Evidence and mechanisms of retrogenesis in Alzheimer's and other dementias: Management and treatment import

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Abstract

Retrogenesis is the process by which degenerative mechanisms reverse the order of acquisition in normal development. Alzheimer's disease (AD) and related conditions in the senium have long been noted to resemble "a return to childhood." Previously, we noted that the functional stages of AD precisely and remarkably recapitulated the acquisition of the same functional landmarks in normal human development. Subsequent work indicated that this developmental recapitulation also applied to the cognitive and related symptoms in AD. Remarkably, further investigations revealed that the same neurologic "infantile" reflexes, which mark the emergence from infancy in normal development, are equally robust indicators of corresponding stages in AD. Neuropathologic and biomolecular mechanisms for these retrogenic processes are now evident. For example, the pattern of myelin loss in AD appears to mirror the pattern of myelin acquisition in normal development. Also, recent findings indicate that mitogenic factors become reactivated in AD, and, consequently, the most actively "growing" brain regions are the most vulnerable. Because of this robust retrogenic process, the stages of AD can be translated into corresponding developmental ages (DAs). These DAs can account for the overall management and care needs of AD patients. A science of AD management can be formulated on the basis of the DA of the Alzheimer's patient, taking into consideration differences of AD from normal development as well as homologies.

Key words: Alzheimer's disease, care concepts, dementia, dementia management, retrogenesis

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Historical background

Retrogenesis can be defined as the process by which degenerative mechanisms reverse the order of acquisition in normal development.[1] General relationships

between aging and development have long been noted by poets and playwrights,[2,3] and are incorporated in the vocabulary of the English and other languages. More than two centuries ago, physicians also began to note similarities between aging and normal infant-child development.[4] In the 1960s and 1970s, de Ajuriaguerra and associates observed that the decline of certain capacities in dementia appeared to reverse Piaget's developmental stages.[5-7]

Functional retrogenesis

Systematic empirical studies of the symptomatology of brain aging and progressive Alzheimer's disease (AD) in the 1980s resulted in the description of 16 successive functional stages and substages that were incorporated in the *functional assessment staging* (FAST) procedure.[8,9] Simultaneously, this functional progression was recognized as reversing the order of acquisition of the same functions in normal human development (Table 1).[10] Also immediately observed was that this functional progression was characteristic, but not pathognomonic, of the dementia of AD.[11,12]

One concern of subsequent research was validating this characteristic functional progression of AD. Strong correlations with existing dementia measures (*e.g.*, the Mini-Mental State Exam [MMSE][13]) were immediately apparent;[8] however, the final six to eight FAST substages occurred after the MMSE produced floor effects. Consequently, new measures needed to be developed for assessment of cognition in severe dementia, and the latter portion of the FAST had to be validated against these new measures. This was accomplished over the next decade.[14] Other investigations concerned the "criterion validity" of the FAST progression of AD. The FAST progression showed unprecedented strong relationships to neuropathologic post-mortem assessments of hippocampal volume loss,[15] cell loss,[16] and neurofibrillary changes[16] in AD. In another "criterion validity" study of the prospectively charted longitudinal course of AD, the FAST accounted for approximately twice the variance in temporal course of that explained by the MMSE.[17]

Consequently, these investigations indicated that:

- A characteristic functional course of AD was identifiable with the FAST staging procedure; and
- This characteristic course reversed normal human functional developmental acquisition.

Cognitive retrogenesis

The FAST staging procedure was developed from efforts to systematically describe optimally concordant ordinal assessments of progressive changes in AD.[18] These efforts, in turn, followed from the development of the Global Deterioration Scale (GDS).[19] One of the concordant ordinal assessments developed was *praxic capacity*.[20] Studies demonstrated that the evolution of praxic deficit in AD followed the retrogenic pattern.[21] Furthermore, if the FAST stages of AD and the corresponding praxis stages of loss in AD were each translated into corresponding developmental ages (DAs), *the loss of praxic capacity in AD occurred, on average, at the same DA as the loss of functional capacity.* In other words, cognitive retrogenesis in AD could be shown as concordantly mirroring functional retrogenesis.

Research from other centers also demonstrated the phenomenon of cognitive retrogenesis in AD. For example, a study of the MMSE, a measure developed for the assessment of cognition in AD and other dementias, was conducted in normal children. The investigators found an equally robust relationship between MMSE scores and mental age (MA), based on IQ scores in children, as has been observed between MMSE scores and any independent, objective dementia assessment in AD.[22]

We adapted a Piagetian test battery, the Uzgiris and Hunt Ordinal Scales of Psychological Development, for use in assessment of residual cognition in AD[23] and observed very strong relationships ($r = 0.8$) between the resulting measure (denoted M-OSPD) and FAST measurements of functional deterioration in AD.[14] Thornbury compared performance on Piagetian tasks by AD patients with MMSE scores and obtained a similar correlation (*i.e.*, $r = 0.8$) to that which we have noted with FAST scores and Piagetian measures.[24]

Therefore, we determined the following:

- Cognitive retrogenesis appears to be as robust as functional retrogenesis. Specifically, *dementia measures appear to be just as good at measuring normal human development as they are at measuring dementia. Conversely, infant-child developmental measures appear to be just as good at measuring dementia in AD as in measuring cognitive development;* and
- Cognitive retrogenesis appears to occur, from certain perspectives, concordantly with AD-based functional retrogenesis. It appears that *cognition and functioning are linked in the same intimate qualitative and quantitative relationship in dementia as they are in normal development.*

Emotional retrogenesis

Once the functional and cognitive landmarks of

Table 1. Functional landmarks in normal human development and Alzheimer's disease*

Normal development (approximate total duration: 20 years)

Approximate age		Approximate duration in development	Acquired abilities	Lost abilities	Alzheimer stage	Approximate duration in AD	Developmental age of patient
Adolescence	13 – 19 yrs	7 yrs	hold a job	hold a job	3 (incipient)	7 yrs	19 – 13 yrs (adolescence)
Late childhood	8 – 12 yrs	5 yrs	handle simple finances	handle simple finances	4 (mild)	2 yrs	12 – 8 yrs (late childhood)
Middle childhood	5 – 7 yrs	2½ yrs	select proper clothing	select proper clothing	5 (moderate)	1½ yrs	7 – 5 yrs (middle childhood)
Early childhood	5 yrs 4 yrs 4 yrs 3 – 4½ yrs 2 – 3 yrs	4 yrs	put on clothes unaided shower unaided toilet unaided control urine control bowels	put on clothes unaided shower unaided toilet unaided control urine control bowels	6a (moderately severe) b c d e	2½ yrs	5 – 2 yrs (early childhood)
Infancy	15 mo 1 yr 1 yr 6 – 10 mo 2 – 4 mo 1 – 3 mo	1½ yrs	speak 5 – 6 words speak 1 word walk sit up smile hold up head	speak 5 – 6 words speak 1 word walk sit up smile hold up head	7a (severe) b c d e f	7 yrs	15 mo – birth (infancy)

Alzheimer's degeneration (approximate total duration: 20 years)

degeneration in AD were established and the DAs corresponding to these landmarks were identified, other aspects of the retrogenic process could be studied. In a series of studies, we identified characteristic behavioral and psychological symptoms of dementia and the stages in the evolution of dementia at which these symptoms emerged.[25-27] Interestingly and importantly, many of these symptoms occurred at precisely the point that would be anticipated from the corresponding DA of the AD patient.[28,29]

Neurologic retrogenesis

Neurologic release signs, also referred to as primitive, developmental, or neonatal reflexes because of their occurrence in normal infancy, have long been known to occur in elderly persons and dementia patients.[30-33] Systematic studies precisely measured these reflexes and established the precise stages in the evolution of AD at which they emerged.[34-36] *These studies indicated that many of the same reflexes that are used to mark the emergence from normal infancy to early childhood appear to be equally robust markers of the emergence of the infantile DA stage of AD* (*i.e.*, movement from the end of FAST stage 6, into FAST stage 7).[36]

Neuropathologic retrogenesis

A neuropathologic pattern of degeneration in AD, which appeared to reverse the normal human developmental pattern, was first observed by Brun and Gustafson a quarter century ago.[37] Subsequently, at least three

other independent investigators have noted a retrogenic neuropathologic pattern in AD in terms of neuronal cell loss,[38] neurometabolic change,[38] neurofibrillary change,[39] and myelin vulnerability.[39,40]

Biomolecular retrogenesis

The major apparent mechanism for the retrogenic phenomenon in AD and related dementing disorders has recently been elucidated. The response of the neuron to stressors, including beta-amyloid, is an attempt to regenerate.[41,42] The result of this mitogenic stimulus is the activation of various mitogenic molecular markers, including the mitogen-activated protein kinase (MAPK) cascade, cyclins, and cyclin-dependent kinases.[43-53] Activation of MAPK in the hippocampus has been shown to be linked to contextual and spatial memory formation in the hippocampus.[54-57] Activation of these factors in some cases appears to precede the development of neuronal neurofibrillary changes.[45,46] Some of these mitogenic factors have been related to the phosphorylation and hyperphosphorylation of tau, and, consequently, the development of neurofibrillary changes in AD.[43,58,59] Reactivation of mitogenic factors has also been related to apolipoprotein (APP) processing into amyloidogenic elements.[60]

Consequently, this biomolecular research in AD indicates that *the most metabolically active regions of the brain in AD, which are the most capable of responding to a mitogenic stimulus, are the most vulnerable in AD*.[48,49] These phenomena clearly appear to account for the neuropathologic, neurologic, cognitive, functional, and emotional retrogenic phenomena reviewed in the preceding sections.

Risk factors for dementia and retrogenesis: Arboreal entropy

Some AD and dementia pathogenic factors currently have been associated with mitogenic factor activation. These include hypoxia and beta-amyloid (1-42).[42] However, other risk factors for AD have, at this time, been related primarily to myelin disturbance. These include low vitamin B12 levels, folate deficiency, increased serum homocysteine levels, and increased serum methylmalonic acid levels.[61-63] Atherosclerosis and cerebrovascular disease are other risk factors associated with AD, which have been primarily associated with myelin disruption.[64-66]

Therefore, a full understanding of the retrogenic process in AD probably encompasses myelin as well as mitogenic neuronal reactivation. The process of myelination is now known to continue well into the latter portion of life. Neurons that are myelinated early in the life become increasingly more thickly myelinated as time progresses. Possibly, myelin plays a role not only in the conduction of electrical impulses in the neuron, but also in protection and maintenance of the oligodendroglial, myelin, and axonal relationship.[1,67] Consequently, the most recently affected, and, as a result, most thinly myelinated brain regions, may be the most vulnerable to injury.[67]

A terminology that appears to describe the pattern of neuronal vulnerability accounting for the retrogenic observations is *arboreal entropy*. Just as the bark of a tree protects it from external injury and, to some extent, the thicker the bark, the greater the protection, the myelin protects the axon and its neuron. Hence, to some extent, we may say the thicker the myelin, the greater the protection. However, just as a tree can also be attacked from the inside, which ultimately rots the bark, the axon can be attacked from the inside. For example, neurofibrillary changes and neurotubular changes, secondary to mitogenic factor activation and tau hyperphosphorylation, can result in axonal destruction and resultant myelin loss. Note that the myelin is a living, metabolically active part of the axon of the neuron, with a membrane running through it, which is an extension of the cell (axonal) membrane. As a metabolically active cellular component, myelin is vulnerable to cellular and axomal injury.

Retrogenesis in non-AD dementias

At present, it is clear that the biomolecular factors and myelin vulnerability factors, which produce the phenomenon of retrogenesis in AD, frequently operate in other dementia disorders as well.

For example, investigators who have studied the M-phase mitotic markers cyclin B1 and cdc 2 in diverse dementing disorders have found increased activity in a variety of dementias, including, in addition to AD, Down's syndrome, frontotemporal dementia linked to chromosome-17, amyotrophic lateral sclerosis (ALS) dementia complex of Guam, Niemann Pick disease type-C, progressive supranuclear palsy, corticobulbar degeneration, and Pick's disease.[53] A common feature in most of these dementias is the occurrence of hyperphosphorylated tau, although not in a form necessarily associated with AD type neurofibrillary tangles. In contrast, these investigators found little or no increased activity of these particular M-phase mitotic markers in Parkinson's disease (PD), Huntington's disease (HD), ALS, multiple sclerosis (MS), pituitary adenoma, AIDS dementia, and fungal infection.[53]

Also, conditions such as vitamin B12 deficiency and hyponatremia clearly can produce myelin disturbances that may result in dementing conditions.

The extent to which non-AD dementias show a retrogenic pattern of progressive clinical pathology is likely

dependent, in part, on the occurrence of retrogenic biomolecular and neuropathologic phenomena.

Management import of retrogenesis in AD

An understanding of the phenomenon of retrogenesis in AD permits the foundation of a new science of AD care.[29] This science is based on fundamental human needs, which apply to humans at all ages, and an understanding of the DA of the AD patient. Fundamental human needs include those for movement, socialization, love, and dignity. Typically, these fundamental needs are frequently not understood in the AD patient.

For example, in nursing homes in the United states, until recently, late-stage AD patients were routinely put into "geri-chairs," which prevented ambulation, to prevent falling. The situation would be analogous to locking infants in chairs to prevent falling. The AD patients commonly developed deformities, probably in large part because of their restricted movement.[68] Infants who were similarly restricted also would probably develop deformities.

To cite another example, although everyone knows infants need overt expressions of love, love is not frequently provided to AD patients. This is especially true of late-stage AD patients in nursing homes.

In many ways, the situation today is quite similar to the 18th century, when psychiatric patients were kept in chains and there was little understanding of mental illnesses. An understanding of retrogenesis provides a basis for more sophisticated principles of care.

A new science of AD care based on retrogenesis

The new science of AD care can be formulated into axioms, postulates, and caveats. *Axioms* in this context are self-evident basic human needs and desires, applicable at all ages. *Postulates* are testable hypotheses of AD patient care. Treatment, based on the postulates, is dependent on satisfaction of the axioms. *Caveats* are exceptions to the DA-retrogenesis model, based on the nature of human aging and AD. The science of AD management is the clinical science and art of AD patient care, based on the interaction of the axioms, postulates, and caveats.

Care axioms

Examples of the axioms of AD management include the following:

Axiom I: All human beings avoid trauma and humiliation. AD patients, at any stage, avoid or rebel against experiences that are perceived as humiliating. The most prominent humiliating experience for the AD patient is appearing "stupid." Therefore, even early in the disease process, patients may avoid being questioned. As the disease progresses, patients may resist the humiliation of requiring a caregiver. So-called "delusions," such as that people are stealing things, have a psychologic basis insofar as AD patients at these stages prefer to accuse others of taking things, rather than accept the humiliation of admitting to themselves or others that they cannot remember.

Axiom II: All human beings seek a sense of accomplishment. In early AD (GDS stage 4), this sense of accomplishment can come from continued productivity. For example, an artist may continue to paint. A lawyer may continue the pretense of working on cases. One judge had his daughter write opinions. GDS stage 5 patients may continue to insist that they are working, even if they have been forced to retire. Later in AD, a sense of accomplishment may come from folding towels and other simple DA-appropriate activities.

This axiom has important corollaries (*i.e.*, consequences or results which follow from the axiom), which are:

- All human beings resist losses;
- A sense of accomplishment can be fostered by beginning with what an AD patient can do and building upon this; and
- A sense of accomplishment comes from practicing an area of residual expertise or learning new things.

Axiom III: All human beings seek a sense of dignity and self-worth. This dignity and self-worth may come from practicing previously mastered skills. It may also come from optimal participation in "adult" activities. Or, it may also be fostered by introducing necessary caregivers as "friends." A corollary of this is that if an AD patient perceives an activity as "infantile" or "childish" and, therefore, as an affront to his or her dignity, they may become angry and refuse to participate.

Axiom IV: All human beings are social organisms. Therefore, the social needs of the AD patient remain throughout the illness process. Even in the late stage (GDS and FAST stage 7), patients continue to require interaction with caregivers and others for mental and physical health and well-being.

Axiom V: All human beings seek praise and acceptance. As social organisms, AD patients continue to require positive social reinforcement throughout the course of the illness process in order to maintain their motivation and skills.

Axiom VI: All human beings have the capacity to learn. One aspect of this capacity to learn is that AD patients can be retrained in many of the skills they have lost by breaking the tasks down into small stages, which are achievable, and praising the patient for his or her accomplishments.

Axiom VII: All human beings require love. This is necessary for the emotional and physical health of the AD patient at all points in the illness process.

Axiom VIII: All human beings have the capacity for happiness if basic needs are fulfilled. This means that AD is a physiologically congruent process. As such, if proper care is provided and social, emotional, and other needs are met, AD patients need not suffer and they can derive satisfaction from their existence.

Axiom IX: All human beings have the need for physical movement. Indeed, movement is sometimes said to be a fundamental feature of animal life. As is the case of the other axioms, this fundamental need is frequently ignored or not recognized in AD patients to such an extent that, until recently, AD patients were routinely restrained in order to prevent falling. Naturally, this restraint actually increased falls in patients, who were made increasingly unstable from the restraints. Hence, the need for movement remains frequently unrecognized in the AD patient.

Axiom X: All human beings have the capacity to remember. As is true of many of the other axioms, this basic human capacity is frequently not recognized, particularly in the late-stage (GDS and FAST stage 7) AD patient. If the person's memory is placed in the context of the DA of the AD patient, his or her memory capacity becomes comprehensible and assessable. Just as a one-year-old child will forget people and events more quickly, a stage 7 AD patient will forget people and events more quickly than a healthy adult. Three weeks is a very long time for a stage 7 AD patient or a one-year-old child. As is true of all humans at all ages, emotional memories are particularly strong in AD.

Axiom XI: All human beings have the capacity to think. As with other basic human capacities, this one is sometimes not recognized in the AD patient—with deleterious consequences. For example, caregivers may sometimes speak unflatteringly about the late stage 6 and early stage 7 AD patient, thinking that, because the patient cannot articulate, he or she does not understand. The patient may become agitated in response to the caregiver's unempathetic comments. Unfortunately, the caregiver, not recognizing the patient's comprehension, may think the agitation is sporadic and arbitrary, rather than a response to the crude and critical remarks.

Axiom XII: All human beings seek to influence their environment. This basic human need and desire is also frequently underestimated in the stage 7 AD patient. For example, although the caregiver may be unable to interpret a stage 7 AD patient's babbling, the patient seeks to make their desire known and many become agitated, or violent, if not "listened to."

Axiom XIII: All human beings have a sense of "taste," i.e.*, likes and dislikes.* Just as infants will throw away a toy they do not like, an AD patient has preferences that are expressed and can be interpreted at any stage. These preferences are sometimes not recognized. For example, a case manager recommended "any ID bracelet" for an early stage 6 AD patient because "she won't notice." In actuality, this patient would have been highly insulted by an unattractive plastic bracelet and wished to maintain a sense of style and beauty.

Care postulates

The postulates are based on the retrogenesis observations and the DA model of the stages of AD, reviewed in the preceding sections. The validity of the postulates is subject to scientific investigation. A summary of some of the major postulates follows.

Postulate I: The magnitude of care and supervision required by an AD patient, at a DA, is mirrored by the amount of care and supervision required by a child or infant at the corresponding DA. For example, an AD patient at GDS and FAST stage 7, corresponding to an infancy DA, requires approximately the same amount of care and supervision as an infant.[29]

Postulate II: The kinds of activities enjoyed by an AD patient, at a particular DA, are mirrored by the kinds of activities enjoyed by children at a corresponding DA. For example, just as child of age two to five years may enjoy working on puzzles, drawing with crayons, or assisting with simple household chores, similar activities are appropriate for the GDS and FAST stage 6 AD patient at a corresponding DA.

Corollaries of postulate II include the following:

- The kinds of activities that children find frightening or upsetting at a DA are mirrored by the kinds of activities AD patients find upsetting at a corresponding DA;
- The kinds of activities that a child considers "childish" or "babylike" at a particular DA, are mirrored by the kinds of activities an AD patient may find humiliating; and
- The kinds of activities that promote healthy and optimal motor development in children are similarly the kinds of activities which minimize motor degeneration in AD.

Postulate III: The capacity of an AD patient to perform in an area of residual expertise is dependent on the patient's DA. If a child at the particular DA can master the task, an AD patient at the corresponding DA potentially can retain the residual capacity. Variability in AD patients' loss of capacity is mirrored by a corresponding variability in children's ability to master the task. Therefore, expectations must be in accord with the DA of the AD patient. A corollary of this postulate is that as an AD patient approaches loss of capacity, they develop anticipatory anxieties. For example, AD patients commonly develop anxieties regarding toileting in FAST stage 6c, prior to loss of urinary continence in FAST stage 6d. Similarly, some patients develop anxieties about completing their income tax in GDS and FAST stage 4.

Postulate IV: Previous experiences may determine the kinds of activities enjoyed by an AD patient. For example, one GDS stage 6, FAST stage 6d AD patient was very anxious about having her front yard clean. Naturally, an urban patient might not be interested in cleaning a yard.

Postulate V: The emotional level of the AD patient is dependent on the DA. For example, just as a two to three year-old child may become "cranky" at various points in the day, a stage 6d AD patient at a corresponding DA may develop "mood swings."

Postulates VI: Life experiences appropriate to the DA become most relevant for AD patients at any particular stage. For example, a man's only interest may have been his work. However, at stage 5 (DA of five to seven years), much of the interest in his previous job (*e.g.*, business, medicine, etc.) is lost. At this point, DA-appropriate activities can be introduced.

Postulate VII: Socialization of the AD patient is dependent on the DA. For example, just as an infant of a year old or less does not yet relate socially with other infants, a GDS and FAST stage 7 AD patient does not relate or socialize with other stage 7 patients.

Postulate VIII: Diversity in children's and infants' activities and interests is mirrored in diversity in AD patient's interests and activities at a corresponding DA. A corollary of this is that just as all normal, healthy, children at a given age clearly can be shown to have much in common, despite acknowledged diversity, all "uncomplicated" AD patients at a given stage have much in common, despite acknowledged diversity. For example, all normal, healthy, one-year-old children have much in common with each other in comparison with normal, healthy, 12-year-old children. Conversely, all GDS stage 7, FAST stage 7a, uncomplicated AD patients have much in common, as compared to all uncomplicated stage 4 AD patients.

Postulate IX: The emotional changes that occur in AD at a DA are mirrored by the emotional changes observed in children at a corresponding DA. This is similar to postulate V, but concerns specifics. For example, delusions occur in AD patients that are very similar to childhood fantasies at the corresponding DAs.[27-29]

Postulate X: Care settings appropriate to AD patients at a DA are mirrored by care settings appropriate to children at the corresponding DA.[29] A corollary of this postulate is that just as institutions would be considered an inappropriate and undesirable care setting for infants and toddlers, institutions are inappropriate settings for the care of GDS and FAST stage 7 and stage 6 AD patients. Therefore, resources currently devoted to nursing home care probably should be shifted to care in community residences.

The analogy of nurseries and schools for children to day-care centers for AD patients also applies in this regard.

Postulate XI: Vulnerability (emotional, physical, and cognitive) of the AD patient at a DA is mirrored by the vulnerability of children at the corresponding DA. For example, just as an infant is vulnerable to social deprivation, poor care, and physical insult, a stage 7 AD patient is vulnerable to social deprivation, poor care, and physical insult. The result of these social, emotional, and physical injuries is excess disability.

Postulate XII: The need of an AD patient for physical movement is mirrored by the corresponding DA. A young child requires more than simply walks or running back and forth for optimal physical growth and attainment. Motor development in children is also dependent on the child dressing, developing eating skills, ball playing, and other skills. The same kinds of skills are required by the AD patient to prevent precipitous physical decline.

Postulate XIII: Just as one judges development in an infant or child by what the infant or child can do and has achieved, not by what the infant or child cannot do, the AD patient at any particular DA should be assessed in terms of his or her residual skills and accomplishments, what they have learned and relearned, not by what they cannot do.

Postulate XIV: The developmental analogy is sufficiently strong to trigger DA-appropriate childhood memories, beliefs, and anxieties in the AD patient. For example, most FAST stage 6e AD patients will state that their parents are alive. These DA-appropriate memories are the basis of the statement, incorporated in the Blessed *et al.* dementia scale, that AD patients tend to dwell in the past.[69]

Postulate XV: The language changes of the AD patient are mirrored by the DA. For example, when

speech abilities break down in the AD patient at FAST stage 6e, patients commonly develop "verbigeration" and neologisms, which are very similar to the babbling of infants as they acquire speech at an equivalent DA.

Care caveats

Caveats which modify the retrogenic-DA model of AD make the care and management of the AD patient a complex art as well as a science. Some of the major caveats are enumerated below.

Caveat I: Development in infants and children is accompanied by increasing expectations, whereas AD at all stages is accompanied by progressively diminished expectations. These contrasting phenomena are accompanied by widely divergent social consequences. For example, the societal tendency is to praise children and to become frustrated with AD patients. However, growth, within the context of an individual's capacity for growth, is dependent on praise for one's accomplishments.

Caveat II: AD patients experience developmentally analogous brain changes; however, they do not undergo developmentally analogous physical changes. Therefore, AD patients are physically larger and more formidably appearing than children. Furthermore, until stage 7, AD patients have the physical habitus of a normal adult. These physical features produce special consequences for AD patients in comparison with children. For example, the AD patient's normal appearance conveys a level of sagacity and competence, which is not assumed to be present in children at the same DA.

Also, because of the absence of a physical retrogenesis, the physical capacities of the AD patient may sometimes exceed those of DA-comparable children and infants. For example, a very well cared for GDS stage 7, FAST stage 7b patient who receives retraining can be relatively dexterous as compared to a one-year-old. For example, one GDS 7, FAST 7b patient was able to lace, button, and slip on clothing.

Another consequence of the AD patients' size and strength in comparison with their DA peers is that a grasp reflex in a stage 7 AD patient can be much stronger and more difficult to release then an infant's grasp reflex, with consequences for the management of the AD patient.[70]

Caveat III: AD patients can, to some extent, draw upon previously mastered skills, whereas infants and children may not have access to these skills. Consequently, AD patients may be relatively skilled and "precocious" in comparison with their chronologically younger DA peers. For example, even in late stage 7, long after serviceable speech has been lost, AD patients may occasionally (*e.g.*, during their sleep, or in response to startle or pain) utter seemingly forgotten words. Infants do not have access to such words.

Caveat IV: AD patients can, to some extent, draw upon previously mastered knowledge, whereas infants and children may not have access to this knowledge. For example, a GDS and FAST 7d AD patient who always had an immaculate household uttered "aagh!" when a caregiver dropped shoes in the middle of the floor. This same 7d AD patient would "whack" a caregiver who put her elbows on the table.

Caveat V: AD patients are older than their DA peers, and old age predisposes to various physical disabilities that influence the life and experience of an AD patient. For example, cataracts predispose AD patients to visual hallucinations.

Caveat VI: AD patients appear to be more prone to rigidity than their DA peers. The causes probably include the AD patients' brain disease in the absence of physical involution and the relative immobility of AD patients. The rigidity can greatly increase disability in the AD patient, ultimately resulting in contractures.

Caveat VII: AD patients can potentially concentrate on a task longer than infants or children at a corresponding DA. Conversely, infants and children are more distractible and impatient than AD patients. For example, one GDS 7, FAST 7c AD patient is known to stare at a newspaper for perhaps an hour. An 11-month-old infant will look at a book for a few minutes.

Caveat VIII: AD patients appear to be less fascinated by the world and less inquisitive than infants and children at a corresponding DA. For example, a two-year-old child may continuously ask questions, such as "What is this?" whereas an AD patient at GDS 6, FAST stage 6e is not inquisitive in this manner.

Care science

Therefore, a care science in AD can be firmly grounded in universal human, retrogenic, and AD-specific principles. The ingredients for the quality care recipe can now be described in considerable detail. These principles can potentially impact positively on the quality of life and excess disability of AD patients at this juncture. Potentially, much of the suffering and distress associated with AD can be relieved.

Pharmacologic treatment of the biomolecular retrogenic process

The nascent understanding of the role of mitogenic factors in the etiopathogenesis of AD has suggested new avenues for fundamental treatment investigations. In many ways, the mitogenic response of biomolecular retrogenesis to AD-associated stressors and toxins is similar to

the mitogenic response to stressors and toxins in non-nervous-system tissues.[71-73] In other organ systems and tissues, the stressors and toxins producing a mitogenic response are termed *carcinogens* and the mitogenic response is termed a *neoplastic response*. In the adult brain, despite the occasional occurrence of neurogenesis, an abortive neurogenesis or abortive mitosis is associated with neurofibrillary changes and, perhaps, apoptosis. Consequently, antineoplastic agents that suppress mitosis may have relevance for the treatment of AD.

Conclusion

In summary, retrogenesis appears to represent a new mechanism of disease with distinct biomolecular, pathologic, physiologic, and clinical manifestations. Distinct management and treatment principles and avenues for pharmacologic research follow from these retrogenic mechanisms and their manifestations. AD is the paradigmatic retrogenic disorder, but the process is applicable to a variable extent to many other dementing conditions.

Authors' note

The methodology described herein of a science of management, care, and treatment of Alzheimer's disease and related dementias is the subject of a pending patent application.

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