions and few answers. However, studies of the parallels between Down syndrome and Alzheimer's disease are clearly opening new doors.—GINA KOLATA