A Common Medical Denominator

Specific neuropathological changes shared by Alzheimer's disease and Down's syndrome are helping scientists to understand both enigmatic disorders — and to hope for new, improved treatments

By DIANE D. EDWARDS

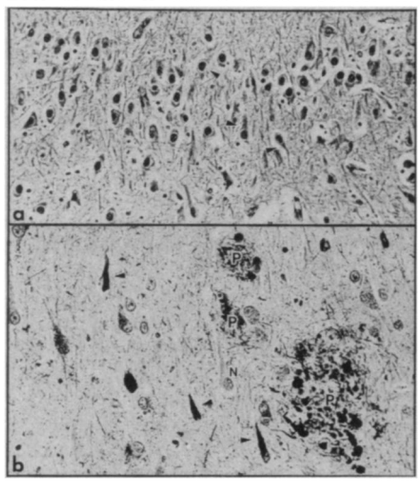
In one, mental maturity never comes. In the other, it disappears. One is a birth defect, the other primarily a disease of old age. On the surface, Down's syndrome with its mental retardation and Alzheimer's disease with its mental regression appear to be linked only by the personal tragedies they create. But scientists have found connections between the two that may lead to more complete understanding and even treatment of both.

A degenerative disease of the central nervous system, Alzheimer's disease — more formally known as senile dementia of the Alzheimer type — is destroying the memory and physical health of an estimated 2 million adults over age 65 in the United States. Down's syndrome, or trisomy 21, is a chromosomal anomaly leading to lower-than-normal mental ability, increased susceptibility to infections and higher incidence of leukemia, as well as to characteristic slanted eyes and skeletal abnormalities. The most common birth defect associated with mental retardation, Down's syndrome occurs in about 1 out of 1,000 live births. Like individuals with Alzheimer's, the more than 250,000 Down's patients in the United States require extra care either from their families or from health professionals.

Medical and technological advances in the last decade have changed the face of both diseases: Improved prenatal care has steadily lowered the incidence of Down's syndrome, and heightened medical surveillance has increased the number of Alzheimer's patients diagnosed. Better medical practices, by raising the life expectancy of Down's patients from 9 years (in 1910) to 50 years, also have magnified the curious common denominator shared by Down's and Alzheimer's: Almost all Down's patients who live beyond age 35 develop the neuropathological characteristics of Alzheimer's, and some show signs of dementia.

As early as the 1920s, the neuropathological characteristics — particularly nerve cell loss and the appearance of abnormal cell lesions called neurofibrillary tangles and neuritic plaques — were observed in the brains of Down's individuals over 35 years of age. But recent advances in fields like neurochemistry and genetics have revitalized scientific interest in the shared pathology. That interest brought together an international group of experts at a recent two-day symposium in New York City organized by the New York-based National Down Syndrome Society.

"Down's syndrome may indeed make a model disease in studying ... neurological disintegration in Alzheimer's," Ira Lott of the Irvine Medical Center in Orange, Calif., said during opening comments at the symposium. "It appears the neuropathology of [individual] lesions in Down's is virtually identical to the lesions in Alzheimer's. One of the major [research] challenges is to try to relate the mental retardation of Down's ... and senile dementia to the anatomy of the brain."



Inst. for Basic Research in Developmental Disabilities

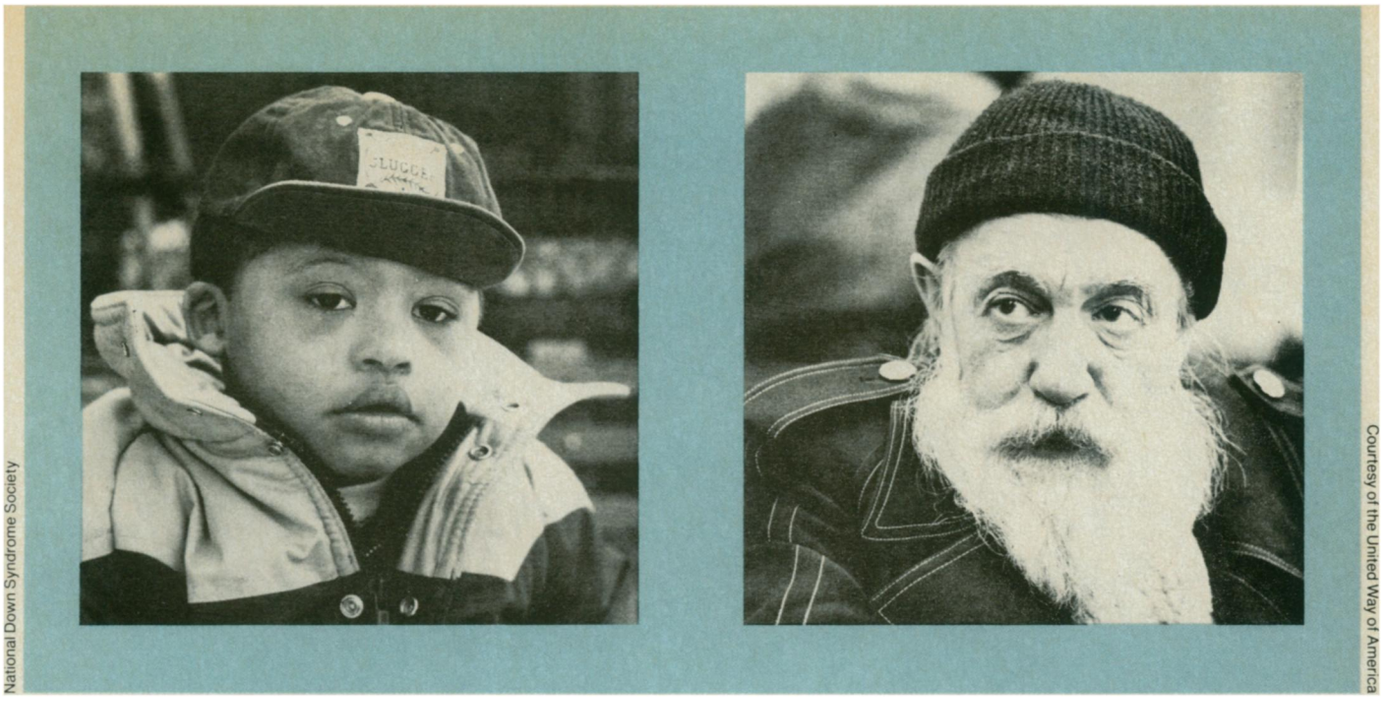
Normal adult human brain tissue (a) contains neurons (arrows) of normal shape and distribution. But tissue from a Down's syndrome adult (b) contains neurofibrillary tangles (arrows) and plaques (P), as well as normal neurons (N). Such tangles and plaques are the most prominent neuropathological signs found in the brains of individuals with Alzheimer's disease.

In addition to the anatomical abnormalities, both Alzheimer's and Down's involve functional and neurochemical abnormalities of the brain; symposium participants pointed out that similarities between the two are being found in all three areas. Still, the strongest laboratory evidence thus far linking Alzheimer's and Down's appears to be rooted in the decades-old study of brain anatomy using brain tissue sections and the microscope.

The central nervous system is built of hundreds of billions of nerve cells (neurons) with long processes that intertwine and meet at synapses to relay neurochemical messages, with the brain acting as control center. Neuroanatomist Krystyna Wisniewski, of New York's Institute for Basic Research in Developmental Disabilities on Staten Island, looked for structural aberrations in postmortem brains from more than 80 Down's patients, who ranged in age from 1 day to 12 years at time of death. She found that about 20 percent had only half the number of neurons present in age-matched controls, and the remaining Down's brains had 20 to 30 percent fewer neurons than did controls. This "tremendous decrease," she says, is found primarily in the second and fourth layers of the cortex and in the hippocampus. Neuronal "dropout" in these areas has also been reported by scientists studying Alzheimer's disease.

The Staten Island group is currently expanding an earlier study showing that Down's patients have 30 percent fewer synapses at age 18 than do controls, and that those synaptic contacts have 20 to 35 percent less surface area. According to Wisniewski, the "most consistent abnormality" seen in Down's brains is this shortened synapse, which she says may lead to fewer nerve impulses transmitted and to impaired memory — another sign of Alzheimer's.

Because autopsy rates in the United States have dropped to 14 percent of all deaths, comparative studies of brain anatomy in Alzheimer's and Down's are difficult. Therefore, few com-



National Down Syndrome Society

Courtesy of the United Way of America

prehensive examinations have been made of the microscopic changes in either disorder, or of Alzheimer-like changes in older Down's patients.

One such study is under way at the University of Western Ontario in London, where Melvyn J. Ball is following 400 Down's patients, studying their brain anatomy, neurochemistry and family histories. When he has permission to perform autopsies, Ball also searches for the microscopic signs of aging: plaques formed by clusters of deteriorating nerve endings, neurofibrillary tangles of "sick neurons" with decreased metabolism, and holes (vacuoles) in neurons. All of these occur in normal aging, but brains of Alzheimer's patients show up to 100 times as many vacuolated cells and 6 to 40 times as many tangles as are found in normal aged brains. The brain of a normal elderly person contains an average of 4 tangles per cubic millimeter (mm^3), the average Alzheimer's brain contains 90 tangles/mm^3, and the average Down's brain contains 53 tangles/mm^3. Both vacuole and tangle formation show a predilection for the hippocampus in Alzheimer's and Down's, according to Ball.

The total number of neurons also is significant, says Ball, who found that brains from Alzheimer's and Down's patients had lost 5 times as many neurons as had normal brain tissue. "The picture is so close," he says, "that physiologically [changes in Alzheimer's and Down's brains] mean the same thing." Though far from definitive, recent research suggests that certain biochemical changes may "mean the same thing" as well. Abnormal ratios of various fatty acids in the brains of Down's patients, which may lead to problems in signal transduction between nerve cells, suggest similarities to aging brains, according to a study by Robert Balazs of England's Institute of Neurology in London.

Another neurobiological aspect of the Alzheimer's/Down's question is that of those chemicals responsible for cell-to-cell message delivery, the neurotransmitters. Several studies reported at the New York symposium, as well as one in the Dec. 14 LANCET, found that levels of biochemical indicators of neurotransmitter function are greatly decreased in both Alzheimer's patients and older Down's patients. There are parallel deficits in the enzyme choline acetyltransferase, responsible for cholinergic neurotransmitter formation, and in the transmitters norepinephrine and 5-hydroxytryptamine. Deficiencies in the cholinergic neurotransmitter system have been documented in Alzheimer's disease (SN: 10/6/84, p. 221), and work like that of Joseph Coyle at Johns Hopkins Medical Institution in Baltimore strongly suggests similar problems exist in Down's syndrome. Coyle found, for example, that levels of choline acetyltransferase in patients with Down's syndrome were 50 to 90 percent below those in normal controls.

Using a custom-built, genetically engineered mouse model of Down's syndrome (SN: 10/13/84, p. 237), Coyle and other scientists have noticed an "intriguing" initial upsurge in neurotransmitter levels in the young mice, followed by regression. Perhaps, Coyle speculates, young Down's patients have a similar up-and-down pattern of nerve activity. Another hypothesis, according to Stanley Rapoport of the National Institute of Aging in Bethesda, Md., is that neuritic plaque formation may be a result of over-compensation to replace degenerating nerves through accelerated nerve growth.

Nerve growth, neurotransmitter expression and synapse formation are regulated at least in part by so-called trophic factors. These factors, which stimulate physiological responses, include the protein nerve growth factor. Concentrating on the human cholinergic system, James McManaman of Baylor College of Medicine in Houston found that trophic-factor-containing extracts from muscle and the hippocampus stimulated growth of processes and acetylcholine production in spinal cord tissue cultures. The November 1985 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES reported similar results from a team at New York City's Cornell University Medical College using cultures of fetal rat brain tissue.

"Right now it's only speculation," McManaman says, "but the evidence is good that trophic factors may be involved in both Alzheimer's and Down's syndrome. . . . The likely explanation is there's too much trophic factor."

Nerve growth factor's role in Down's and Alzheimer's is unclear, but the Baylor and Cornell studies suggest it affects both fetal brain development (disturbed in Down's) and maintenance of healthy adult brain function (lost in Alzheimer's). Research is continuing on other biochemical networks in the brain, such as neural cell adhesion and electrolyte transport across membranes.

At the center of the abnormalities common to Alzheimer's and Down's is the hippocampus. Part of the system that influences hormonal secretion and involuntary muscle activities, as well as motiva-

Courtesy of the United Way of America

National Down Syndrome Society

tional and mood states, this area of the brain apparently fares the worst in both Alzheimer's and Down's, according to several researchers attending the symposium.

Why should problems in this area lead to either mental retardation or regression? "The consensus view," says psychology professor Lynn Nadel of the University of Arizona in Tucson, "is that the hippocampus receives [messages] from all over the brain and acts to link them together to rapidly form a sort of template [that stores and disseminates the information] . . . a kind of index to the records across the neocortex [an area of the cortex unique to mammals]."

Although Down's patients handle some cognitive tasks better than do other mentally handicapped individuals, they, like Alzheimer's victims, have difficulty in abstract thinking, certain types of memory and tasks involving spatial perception. In earlier work Nadel found that rats had difficulty in mazes when electrodes were used to disturb areas of the hippocampus.

Despite this growing knowledge of the aberrant neurology in Alzheimer's and Down's, there are caveats attached to any interpretation. First, as Ball points out, it isn't proved that the observable pathology accounts for the disorders. Nor is it clear that many older Down's patients actually develop the debilitating clinical dementia; it has been difficult to assess demented behavior in mentally handicapped individuals. Estimates of older Down's patients with dementia range from 15 percent to 100 percent, says Wisniewski, who is now working with other scientists to improve the detection of Alzheimer's in Down's patients.

The etiology of Alzheimer's remains equally obscure. Various scientists believe it may be caused by infection from a slow virus, toxic agents, autoimmunity or genetic factors (one study found relatives of Alzheimer's patients more likely to have children with Down's).

But the multidisciplinary assortment of data presented at the symposium piques interest in two treatment-related concepts: "plasticity" and "intervention." In the Dec. 6 SCIENCE, Lott and his coworkers conclude, after comparing regenerative responses in Alzheimer's brains and in hippocampus-damaged rats, that "the central nervous system is capable of a plastic response in Alzheimer's disease [through axon budding and increased neurotransmitter receptor distribution]." If such activity were ever harnessed therapeutically, suggest scientists, perhaps the use of trophic factors, brain tissue grafts, cellular adhesion factors and selective elimination of defective neurons could also offer relief from symptoms.

Even more compelling to Nadel, Lott and others is the potential for intervention in Down's syndrome. "The decline in IQ [seen in Down's patients between 15 and 41 years of age] is not necessarily inevitable," says Lott. "When it occurs, it may in fact be due to a pathological abnormality such as Alzheimer's." The same research findings that may give hope in Alzheimer's, he says, could lead to less retardation in Down's patients, who "lack functional plasticity" in their response to a changing environment. Creating a stimulating environment is essential, according to Lott, who is currently studying stimulated and nonstimulated Down's patients. "The implication for infant stimulation is enormous," he says. "We now see [after an eight-year study] that stimulated patients are less severely retarded." Controls in his study were Down's patients raised at home with regular care but without any special efforts to stimulate them.

Emerging evidence suggests that such stimulation should begin at birth. Although controversial, interpretation of data from several research groups could mean that the brain's "wiring" is improved in stimulated Down's patients through increased cortical thickness and synaptic density.

Whatever the final conclusions made regarding Alzheimer's and Down's, their shared pathology should make fitting all the pieces together less puzzling. □