

Epidemiology of Alzheimer Disease in Mental Retardation

Results and Recommendations from an
International Conference

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Report of the AAMR-IASSID Workgroup on
Epidemiology and Alzheimer Disease

For Additional Copies or Comments Contact
American Association on Mental Retardation
ATTN: Alzheimer Disease Workgroup
444 North Capitol Street
Suite 846
Washington, DC 20001-1512

_ 1-202-387-1968
FAX 1-202-387-2193

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Diagnosis of Dementia in Individuals with Intellectual Disability

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Author's Affiliations:

Warren Zigman, Ph.D. (New York State Institute for Basic Research in Developmental Disabilities, Staten Island, NY, USA), Nicole Schupf, Ph.D., Dr.P.H. (New York State Institute for Basic Research in Developmental Disabilities, Staten Island, NY, USA), Meindert Haveman, Ph.D. (University of Limburg, Maastricht, The Netherlands), Wayne Silverman, Ph.D. (New York State Institute for Basic Research in Developmental Disabilities, Staten Island, NY, USA)

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Epidemiology of Alzheimer Disease in Mental Retardation

Results and Recommendations from an International Conference

*Warren Zigman, Ph.D., Nicole Schupf, Ph.D., Dr.P.H., Meindert Haveman, Ph.D.,
Wayne Silverman, Ph.D.*

Advisory Group: Deborah Anderson, Ph.D., Maureen Babula,
Richard Collacott, D.M., Ph.D., Sally-Ann Cooper, MRCPsych, Todd Gerber, M.S.P.H.,
Florence Lai, M.D., Vee Prasher, MRCPsych, MD, April Zigman, Ph.D.¹

Abstract: The elderly represent one of the fastest growing segments of society, resulting in a concomitant increase in the prevalence of age-associated diseases. One such condition is Alzheimer disease, the most common cause of old-age associated dementia. Among adults with mental retardation, virtually everyone with Down syndrome over the age of 40 has neuropathology currently viewed to be consistent with a diagnosis of Alzheimer disease, while other adults with mental retardation without Down syndrome display an increased prevalence of Alzheimer-type neuropathology after they reach age 65. This report considers the discussions and recommendations of an epidemiology workgroup, formed at an international conference convened to discuss Alzheimer disease among people with mental retardation, concerning: (a) the incidence and prevalence of clinical dementia in adults with mental retardation; (b) risk factors for the development of Alzheimer disease in adults with mental retardation; and (c) a minimum data set that would be of great utility for future research on Alzheimer disease in adults with mental retardation.

The elderly population is currently one of the fastest growing segments of society. Comparable increases in the elderly population of individuals with mental retardation and other develop-mental disabilities have been noted, with an estimated population of 173,000 adults with developmental disabilities age 60 and older now living in the United States. This group is estimated to reach 332,900 by the year 2025 (Rehabilitation Research and Training Center on Aging with Mental Retardation, The University of Illinois at Chicago, 1995).

With the dramatic increase in the population of adults over the age of 65, there has been a concomitant increase in the prevalence of age-associated diseases. One such condition is Alzheimer disease, the most common cause of old-age associated dementia (Katzman, 1981). Current projections indicate that by the turn of the century an estimated 10

million Americans will have Alzheimer disease (Evans, 1990).

Diagnosis of Alzheimer disease requires both the presence of a progressive dementia (a deterioration of cognitive, physical, and adaptive status), and a characteristic pattern of neuropathology. The neuropathological characteristics of Alzheimer disease are defined by the presence of two classes of microscopic lesions, beta-amyloid plaques and neurofibrillary tangles.

Virtually all adults with Down syndrome over the age of 40 have neuropathology consistent with a diagnosis of Alzheimer disease (Ball & Nuttall, 1980; Burger & Vogel, 1973; Ellis, McCulloch & Corley, 1974; Fraser & Mitchell, 1876; Jervis, 1948; Malamud, 1972; Ropper & Williams, 1980; Solitaire & LaMarche, 1966; Struwe, 1929). Adults with mental retardation without Down

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For workgroup member affiliations see page 12.

syndrome display an increased prevalence of Alzheimer-type neuropathology after age 65 (Barcikowska et al., 1989; Popovitch et al., 1990).

The extent to which individuals with mental retardation and other developmental disabilities are at increased risk of developing the clinical dementia associated with Alzheimer disease is less clear. Findings from numerous studies have suggested that a substantial proportion of aging adults with Down syndrome (i.e., those over age 40) develop clinical, as well as neuropathological, signs of dementia (e.g., Dalton & Crapper, 1977; Evenhuis, 1990; Hewitt, Carter & Jancar, 1985; Lai & Williams, 1989; Olson & Shaw, 1969; Schupf, Silverman, Sterling & Zigman, 1989; Thase, Tigner, Smeltzer & Liss, 1984; Wisniewski, Wisniewski & Wen, 1985; Zigman, Schupf, Lubin & Silverman, 1987). However, these estimates of clinical dementia are clearly lower than estimates of the prevalence of neuropathological signs of Alzheimer disease (Zigman, Schupf, Sersen & Silverman, in press). Only a few studies have provided prevalence estimates of clinical signs and symptoms of dementia of the Alzheimer-type for adults with mental retardation without Down syndrome (e.g., Haveman, Maaskant & Sturmans, 1989). Here also, estimated prevalence of dementia appears to be lower than predicted based upon neuropathological studies.

An international conference on Alzheimer disease in people with mental retardation was convened in July, 1994 in order to develop consensus reports regarding three major issues. The aims of the conference included development of international consistency regarding: (a) diagnostic criteria for Alzheimer disease in people with mental retardation; (b) incidence and prevalence estimates, risk factors for Alzheimer disease in this unique population, and a minimum data set to be

incorporated into future relevant research; and (c) the development of practice guidelines for adults with mental retardation with Alzheimer disease. Approximately 60 scientists, practitioners and clinicians from North America and Europe convened in one of three workgroups for a three day period to reach preliminary consensus on these issues. Continuation meetings over the following year have led to the development of three reports, each of which focused on one of the conference's major aims.

The mandate of the epidemiology workgroup was to review incidence and prevalence rates for Alzheimer disease in people with mental retardation, to generate a list of risk factors for Alzheimer disease in adults with mental retardation, and to develop recommendations regarding study designs and a minimum core data set that should be included in future research on Alzheimer disease in adults with mental retardation. This report presents the results of discussions of the epidemiology workgroup.

Incidence and Prevalence

Incidence is defined as the number of new cases of a disease or disorder in a specified population over a defined time period. Thus, incidence rate reflects most accurately the probability that healthy people will develop a disease. There were too few studies with samples sizes sufficient to estimate valid or reliable incidence rates, and therefore none will be presented here.

Prevalence is defined as the number of existing cases in a population at a given time. Prevalence depends on both the number of people who have developed the disease and the duration of their illness. If the disease is chronic, then prevalence will be greater than incidence. Thus, a prevalence rate reflects

most accurately the burden of disease in the population and is useful for estimating the need for medical care and other health related services.

The *Table* on page 4 presents the results of a number of studies of the prevalence of dementia of the Alzheimer-type (hereafter called Alzheimer-dementia) among adults with Down syndrome (Burt, Loveland & Lewis, 1992; Cole, Neal, Fraser & Cowie, 1994; Dalton & Crapper-McLachlan, 1984; Evenhuis, 1990; Francheschi, Comola, Piattoni, Gualandri & Canal, 1990; Haveman et al., 1989; Hewitt et al., 1985; Lai & Williams, 1989; Prasher, 1995; Ropper & Williams, 1980; Schupf et al., 1989; Thase, Liss, Smeltzer & Maloon, 1982; Wisniewski et al., 1985; Zigman et al., in press). The *Figure* on page 5 presents the results of several studies to demonstrate the clear age-related patterns of change.

An examination of the *Table* and the *Figure* demonstrates that estimates of overall and age-specific prevalence rates of Alzheimer-dementia in adults with Down syndrome vary widely across different studies, even among those employing population-based sampling (e.g., Haveman et al., 1989; Prasher, 1995; Sil verstein et al., 1988; Zigman et al., 1987; Zigman, Schupf, Silverman & Sterling, 1989). Possible causes of the variability in prevalence estimates include different sampling techniques and subject populations, different assessment instruments and different diagnostic criteria. Nevertheless, the age-specific prevalence rate of Alzheimer-type dementia in adults with Down syndrome, even at the oldest ages, is consistently found to be less than 100% (Prasher, 1995; Prasher & Krishnan, 1993; Zigman et al., in press). Clearly, the relationship between Alzheimer-type neuropathology and observed dementia is not straightforward in adults with Down

syndrome, and other factors that influence risk or modify age of onset of dementia need to be identified.

Recent neuropathological research (Wisniewski & Silverman, in press; Wisniewski, Weigel & Popovitch, 1995) reinforces this interpretation of the findings. Detailed analyses of beta-amyloid plaques (the hallmark neuropathological lesion of Alzheimer disease that is most predominant in Down syndrome cases) suggests that there are two qualitatively distinct forms of these lesions. First, there is a benign nonfibrillar form that does not appear to interfere significantly with brain function. These are the plaques that are typically seen in large numbers in the brains of adults with Down syndrome 30 through 50 years of age (and sometimes older) who do not show signs of decline in functioning. Second, there are plaques that contain fibrils, and these fibrillized plaques are associated with both damage to neurons and clinical expression of Alzheimer dementia. There may, however, be older individuals with Down syndrome with fibrillized plaques who do not display dementia, and therefore further detailed neuropathological studies must determine the multiple factors determining vulnerability subsequent to the onset of Alzheimer neuropathological changes.

Few studies could be found that have attempted to estimate the incidence or prevalence of Alzheimer disease among individuals with mental retardation without Down syndrome. One study (Haveman et al., 1989), found a significant age-related increase in dementia in adults with mental retardation without Down syndrome, although the observed rates were very low (e.g., < 10% of the adults over age 60 were diagnosed as having dementia). These low rates could be due to the fact that reports of dementia in adults with mental retardation without Down

syndrome tend to focus on groups of people matched in age to samples of adults with Down syndrome. Adults with Down syndrome have higher age-specific mortality rates than their peers without Down syndrome (Thase, 1982), and few survive past age 65. Therefore, these samples will not be representative of the more general population of older adults with mental retardation because the samples will tend to be younger than the age at which risk for Alzheimer disease increases (i.e., above age 65, Popovitch et al., 1990). Prevalence estimates are likely to increase when samples of adults over 70-75 years of age are explicitly examined.

Duration and Age-at-Onset of Dementia

Measurement of duration and age-at-onset of Alzheimer disease depends on clear criteria for disease onset. Unfortunately, it is not yet possible to diagnose Alzheimer disease at an early stage with a biological marker, and case identification has to be based on signs and symptoms of the disease. The lifelong cognitive and adaptive impairments of adults with mental retardation make clinical symptoms of dementia extremely difficult to detect, especially in people with severe and profound levels of mental retardation. No consistent diagnostic methods or criteria are yet established for diagnosing early Alzheimer disease in adults with mental retardation. Therefore, recognition and diagnosis of Alzheimer disease is often made only at late or final stages of the disease process, and of course, as in the nonretarded population, a definite diagnosis of Alzheimer disease requires post-mortem confirmation.

Despite these limitations several studies have attempted to review findings on age at onset and duration of Alzheimer disease in adults with Down syndrome. Mean age at

onset across a series of over 20 studies reviewed by Prasher and Krishnan (1993) was established to be 51.7 years (range of from 31 to 68 years). Estimates of duration of disease in people with Down syndrome have been reviewed by Dalton and Wisniewski (1990), and varied from 3.5 to 10.5 years from recognition of initial symptoms until death. Lai (1992) reported a mean duration of approximately five years, and Prasher and Krishnan (1993) reported a mean duration of 6 years. These estimates are considerably shorter than the 2 - 20 years estimated for Alzheimer disease in the general population (U.S. Department of Health & Human Services, 1984), suggesting that the disease may have a more aggressive course in people with Down syndrome, or, more likely, that the disease is being detected at a later stage. It is clear that onset of dementia of the Alzheimer type is insidious, and the subtle early symptoms can last as long as seven years (Reisberg et al., 1989); these subtle symptoms may go unrecognized in people with mental retardation.

Because there is still no effective treatment for Alzheimer disease, it must be emphasized that a false positive diagnostic decision could be more harmful for the individual and his or her relatives than a false negative. A diagnosis of Alzheimer disease may inhibit treatment of symptoms displayed by the individual. Many systemic conditions may cause symptoms that mimic dementia when not treated (e.g., hypothyroidism, infections, hypercalcemia), and it is necessary both to rule out alternative conditions and to aggressively treat any observed symptoms before a presumptive diagnosis of Alzheimer disease is made. As in the population of people without mental retardation, the diagnosis of Alzheimer disease should be based on a process of systematically excluding other possible causes of symptoms.

Risk Factors

Increasing age, a positive family history of Alzheimer disease, low educational level, history of head trauma and cardiovascular disease have been identified as risk factors for Alzheimer disease in the general population (Van Duijn, Stijnen & Hofman, 1991). While the findings are controversial, it has been suggested that exposure to aluminum increases risk of Alzheimer disease (Flaten, 1990; Forbes, Hayward & Agwani, 1991; Martyn et al., 1989). Use of nonsteroidal anti-inflammatory medications and estrogen replacement therapy have been suggested to be protective against the development of Alzheimer disease (Breitner et al., 1994; Brenner et al., 1994; Henderson, Paganini-Hill, Emanuel, Dunn & Buckwalter, 1994; Paganini-Hill & Henderson, 1994; Rich et al., 1995).

Among persons with mental retardation, the only risk factors that have been identified are age and Down syndrome, although Popovitch et al. (1990) presented some preliminary indication that a history of head trauma may also increase risk. Persons with mental retardation are more likely to have chromosomal abnormalities, neurological deficits, and genetic metabolic disorders compared with persons in the general population (Durkin, Schupf, Stein & Susser, 1994). Therefore, both the type and the distribution of risk factors may be different from those in the general population. For example, the presence of psychiatric and behavioral disorders, as well as the use of psychoactive medications, especially neuroleptics, have not been explored as potential risk factors for dementia in people with mental retardation, despite the well documented increase in the prevalence of psychiatric conditions in this population and the high rate of psychoactive medications

usage (Collacott, Cooper & McGrother, 1992; Day & Jancar, 1994). Investigation of the epidemiology of Alzheimer disease will need to take into account the special biology of this population when developing case-definitions and investigating risk factors.

Recommendations of the Conference for Epidemiologic Studies

The conference provided a forum for considering: (a) what study groups of interest need to be assembled on the basis of categorical or risk characteristics; (b) how diagnostic criteria might be operationalized; (c) which study designs would be most appropriate for furthering our current state of knowledge; (d) which risk factors might be important for adults with mental retardation; and (e) the basis of a minimum data set for future research. These will be discussed in turn.

Study Populations

Given the recent findings of an increased prevalence of Alzheimer-type neuropathology in adults with mental retardation *without* Down syndrome, it will be important to identify risk factors in addition to chronological age and Down syndrome etiology. While age at onset is later than that seen in adults with Down syndrome, Alzheimer disease will be a significant concern for all older populations with mental retardation. Because adults with mental retardation without Down syndrome will outnumber by far adults with Down syndrome, this finding has significant planning implications. We suggest that studies of incidence and prevalence should include individuals with mental retardation due to all etiologies, as well as people with other developmental disabilities (e.g., autism,

cerebral palsy, epilepsy, and neurological impairment).

When the cause of mental retardation is unknown, vigorous efforts should be undertaken to identify underlying etiological or categorical disability. Diagnosis should be specified by ICD-10 (World Health Organization, 1992) codes whenever possible. Criteria for categorical diagnosis should be described objectively, and preferably with reference to current standard diagnostic criteria (e.g., as described by the American Association on Mental Retardation and/or the International Association for the Scientific Study of Intellectual Disability). It should be noted that even with vigorous diagnostic efforts, fully 30% to 50% of people with mental retardation will remain without an etiological diagnosis.

Case Definition

Detailed discussion of guidelines for case definition is reported elsewhere (Aylward, Burt, Thorpe, Lai & Dalton, 1995). Rather than duplicate this information here, we will only review a number of suggestions regarding the dimensions which need to be measured within any case classification system.

As mentioned earlier, Alzheimer disease currently is always a diagnosis of exclusion. Therefore, all alternative possible causes of age-associated deterioration must be eliminated before arriving at a diagnosis of dementia of the Alzheimer type. Initially, a physical assessment should be conducted to determine whether there are any specific medical explanations for the symptoms that suggest the presence of Alzheimer disease. Subsequently, an assessment of cognition, adaptive functioning, and neurological and psychiatric status should be undertaken. The comprehensive evaluation should include

complete and standardized diagnostic assessments by neurologists, neuropsychologists, psychiatrists, and behavioral specialists and/or psychologists.

The neurological examination should include: (a) the development of a complete medical history and an indication of current medical status, (b) a standard neurological exam, and (c) the administration of a mental status examination.

At least two neuropsychological evaluations should be administered (i.e., at 6-18 month intervals) to determine whether there is a progressive decline in status. If objective historical data can be obtained, there should be an examination of the amount of decline from premorbid levels of global intelligence, and specific cognitive functions such as attention, information processing skills, memory, language fluency and construction ability. Behavioral assessment should include measurement of functional abilities through the use of standard adaptive behavior scales. Standard conditions for behavioral assessment should be specified and selected methods should be valid, reliable, sensitive to changes in functioning, and appropriate for use with elderly people at specific premorbid levels of intellectual impairment (ranging from mild to profound levels of mental retardation). One such instrument that has shown promise in the measurement of Alzheimer disease in adults with mental retardation is the American Association on Mental Retardation Adaptive Behavior Scale, (Nihira, Foster, Shellhaas & Leland, 1974), which has been used successfully in research conducted by Miniszek (1983) and Prasher, Krishnan, Clarke and Corbett (1994).

The psychiatric evaluation should include documentation of: (a) past and present medical and psychiatric history (to rule out any disorder with symptoms that could mimic dementia due to Alzheimer disease), (b) history of dete

rioration, and (c) routine psychiatric symptoms (to rule out major depression). Also, the use of neuroleptics and other psychoactive medications should be catalogued.

For adults with mental retardation, many conditions can present atypically, especially in people with severely limited communication skills. Therefore, any conditions with symptoms that could be associated, even remotely, with dementia should be vigorously treated before a diagnosis of Alzheimer disease is made (e.g., hypothyroidism, depression, or even urinary tract or gastro-intestinal disturbances). This will lead to conservative estimates of incidence and prevalence. However, given the uncertain precision of current diagnostic methods, these may be the best estimates that currently can be obtained.

Because of the potential for differences in age-specific incidence and prevalence among people with different biological constitutions and/or different historical patterns of treatment (e.g., different residential environments), it is important that estimates of incidence and prevalence now be stratified by level of mental retardation, environmental factors such as placement history, and gender (see Prasher and Krishnan, 1993).

Study designs

Much of the current epidemiologic research on Alzheimer disease in adults with mental retardation is descriptive in nature, cross-sectional in design, and uses samples of convenience for ease of investigation. In investigations of aging processes, results from cross-sectional research designs, which are subject to confounds associated with cohort and healthy survivor effects, are especially difficult to interpret.

Cohort effects can be associated with the different life experiences and exposures of individuals who reach specific ages at different historical points in time, when different treatment practices and policies may have been in place. Thus, someone who currently is 60 years of age will have had different life experiences and exposures when they were 20, compared with an individual who currently is 20 years of age. Healthy survivor effects can be associated with the fact that individuals who survive to be assessed in various studies of aging are likely to be healthier as a group than those who died at earlier ages. Therefore, observed data can be biased toward underestimating the incidence and prevalence of health related problems in the entire population.

Three major study designs are used in epidemiological studies of Alzheimer disease. *Case-control studies* utilize analyses of retrospective data to compare people with Alzheimer disease (i.e. cases) to people without Alzheimer disease (i.e., controls) in order to determine whether the two groups differ with respect to an exposure to one or more risk factors (i.e., possible factors related to an increased incidence of the condition). For example, in order to determine the effects of a history of head trauma on the development of Alzheimer disease, the backgrounds of two groups of adults who are similar in all characteristics except the diagnosis of Alzheimer disease would be studied to determine the relative prevalence, in the two groups, of a positive history of head trauma. If there were statistically significant differences between the two groups in such history, then there would be evidence suggesting that head trauma is a risk factor for Alzheimer disease. It is important to use newly diagnosed incident cases in these studies to avoid spurious associations with factors associated with survival rather than with etiology.

Prospective studies examine two or more groups of individuals who are free of Alzheimer disease at the start of the research project but who vary with respect to risk factors for the condition. These people are followed longitudinally in order to determine whether incidence rates differ as a function of the presence or absence of the risk factor. Using the previous example, the groups chosen for study would be selected based upon whether they displayed a history of head trauma.

In *historical cohort studies*, groups to be compared are assembled on the basis of earlier (historical) risk factor status and examined for current Alzheimer disease status. Historical cohort studies, by utilizing data collected prospectively for other than the current research purpose, can allow the analysis of large multivariate data sets with few of the costs associated with large scale prospective studies. For example, Zigman et al. (in press) were able to analyze prospectively collected data on 18,716 people with mental retardation with and without Down syndrome, and were able to document that individuals with Down syndrome over 50 years of age were more likely to be subject to significant regression in adaptive functioning than were subjects with other forms of mental retardation, without having to collect any primary data.

Because true longitudinal research is not a practical option for assessing development across the lifespan, cross-sequential designs seem best suited for studies focusing on age-associated changes in the characteristics of adults with mental retardation. Cross-sequential studies, which follow longitudinally cohorts varying in age (which can, for example, bridge the entire lifespan) can investigate individual age-related changes over a manageable time interval thereby allowing examination of age-related

differences in the dependent variable(s) of interest. It is imperative that these studies employ population-based sampling (i.e., random samples drawn from the entire population of individuals of interest) to allow for estimation of population rates as well as generalization of results, and that analyses of cohort effects be included. Without population based sampling, severe biases can be introduced inadvertently into study results (Rothman, 1986).

Risk Factors

There are a number of risk factors for Alzheimer disease in the population of adults who are not mentally retarded that should also be investigated within the population of adults with developmental disabilities. Prior head injury, prevalent among adults with mental retardation, has been found to be a risk factor for Alzheimer disease (Roberts et al., 1994), and should be examined as a risk factor for adults with mental retardation (a history of head banging may be included in this category). Other risk factors might include a family history of Alzheimer disease (Van Duijn et al., 1991), level of mental retardation as an analogue for level of education (Stern et al., 1994), gender, age, residential situation, and seizure history.

More speculative risk factors that could be investigated include: maternal characteristics (e.g., mother's age at proband's birth, mother's age at menopause); autoimmune status; aluminum exposure; biomarkers (e.g., APOE-É4 (Strittmatter et al., 1993); smoking history; thyroid status, medication and polypharmacy history, psychiatric history (e.g., depression and other psychiatric conditions) and cardiovascular disease. Given the brisk pace of new research in this area, it would be valuable to bank blood for investigations of genetic or biomarker tests that will be developed in coming years.

Elements of a Minimum Data Set

The goals of utilizing a core minimum data set uniformly across research projects are: (1) to standardize collection of key data elements; (2) to permit comparison of rates and risk factors between studies; and (3) to make available an archive of key functional and biological data for future analyses and meta- analyses. In the case of studies focusing on Alzheimer disease, the elements can be classified roughly as *Demographic Information*, *Diagnostic Criteria*, and *Medical Information*. Some of these core information elements may be part of routine data collected at residential and other treatment facilities or as part of annual medical and psychiatric evaluations. Information to be included needs to be determined with both relevance and practicality of data collection in mind. Thus, results of neuro-imaging studies, while highly desirable, were not included because their costs in large scale population-based studies would be prohibitive.

Demographic Information

Subject demographics to be included within the core data set should be: (a) age (full date of birth), (b) sex, (c) level of mental retardation following current ICD-10 criteria (i.e., measuring through a combination of intellectual and adaptive functioning - mild, moderate, severe, profound), (d) other disabilities, (e) ethnicity, (f) residential placement, and (g) occupation or occupational activity. Additional information should indicate: (a) etiological and categorical diagnosis (whenever possible), (b) height and weight, (c) sensory status (i.e., current and past hearing and vision level), (d) general physical condition, and (e) major life events over the previous 10 years. These events would include, but not be limited to, the death of a parent or significant other, major residential transfer, or a major illness. Information regarding who is the source of the

data also should be collected, including, of course, when the data was collected, as well as the informants: (a) age, (b) sex, (c) job title, (d) relationship to subject, (e) familiarity with subject, and (f) occupational and educational training.

Diagnostic Criteria

Criteria employed to arrive at a diagnosis should be described with respect to: (a) operational criteria for significant regression in adaptive/functional skills, (b) core symptoms of Alzheimer disease measured by standardized scales such as impairment of memory, information processing, verbal skills, functional and adaptive ability, and disorientation (note that there are no standardized scales that measure symptoms of Alzheimer disease in this population, standardized measures only assess level of impairment), (c) operational criteria for case definition clearly defined according to the diagnostic criteria of the working group on diagnosis of Alzheimer disease in people with mental retardation; (d) suspected stage of Alzheimer disease; and (e) diagnostic certainty (probable, possible, uncertain).

Medical Information

Medical data collected should include: (a) risk factor or family history information for Alzheimer disease: medication data, history of head injury, seizure status, hepatitis status, psychiatric status; (b) indication of whether blood was banked for future tests (where blood is located and case numbers should be included)²; (c) blood samples for current tests (karyotypes, APOE-genotype, thyroid

² In the United States, blood samples from individuals with severe or profound mental retardation currently may be collected for research purposes with informed consent provided by legally responsible kin or correspondents. All such informed consent procedures must, however, include a proviso that blood samples will not be drawn if the person appears disturbed or unwilling. For individuals with milder forms of mental handicap, personal informed consent is required.

function, full blood chemistries) and (d) any current and historical neuroimaging data that may be available.

Conclusion

During the last decade research has made great strides toward understanding the role that Alzheimer disease plays in the lives of people with mental retardation, especially those with Down syndrome. Yet, considerably more needs to be learned.

- First, studies focusing on incidence and prevalence rates, risk factors, and natural history of the disease need to be conducted, and then replicated.
- Second, evaluation of adults with mental retardation without Down syndrome, a much larger group than those with Down syndrome, should be emphasized.
- Third, collection of the minimum data set suggested above, by various investigators, should allow meta-analytic studies of sufficient breadth and depth to be conducted to develop and validate hypotheses regarding the variables of interest specified above.
- Fourth, studies including national and international collaboration should be undertaken to utilize shared data and knowledge.
- Finally, efforts should be made by researchers and clinicians alike, to interest funding agencies to support research in these areas.

Epidemiology Workgroup Members

Deborah Anderson, Ph.D.; University of Minnesota, Minnesota Project on Aging & Developmental Disabilities, Upton Avenue South, Minneapolis, Minnesota 55405.
Maureen Babula, President; National Down Syndrome Congress, Buttonwood Lane, Phillipsburg, New Jersey 08865.

Richard Collacott, D.M., Ph.D.; Department of Psychiatry, University of Leicester, Groby Road, Leicester, England LE3 9QF. *Sally-Ann Cooper, MRC Psych*; Department of Psychiatry, University of Leicester, Groby Road, Leicester, England LE3 9QF. *Todd Gerber, M.S.P.H.*; NYS Department of Health, Bureau of Audit & Gerontological Health, Corning Tower #557 - Empire State Plaza, Albany, New York 12237. *Meindert J. Haveman, Ph.D.*; Univ. of Limburg Dept. of Epidemiology, Box 616, MD Maastricht, The Netherlands. *Florence Lai, M.D.*; Eunice Kennedy Shriver Center, Mental Retardation Research Center, 200 Trapelo Road, Waltham, Massachusetts 02254. *Vee Prasher, MRC Psych, MD*; Department of Psychiatry, University of Birmingham, Queen Elizabeth Psychiatric Hospital, Mindelsohn Way, Birmingham, England B15 2QZ. *Nicole Schupf, Ph.D., Dr. P.H.*; Laboratory of Epidemiology, New York State Institute for Basic Research in Developmental Disabilities, 1050 Forest Hill Road, Staten Island, New York 10314. *Wayne Silverman, Ph.D.*; Department of Psychology, New York State Institute for Basic Research in Developmental Disabilities, 1050 Forest Hill Road, Staten Island, New York 10314. *April Zigman, Ph.D.*; Department of Psychology, New York State Institute for Basic Research in Developmental Disabilities, 1050 Forest Hill Road, Staten Island, New York 10314. *Warren Zigman, Ph.D.*; Department of Psychology, New York State Institute for Basic Research in Developmental Disabilities, 1050 Forest Hill Road, Staten Island, New York 10314

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