Alzheimer's Disease
Talk to Merck-Frosst employees
28 May 1998
Henry Olders, MD, FRCPC

Story of Mrs. A.

I am going to tell you a story. It's about Mrs. A., who is 86 years old, a widow living in her own apartment since her husband died 12 years ago. She and her husband were both born in Poland, and were in concentration camps during the war. Each had family members killed in the Holocaust. Individually, they came to Montreal after the war, and met each other here. Her husband became successful in the garment industry, and she stopped working as a secretary when she became pregnant with her first child.

Mrs. A. nursed her husband at home when he became ill with diabetic complications, until he died. At that point, she extracted a promise from her daughter and son that they would not put her into a nursing home. Now Mrs. A. can no longer go out because of her arthritis; she recognizes that she has memory problems, and is fearful of using the stove, worried that she might forget to turn it off and start a fire. She depends on her daughter who shops for her, cooks extra meals which can be heated up in the microwave, and who stops in daily after her work to tidy up and visit before going home to her husband and children. She also bathes her mother twice a week. Mrs. A.'s son, also married and in business for himself, looks after her financial affairs and tries to visit several times a week, although this is less predictable because of the demands of his business.

Mrs. A. calls her daughter at work several times every day to tell her about her arthritic pain and to ask her when she will be coming over. She also pages her son on his beeper frequently. If he doesn't call back right away, she will page him again. He thinks it's an emergency, and drops whatever he's doing to call her.

I saw Mrs. A. and her children in the Psychogeriatrics Clinic at the Jewish General Hospital, where I work.

The son and daughter brought Mrs. A. to us, feeling she was depressed. I asked if the mother was getting Meals on Wheels, if she was getting home care help from the CLSC or elsewhere. No, they said, Mother doesn't like their food, and she refuses to have strangers in the house.

I felt the daughter was much more depressed than her mother, and was at risk for burnout, if not a breakdown. Her marriage was already in trouble. The son was considering moving to Toronto.

This story illustrates some of the issues facing an individual who develops Alzheimer's disease, and the impact of the illness on family members.

Although the topic of my talk is Alzheimer's disease, keep in mind that Alzheimer's refers to only one kind of dementia. Many people use the word Alzheimer's to refer to dementia in general; the word "demented" has too many negative connotations. And the reality is that many of the things that are important in Alzheimer's are equally important in the other forms of dementia. So I will be talking a lot about dementia in general, not just Alzheimer's.

What is Dementia?

Slide 1

One definition is provided by the International Classification of Diseases, the ICD. Here is the definition from the 10th revision of the ICD:

ICD-10 Diagnostic Criteria for Dementia (any cause)

G1.1

A decline in memory, which is most evident in the learning of new information; in more severe cases, recall of previously learned information may also be affected. The impairment applies to both verbal and nonverbal material

G1.2

A decline in other cognitive abilities characterized by deterioration in judgment and thinking, such as planning and organizing, and general processing of information. Deterioration from a previous level of performance should be established

G2

Preserved awareness of the environment (that is, the absence of clouding of consciousness) during a period long enough to enable the unequivocal demonstration of G1. When episodes of delirium are superimposed, the diagnosis of dementia should be deferred

G3

A decline in emotional control or motivation, or a change in social behaviour, manifested as at least one of the following: emotional lability ,irritability, apathy, coarsening of social behaviour

G4

For a confident clinical diagnosis, criterion G1 should have been clearly present for at least 6 mo; if the period since the manifest onset is shorter, the diagnosis can only be tentative

Slide 2

Epidemiology of Dementia

How common is dementia

prevalence

increases exponentially with age
in Canada, 8% of those over 65, 35% of those over 85, and 58% of those over 95, have some type of dementia. As the population ages, the number of dementia cases is expected to triple by the year 2031
The good news is that less than 0.5% at ages 65 to 70
There are at least 250,000 Canadians with dementia

incidence

dementia develops in approximately 1% of the elderly each year, this is more than 25,000 new cases annually

Slide 3

Classification of Dementias

This slide shows how the various dementia illnesses are classified. The first subdivision is into the irreversible and the reversible dementias. Within the irreversible dementias, we have neurodegenerative, which includes Alzheimer's disease; vascular dementias which account for up to one-third of dementias, and mixed vascular and Alzheimer's, again up to about a third. The reversible dementias account for a much smaller number of cases.

Slide 4

This slide breaks down the first group of irreversible dementias, the neurodegenerative illnesses. We have:

- Alzheimer's disease (60%)
- diffuse Lewy body disease (15 – 27%). I'll bet you haven't heard about this one, even though some experts think is the second most common type of dementia, even more common than vascular dementia. It has some similarities to Parkinson's disease, and it may be that both Parkinson's and diffuse Lewy body disease are increasing because of toxins in the environment.

We then have these other diseases, and I won't bore you with details.

- Pick's disease
- Parkinson's disease
- Huntingdon disease
- progressive supranuclear palsy
- amyotrophic lateral sclerosis with dementia
- olivopontocerebellar degeneration

Slide 5

This slide breaks down the vascular dementias

VASCULAR DEMENTIA (9 – 33%)

- cardiac disorders
- vasculitis, or inflammation of the blood vessels, affecting the brain
- delayed effects of irradiation used to treat brain tumours, for example
- hemorrhage (subdural hematoma, subarachnoid hemorrhage, cerebral hematoma, vascular malformations)
- hypoperfusion or insufficient blood getting to the brain, due to cardiac arrest, profound low blood pressure
- multiple infarcts which you've probably heard referred to as multi-infarct dementia
- a single infarct in certain specific areas of the brain

mixed—vascular and Alzheimer's (10 – 36%)

Slide 6

This next slide looks at the first group of reversible dementias, the so-called secondary dementias because they are secondary to, or caused by, another medical condition, such as:

- **normal pressure hydrocephalus**
- **mass lesions**
- **infectious diseases:** bacterial meningitis (chronic or partially treated), fungal, parasitic; AIDS-related dementia; neurosyphilis; Whipple disease; Lyme neuroborreliosis; Creutzfeldt-Jacob disease
- **Collagen-vascular diseases:** systemic lupus erythematosus; temporal arteritis; other collagen-vascular diseases which may cause dementia
- **endocrine disorders, especially hypothyroidism, a condition which may affect up to 10% of elderly women;**
- **nutritional dementias:** vitamin B12 deficiency; folate deficiency; pellagra; thiamine deficiency, found in chronic alcoholism
- **miscellaneous:** obstructive sleep apnea; chronic obstructive pulmonary disease; limbic encephalitis; radiation-induced dementia; dialysis encephalopathy

Slide 7

medical conditions usually resulting in chronic delirium. Delirium is the medical term for what people usually call confusion. We consider delirium a medical emergency, because if the cause isn't found and fixed quickly, the delirium may turn into an irreversible dementia.

- disturbances in fluid and electrolytes, especially sodium, calcium
- liver failure
- kidney failure
- lung failure
- infection, eg urinary tract infection, pneumonia, infection of the blood
- cardiovascular disorders, such as congestive heart failure, hypertensive encephalopathy, myocardial infarction
- having had surgery; we know that general anesthetic kills some brain cells; depending on how many of those cells you have to spare…and finally, medication toxicity.

From 5-10% of pts seen in geriatric clinics for mental impairment have a potentially reversible drug-induced dementia
elderly are at high risk for a number of reasons:

- receive more prescriptions, more polypharmacy
- the liver is less effective at metabolizing drugs
- often more body fat; many drugs tend to stay in the fat for a long period of time
- the kidneys may be less effective at eliminating drugs from the body

- polypharmacy, illness may ⇨ altered drug absorption, protein binding

Slide 8

This slide show the classes of drugs which can cause cognitive impairment:

- tricyclic antidepressants (anticholinergic, sedating)
- neuroleptics, also called antipsychotics (anticholinergic, sedating
- benzodiazepines
- lithium
- psychostimulants such as ritalin
- barbiturates; non-barbiturate sedatives (eg glutethimide; meprobamate), which, thankfully, most doctors don't prescribe any longer
- anticholinergic agents which may be prescribed for side effects of neuroleptic medications
- antihypertensive agents (eg methyldopa; propranolol; clonidine); diuretics
- anticonvulsants (barbiturates; phenytoin; ethosuximide)
- antihistamines
- narcotic analgesics
- antiparkinsonian agents (l-dopa; bromocriptine; pergolide)
- cardiovascular agents (digitalis; quinidine; procainamide)
- others: corticosteroids; cimetidine; metoclopramide; antibiotics; antineoplastic agents; disulfiram; oral contraceptives; ergot

psychiatric pseudodementias

- definition of pseudodementia: "an intellectual impairment in patients with a primary psychiatric disorder, in which the features of intellectual abnormality resemble, at least in part, those of a neuropathologically induced cognitive deficit"
- depression is the most common cause of pseudodementia
- it's very important that we do our best to make this diagnosis, because if the depression continues, the pseudodementia turns into a permanent, irreversible dementia.

Slide 9

Warning Signs of Alzheimer Disease (Alzheimer's Association, U.S.)

Memory loss that affects day-to-day function

It's normal to occasionally forget appointments, colleagues' names or a friend's phone number and remember them later. A person with AD may forget things more often and not remember them later, especially things that have happened more recently.

Difficulty performing familiar tasks

Busy people can be so distracted from time-to-time they may leave the carrots on the store and only remember to serve them at the end of the meal. A person with AD may be unable to prepare any part of a meal or forget they ate it.

Problems with language

Everyone has trouble finding the right word sometimes, but a person with AD may forget simple words of substitute inappropriate words, making his or her sentences difficult to understand.

Disorientation of time and place

It's normal to forget the day of the week or your destination for a moment, but a person with AD can become lost on their own street, not knowing how they got there or how to get home.

Poor or decreased judgment

People may6 sometimes put off going to a doctor if they have an infection before eventually seeking medical attention. A person with AD may not recognize the infection as a problem or even go to the doctor at all. They may also dress inappropriately, wearing heavy clothing on a hot day.

Problems with abstract thinking

From time to time, people may find balancing a cheque book difficult. Someone with AD could forget completely what the numbers are and what needs to be done with them. Celebrating a birthday is something many people do, but a person with AD may not understand what a birthday is.

Misplacing things

Anyone can temporarily misplace a wallet or keys. A person with AD may put things in inappropriate places: an iron in the freezer or a wristwatch in the sugar bowl.

Changes in mood or behavior

Everyone becomes sad or moody from time to time. Someone with AD can exhibit rapid mood swings—from calm to tears to anger—for no apparent reason.

Changes in personality

People's personalities can change somewhat with age, but a person with AD can change dramatically, becoming extremely confused, suspicious or withdrawn. Changes may also include apathy, fearfulness or acting inappropriately.

Loss of initiative

It's normal to tire of housework, business activities or social obligations, but most people regain their initiative. A person with AD may become very passive, requiring cues and prompting to become involved.

Slide 10

Why Screen for Dementia?

There are several drug treatments available that benefit AD patients

To identify patients at risk for delirium
To identify patients in whom medications with anticholinergic effects will worsen cognition or precipitate delirium
For medical-legal purposes: earlier identification of cognitive impairment will give the patient and family more opportunity to plan for the future, eg mandates, participation in research protocols.
To identify elderly drivers at risk for motor vehicle accidents

Slide 11

Severity of Dementia

These next two slides outline two systems for rating severity of dementia. This first one, by Dr. Mark Clarfield, who was head of geriatrics at the Jewish General Hospital when he chaired a Canadian Consensus Conference on the Assessment of Dementia, is simple, with only 3 levels of severity.

mild

although work and social activities are significantly impaired, the capacity for independent living remains, with adequate personal hygiene and relatively intact judgment

moderate

independent living is hazardous, and some degree of supervision is necessary

severe

activities of daily living are so impaired that continual supervision is required (eg unable to maintain minimal personal hygiene, largely incoherent or mute

Slide 12

Global Deterioration Scale (GDS)

The Global Deterioration Scale has finer gradations, with 7 stages:

Stage	Cognitive Decline	
1	None	• Experiences no problems in daily living
2	Very mild	• Forgets names and locations of objects • May have trouble finding words
3	Mild	• Has difficulty travelling to new locations • Had difficulty handling problems at work
4	Moderate	• Has difficulty with complex tasks (finances, shopping, planning dinner for guests)
5	Moderately severe	• Needs help to choose clothing • Needs prompting to bathe
6	Severe	• Needs help putting on clothing • Requires assistance bathing; may have a fear of

		bathing • Has decreased ability to use the toilet, or is incontinent
7	Very severe	• Vocabulary becomes limited, eventually declining to single words • Loses ability to walk and sit • Becomes unable to smile

Alzheimer's Disease

How do we diagnose Alzheimer's?

Slide 13

There are three diagnostic systems in current use; I'll show you one of them, just to give you an idea:

Diagnostic Criteria (NINDS-ADRDA: National Institute of Neurological Disorders and Stroke-Alzheimer's Disease and Related Disorders Association)

Definite AD

- Clinical criteria for probable AD
- histopathologic evidence from autopsy or biopsy

Slide 14

Probable AD

dementia established by clinical examination, documented by mental status testing, and confirmed by neuropsychologic tests

deficits in two or more areas of cognition

progressive worsening of memory and other cognitive functions

onset between ages 40 and 90 yrs

absence of other disorders that could account for the dementia

Possible AD

dementia syndrome with:

- variations in onset, presentation, or clinical course, or a second disorder capable of producing dementia, but not thought to be the cause of dementia
- gradually progressive deficit in a single area of cognition, without identifiable cause

Slide 15

Features which suggest other diagnoses

(Klatka et al 1995):

- presence of certain parkinsonian signs, especially resting tremor and cogwheel rigidity
- absence of language impairment, especially in moderate to severe dementia

- absence of visuospatial impairment (eg spontaneous drawing and copying of complex designs, identification of incomplete pictures)
- early, marked personality change (eg inappropriate spending, hoarding, hyperreligiosity, irritability, aggressiveness)
- focal neurologic signs

Slide 16

Risk Factors for Alzheimer's

family history of dementia

relative risk 3.5 for those with a 1° relative with dementia; risk ⇧ with increasing number of relatives affected

family history of Down's syndrome

relative risk 2.7 for those with a 1° relative with Down's

family history of Parkinson's disease

relative risk 2.4 for those with a 1° relative with Parkinson's

late maternal age

relative risk 1.7 for maternal age 40 or higher; higher risk in sporadic cases and in women
early maternal age may also be a risk factor

head trauma

relative risk 1.8 for reported head trauma with loss of consciousness; higher risk in men
records-linkage study failed to confirm this association

viral agents

even though neurofibrillary tangles are found in brain diseases with proven viral causes, no association was found between AD and a history of encephalitis, meningitis, or infection with a neurotropic virus.

smoking

most studies show a ⇩ risk of AD in smokers (relative risk 0.8)

aluminum and other toxic agents

conflicting findings for aluminum; no positive associations found for other toxic agents, including solvents, lead

depression

relative risk 1.8 for late-onset depression

vitamin B12

serum B12 levels were significantly correlated with MMSE scores in AD pts, but not in pts with other dementias or with mild cognitive impairment (Levitt & Karlinsky 1992)

apolipoproteins (Gauthier et al 1996)

lipid carrier molecules; regulate lipid metabolism following peripheral & central nervous system injury
encoded on long arm of chromosome 19
three major isoforms (alleles): E4, E3, E2
three homozygous phenotypes (E4/4, E3/3, E2/2) and three heterozygous (E4/3, E3/2, E4/2)
both sporadic as well as late-onset familial AD have markedly ⇧ apoE4 allele frequency, ie E4/4 ⇧ risk of developing AD by 30, while the relative risk is 3.7 for the heterozygous condition (Burns & Murphy 1996)
an association has been found between apoE4 and ⇩ parietal lobe metabolism on PET scan in relatives of AD patients who are clinically unaffected (Filley 1995)
preliminary evidence suggests that the E2 allele, which is only half as frequent as E4, may be protective against AD (Anonymous 1995)
at present, apoE genotyping is not sufficiently sensitive or specific to be useful as a diagnostic test, and is not recommended as a predictive test (Anonymous 1995)

estrogen

cognitive function deteriorated in patients who had had a hystero-oophorectomy but not in those having had a hysterectomy alone (Burns & Murphy 1996)

atherosclerosis

atherosclerosis is associated with both Alzheimer's and vascular dementia

Slide 17

Course

Progression	Manifestations
Stage I (1 to 3 years)	• recent memory dysfunction • anomia • topographic disorientation • depression
Stage II (2 to 10 years)	• prominent amnesia • fluent aphasia • constructional impairment • acalculia • personality change
Stage III (8 to 12 years)	• severe dementia • nonsense speech or mutism

	• rigidity and flexion posture • incontinence

Slide 18

Behavioural Disturbances in Dementia

up to 90% of dementia pts exhibit behavioural disturbances. eg, disinhibition (including aggression or wandering) 35%; apathy-indifference 31%; catastrophic reaction 32%, sundowning 62%; denial 37%
low prevalence behaviours: sexual disinhibition 3%; self-destructive behaviours 3%
some studies found no relationship between degree of cognitive impairment and behavioural disturbance

Slide 19

The most frequently reported behavioural problem is agitation, including: pacing, aimless wandering, inappropriate dressing or disrobing, spitting, hitting/kicking, throwing objects, making strange noises or screaming, biting, self-destructive acts, cursing or verbal aggression, constant unwarranted complaints/requests/statements, and general restlessness.
agitation can be broken down into 3 categories: aggressive (eg kicking); repetitious (eg wandering, repetition of words, unintelligible sounds); and socially objectionable (sexual disinhibition, undressing, screaming)

Slide 20 through 26

This next series of slides shows the possible causes or trigger factors responsible for some of these problem behaviours. I'll let you read these yourselves.

Behaviour	**Potential Causes or Antecedents**
Wandering	stress—noise, clutter, crowding lost—looking for someone or something familiar restless, bored—no stimuli medication side effect lifelong pattern of being active or usual coping style needing to use the toilet environmental stimuli—exit signs, people leaving
Difficulty with personal care tasks	task too difficult or overwhelming caregiver impatience, rushing cannot remember task pain involved with movement cannot understand or follow caregiver instructions fear of task—cannot understand need for task or instructions inertia, apraxia; difficulty initiating and completing a task
Suspiciousness, paranoia	forgot where objects were placed misinterpreting actions or words misinterpreting who people are; suspicious of their intentions change in environment or routine misinterpreting environment physical illness social isolation someone is actually taking something from patient
Agitation (also: "sundowning", catastrophic reactions)	discomfort, pain physical illness (such as urinary tract infection) fatigue overstimulation—noise, overhead paging, people, radio, television, activities mirroring of caregiver's affect overextending capabilities (resulting in failure); caregiver expectations too high patient is being "quizzed" (multiple questions that exceed abilities) medication side effect patient is thwarted from desired activity (for example, attempting to escape) lowered stress threshold unfamiliar people or environment; change in schedule or routine restless

Incontinence	infection, prostate problem, chronic illness, medication side effect, stress or urge incontinence difficulty in finding bathroom lack of privacy difficulty undressing difficulty in seeing toilet impaired mobility dependence created by socialized reinforcement cannot express need task overwhelming
Sleep disturbance	illness, pain, medication effect (for example, causing daytime sleep or nocturnal awakening) depression less need for sleep too hot, too cold disorientation from darkness caffeine or alcohol effect hunger urge to void normal age- and disease-related fragmentation of sleep (like that of an infant or toddler) daytime sleeping fear of darkness restless
Inappropriate or impulsive sexual behavior	dementia-related ⇩ judgment and social awareness misinterpreting caregiver's interaction uncomfortable—too warm, clothing too tight; need to void; genital irritation need for attention, affection, intimacy self-stimulating, reacting to what feels good

Slide off

Before I talk about treatments, I'd like to tell you a story about my mother. This story begins in the spring of 1996, when my sisters began expressing concerns that my mother's memory seemed to be failing. She would ask the same question over again several times, and she could no longer recall the names of spouses or grandchildren without considerable effort. I spoke to my parents, who were living in Brampton, Ontario, and they agreed to have my mother take vitamin E as well as gingko biloba extract. That summer, when I visited, I was struck by her memory difficulties, and obtained their agreement that I speak to their family doctor about prescribing estrogen for my mom. The doctor said he would consider it. To help him, I suggested I send him a file of clippings and articles on estrogen and Alzheimer's which I had been collecting, which I did after returning to Montreal.

I will read to you parts of an e-mail exchange with my two sisters, Hannie and Ine, both of whom live in Oakville, about a half hour's drive from my parents'. This first message to Hannie was shortly after installing my new computer, in September 1996.

How's mom doing? any more news on the estrogen front?

Two days later, Hannie replied:

Re. Mom and estrogen - I had a long talk with the doctor but he will not prescribe estrogen. Then I called the Alzheimer Society here in Toronto, and asked one of the counsellors. She said, in view of Mom's advanced age, she would not recommend estrogen because starting it at this point would be too much of a shock to the system. What are your thoughts on that? The doctor told Dad that he would make an appointment with a geriatric psychiatrist for Mom. I told Dad to call me with the name and I could let you know in case you have heard of him. Dad feels the gingko is doing some good, and as well Mom takes valerian for her insomnia. Both of these herbal remedies are included in lists of common herbals, whether in a popular magazine, or in a specialized one, so they are probably not harmful. If Mom stays the way she is now, I am not too concerned. The crunch will come if something happens to Dad or she herself gets sick, and then I think her memory will deteriorate very rapidly.

I anwered her back:

Disagree about the shock. It's possible to start it at a low dose. Maybe a gynecologist would be a better bet, because I don't know any geriatric psychiatrists that prescribe estrogen themselves. I certainly don't - I don't have the experience that gynecologists do in this area.

Skip forward to early December 1996. The plan was for my parents, as well as the rest of the family, to come to Montreal for the annual family reunion between Christmas and New Year's. I wrote to Hannie:

By the way, I recently saw another article about the beneficial effects of estrogen on Alzheimer's. I spoke to one of the GP's I work with to check dosages, and he suggests Estraderm skin patch starting at 25 mg, twice per week, and provera 2.5 mg daily (I assume Mom hasn't had a hysterectomy). If she is still not on estrogen at Christmas, do you think it would be worthwhile for me to prescribe it for her when she's here and get 6 months' worth to take back home?

Hannie replied:

>Re. estrogen. We are never going to get a prescription for estrogen
>from Mom's doctor, so if you can prescribe it, that would be best. Is
>the patch twice a week a special dosage level for geriatric patients,
>or what? Mom has had a hysterectomy, so does that cut out the need

>for provera? My only concern is if Mom reacts badly to the estrogen,
>what kind of care could she expect from her doctor?

And I fired back:

Re estrogen: the provera is only necessary to eliminate increased risk of uterine cancer. It's better that mom had a hysterectomy - makes things simpler.
Re her doctor: what kind of care is she getting now? But it really doesn't matter - if she thinks she is having a bad reaction to the estrogen patch, simply take it off. But side effects are really minimal - breakthrough bleeding is possible if the dose is too high, but of course you can't bleed if you've had a hysterectomy.

As it turned out, my parents didn't make it to Montreal. My father wasn't feeling all that well.
This next message was directed to my other sister, Ine, at the end of January 1997.

I called up mom's pharmacy on tuesday and ordered estrogen patches. I hope she's wearing one. I'm interested in seeing how it works. There's a couple of recent studies from Japan on the use of estrogen as a treatment in already established Alzheimer's disease which show positive results.

Ine answered:

Hannie and I visited Brampton yesterday. Dad put on Mom's first patch yesterday and he spoke quite hopefully about the results. He seems to have it well in hand. Too bad it's not covered, but they will try to claim it through the teachers' medical insurance.
Mom fell on the stairs Friday and got a huge lump on her forehead, but the swelling is mostly gone. She is quite black and blue and green and yellow. She's also sporting a magnificent black eye.

After my mom had been on the estrogen patch for 8 days, I received this message from Hannie:

Good job, getting that prescription for estrogen to the folks. I guess you heard what happened when Dad tried to get it filled. He could only get it if he paid for it, but that is worth it if it helps! As you can imagine, I've been monitoring Mom fairly closely, and last week I was rather concerned because she was unable to remember names, like Andrea's and Chris's. I told them to call more often if they wanted to remembered by their grandmother, and they agreed to do so. But is seemed as if Mom was going downhill, instead of getting better. However, this morning, on the phone, she told me about the things they had done that morning without having to ask Dad, which is a big change. So I'm keeping my fingers crossed.
Almost every day there seems to be an announcement about a new drug for Alzheimers. Don told me about one he just heard of a couple of

days ago. Couldn't remember the name but it is being used in Europe, has been approved for the States and will soon be for Canada. Apparently is really helpful in old age Alzheimers - it repairs some of the neural connections? Anything you can find out about it, I'd like to know too.

My answer was:

You probably hear more about new drugs than I do; after all, I don't get the Globe & Mail! In any case, if you send me a name, I can always do a literature search on medline.

I guess we'll have to keep our fingers crossed about Mom.

And after Mom had been on estrogen 2 weeks, another missive from Ine:

I'm sure Hannie will be communicating this info to you shortly, as well, but I wanted to let you know that this weekend I saw quite an improvement in Mom. The apartment was tidy, so was she, and she was animated and conversational. She had lovely colour in her face too. I had brought the movie American President, to share with them, and she wanted her chair up closer and the volume up, so that she wouldn't miss anything. Two weeks ago she wouldn't have cared. Hannie says that their daily conversations can be held without having to ask Dad what they did that morning. All in all, its very soon to tell, but I like the changes.

A month later, in March 1997, I visited my parents in Brampton and stayed overnight with them. I learned that my mom had complained of breast tenderness, and so my dad had stopped applying the patches. Didn't get to talk to my sisters, so I sent Hannie this message:

Wow, Mom's memory has really deteriorated! In any case, I ordered some more estrogen patches from the pharmacy (25 micrograms instead of 50) which Dad will hopefully start using soon. At the lower dose, mom should have no or little breast tenderness.

Let me know how it goes.

Hannie replied:

I'm glad you took Mom and Dad out Tuesday night. Unfortunately, with Peter's birthday, and your visit, and all, I think you probably saw Mom at her worst. She does not respond well to non-routine events, I think, no matter how pleasurable. The best thing we can probably do is get in touch as often as possible, send pictures, etc. so we keep her in the circle. Dad is going to start the estrogen again on Sunday, he said, but he didn't feel there had been much improvement

the first time, so I don't know what to think.

My answer:

Regarding Dad's assessment of how Mom is doing on or off the estrogen, I have the feeling that Dad has some resistance to using the estrogen, or perhaps to any intervention that may help. I'm not sure why. What do you think?

Last July, my dad was diagnosed with stomach cancer, and he died peacefully at home several weeks later. My mom was aware that he was ill, but always talked as if he were getting better. In retrospect, I feel that my father may not have wanted my mom's memory to be functioning too well, so that she might be spared some pain and anguish on his death. And that seems to be the case; although my mother is aware of his having died, for her it seems much longer ago than it actually was.
She continues to wear the estrogen patch, and since August has also been taking Aricept, the new medication for Alzheimer's disease. I am happy to report that she seems to have improved with this: she no longer needs to be constantly reminded to switch to English when talking to friends and family who do not speak Dutch; she readily recognizes her children's voices over the telephone; she concerns herself once again with keeping up-to-date with birthday greetings to her grandchildren and greatgrandchildren.

Slide on

Slide 27

This slide gives an overall summary of the treatments used for dementia.
There are 2 major groups: Treatments to improve cognition, and approaches to manage problem behaviours. In both groups, there are medications, and then a number of other types of treatments.
We'll start with the medications used to treat the cognitive impairment, but first, a joke.
This fellow Al was telling his friend about the marvellous new medication that his doctor had prescribed for him, to help his failing memory. "Sam", he said, "This stuff really works! You should try it! Why don't you go see my doctor?"
Sam, not quite convinced, said, "Well, maybe I should. What's your doctor's name?"
Al thought for a moment, then said brightly, "Help me out, Sam. What's the flower that has a long stem and thorns?"
"You mean a rose?"
"Yeah, that's it!" Sam turned to his wife, "Hey, Rose, what's the name of that doctor I've been seeing?"

Slide 28

Selegiline

Used for Parkinson's disease

Believed to reduce neural damage by acting as an antioxidant

In a study with vitamin E, selegiline was found to increase the time until a primary outcome, defined as death, institutionalization, development of marked dependency, or progression to severe dementia.

Adverse effects: falls, fainting; also nausea, hallucinations, confusion, depression, loss of balance.

Slide 29

Vitamin E

Functions in the body as an anti-oxidant

Thought to help stabilize or "slow down" the degenerative process in AD

Found to be as effective as selegiline in delaying time to primary outcome, but is safer and cheaper

May have an anticoagulant effect if taken in megadoses

The dose studied was 2000 IU, but many people recommend 800 IU.

Slide 30

Ginkgo biloba

Approved in Germany for treatment of dementia

The extract is a combination of substances which act as antioxidants.

As for vitamin E and selegiline, though to be a stabilizing agent.

In North America, there are no standards, so potency can vary considerably.

The dose used in the study was 40 mg 3 times daily before meals.

Slide 31

Donepezil

An acetylcholinesterase inhibitor, ie prevents the breakdown of acetylcholine, the substance thought to be in short supply in Alzheimer's.

Families report improvements in functioning which are bigger than suggested by improvements in tests of cognitive functioning.

Can potentially cause a slow heart rate, bladder obstruction, increased stomach acid, seizures, and can worsen obstructive lung disease

Side effects: nausea, diarrhea, vomiting, insomnia, fatigue, anorexia, muscle cramps.

In practice, is very well tolerated.

Usual to start at 5 mg per day; increase to 10 mg after 4-6 weeks if well tolerated.

Slide 32

This slide shows the results of a very recent study comparing the two dosages. Clearly, the higher dose is more beneficial, if the patient can tolerate the side effects which may be more bothersome at the higher dose.

Slide 33

Estrogen

Because women are affected much more by Alzheimer's disease than men, it has been hypothesized that estrogen plays a role.
This slide shows results of two representative studies:
The first study was of 138 elderly women who met clinical criteria for probable AD: 10 were ERT users. ERT users did not differ significantly from nonusers in terms of age, education, or symptom duration, but mean MMSE scores were significantly better (14.9 vs 6.5)
The second study was of 1124 women aged 70 or older, followed for 5 years. Overall, 14.9% developed AD: 16.3% of estrogen nonusers, vs. 5.8% of users.
There is an ongoing study - Women's Health Initiative Memory Study (WHI-MS) at Wake Forest University, May 1997. This $16 million (funded by Wyeth-Ayerst) nationwide (U.S.) study will recruit 8000 postmenopausal women who will be followed for 6 to 9 years to determine if ERT delays development or slows the progression of AD.

Estrogen in treating AD

If estrogen can prevent AD, would it be helpful in treating people who already have AD? This is the question which is important to my mother. I was able to find only two studies, both by the same group in Japan.

The first, for 6 weeks, compared 15 women with AD who were given estrogen to 15 AD patients who served as controls. The treated women improved on the MMSE. Incidentally, their depression scores improved also.
Regional cerebral blood flow as measured by SPECT also increased significantly in the lower frontal region and primary motor areas.
The second study, on long term estrogen:
7 mild to moderate AD patients received for 5 to 45 months
In 4 out of 7 patients, MMSE and daily activities were significantly improved during ERT, and decreased on termination of ERT.

Ongoing study
A study will recruit 120 patients for a year-long trial of the effects of estrogen in AD. 25 centres are participating. Only women who have had a hysterectomy will be included, because of fear of uterine cancer. (Johns Hopkins, July 1997)

Slide 34

Estrogen may also have a role in treating vascular dementia
studies show that more than 50% of dementia patients have some evidence of vascular disease
in those with significant vascular disease, about 1/2 will have evidence of AD
the original patient described by Alois Alzheimer in 1906, in retrospect appears to have had a vascular dementia of the small vessel type
in both AD and vascular dementia, cerebral blood flow is diminished in regions affected by the disease

Estrogen and vascular disease
most epidemiologic studies indicate that HRT reduces risk of cerebral vascular strokes by nearly 50%, so it should also reduce risk for multi-infarct dementia. Unfortunately, studies on this have not been done.
Funk et al studied 51 women with vascular dementia of the small vessel type diagnosed with CT or MRI scans, over 18 months; 16 received unopposed estrogen. This group had significant improvement in cognitive function, which was associated with an increase in cerebral blood flow.

Slide off

Then we have a couple of other treatments, such as

psychostimulants

eg methylphenidate: ⇧ alertness and attention in pts with depression; ⇧ mental status and behaviour in withdrawn, apathetic pts; does not improve cognitive functioning in dementia

aspirin

- AD pts often have vascular risk factors: active treatment with indomethacin in AD pts resulted in less cognitive decline cf placebo.

Treatments in the pipeline

Metrifonate

Like donepezil, an acetylcholinesterase inhibitor
Appears to control psychiatric and behavioural disturbances as well as mental performance
People who took this drug were less likely to have hallucinations or be apathetic, depressed and agitated than the placebo group

Slide on

Slide 35

3R Mental Stimulation Programme

Reminiscence, reality orientation, remotivation
Community-based seniors attending a day care in Singapore; 15 treatment, 15 in control group.
Treatment group attended weekly sessions over an 8-week period. Each session had a specific topic for discussion: money, hobbies, pets, water, clocks, fruit, festivals, and transport. The goal was to stimulate the visual, tactile, olfactory, and gustatory senses using a variety of objects such as photographs, food, flowers and household objects. Hearing was stimulated with voices and music.

Slide 36

This slide repeats the treatment options for difficult behaviours.

Medications

antipsychotic agents

behaviours which may respond include anxiety, hostility, hallucinations, excitement, and emotional lability.
a meta-analysis showed 18% of pts benefited from neuroleptics beyond that with placebo, esp for agitation, uncooperativeness, and hallucinations
sedation is common, may account for some of the “improvement”
anti-ACh effects can accelerate cognitive decline, impair memory, result in confusional states
risperidone may be useful because of minimal extrapyramidal symptoms and low incidence of cardiovascular effects (Lantz & Marin 1996)
clozapine has been successfully used in pts with dementia and severe parkinsonian syndromes who were refractory or intolerant to other neuroleptics (Lantz & Marin 1996)

anxiolytic agents

BDZ may be useful in anxiety, fearfulness, or insomnia
efficacy in management of agitation in dementia pts has not been adequately demonstrated

SE include cognitive impairment, confusion, dysarthria, unsteady gait, incoordination, amnesia, sedation, disinhibition with paradoxic agitation, falling, and physical dependence
repeated doses can cause accumulation⇨prolonged sedation, habituation withdrawal Sx on treatment cessation
short-acting agents without active metabolites (eg lorazepam, oxazepam) may be helpful for recurrent behaviour disruptions associated with predictable situations
buspirone, a 5HT1a agonist, may help control aggression at doses of 5 - 15 mg tid. Onset of action may take up to 2 months

antidepressants

improvement can occur even when criteria for a mood disorder are not met
SSRIs are generally safest; however, may worsen baseline agitation
trazodone (50-400 mg/day), with or without tryptophan, may be useful for anxiety, sleep disruptions, agitation, and other behavioural problems, including aggression, according to a number of case reports

carbamazepine

an anticonvulsant, is effective in decreasing impulsivity & aggression in wide variety of psychiatric pts, used a lot for treating manic-depressive illness
in one study, it⇧ cooperation and ⇩ tension, hostility, agitation in 5/9 AD patients who had not responded to neuroleptics
may take up to 7 weeks to demonstrate improvement
valproate, another anticonvulsant, has been found effective; note that AD brains have GABA deficits

β-blockers

β-blockers control aggressive behaviours 2° traumatic brain injury; usefulness in dementia is anecdotal; propranolol (40-520 mg/day in divided doses) or pindolol (60-100 mg/day)
response time varies from days to several months
cardiac failure, COPD, diabetes, asthma, hyperthyroidism are relative contraindications
propranolol may cause confusion and depression in elderly

other medications

lithium may control agitation when Sx are manic in character (sleeplessness, hyperactivity, pressured speech)
conjugated **estrogens** may control aggressive behaviours in elderly men with dementia

ECT

several cases are reported of improvement in uncontrollable screaming or severe verbal disruption with ECT (Lantz & Marin 1996)

Bright light therapy

8/10 pts with late afternoon/early evening confusion leading to agitation and irritability (sundowning syndrome) improved with 2 hrs of bright light therapy each evening
Installing high-intensity lighting in the room where patients spend most of the day is also effective

Slide 37.

Behaviour modification

behavioural approaches involving the application of operant conditioning are effective with demented elderly for a variety of problems in a variety of settings
behaviours are manifested because they fulfill a need; to change a behaviour, either the need has to be satisfied with a different behaviour, or the behaviour has to have a different consequence
problem behaviours occur when the physical environment or caregivers inadvertently reinforce and thus maintain maladaptive behaviours

steps:

identify the behaviour to be changed

identify an appropriate & acceptable alternative behaviour

complete a behavioural analysis: documentation of the behaviour's occurrence

identify the antecedents/precursors to the problem behaviour

identify the reinforcer(s) of the problem behaviour; eg an Alzheimer's patient who screams when the caregiver is not in the room. Each time the screaming behaviour occurs, the caregiver returns and the screaming stops. Here, the return of the caregiver reinforces future screaming behaviour whenever the patient is left alone.

identify reinforcer(s) which will reduce or eliminate the problematic behaviours, eg the caregiver needs to come into the room when the Alzheimer patient is not screaming and leave or not enter the room when the pt is screaming.

finally, develop a strategy to facilitate the occurrence of an alternative/acceptable behaviour and its reinforcement. This behaviour may need to be cued or prompted

dementia patients respond well to praise and poorly to negative reinforcers or punishment
the reinforcer must be presented immediately on occurrence of the desired behaviour
given the cognitive impairment, reinforcement may have to be continued indefinitely

Slide 38

other interventions for disruptive behaviours

A review by Beck & Shue (1994) describes and gives references for the following therapeutic interventions:

- validation therapy: aims to maintain the dignity and well-being of disoriented elderly people

- multimodal approaches, eg the Progressively Lowered Stress Threshold (PLST) model and plan of care
- group programs, such as Self-Esteem, Relaxation, Vitality, and Exercise (SERVE): listening to music, exercising, and relaxing for 1 hr, 3x/week
- low lighting (or avoidance of fluorescent lights) and music during mealtimes, ⇩ noise level, feeding time, and ⇧ food consumption
- nature sounds, soothing music, or white noise to ⇩ screaming
- touch, eg stroking across the back, to ⇩ agitation
- massage and therapeutic touch to induce relaxation
- pet therapy
- stimulus items, such as busy boxes, entertain patients, hold their attention, and may ⇩ agitation & combativeness
- education for nursing assistants in nonverbal communication techniques and other aspects of working with dementia pts

last slide 39

Other issues

Resuscitation

Futile treatments, family conflict, and euthanasia

- some would consider it unethical to admit a patient to a hospital or nursing home without consideration of the patient's CPR status.
- Patients should not be placed at risk of receiving highly invasive and perhaps inappropriate therapy.
- When no advance directive is available, and families are in conflict with the physician's medical judgments, pts would prefer that their families' wishes be honoured.

Tube feeding

Termination of life-prolonging treatments and quality of life issues

- important to recognize the influence of physicians' perception of the patient's quality of life; studies show that physicians use different measures to rate quality of life and undervalue it compared with their pts. They were less likely to resuscitate and would terminate life-prolonging treatment sooner than their pts desired.
- Artificial feeding is now considered a life-prolonging treatment. In the US, the courts permit incompetent pts the right to terminate artificial feeding through substituted consent-givers.

Mandates

Decision-making capacity

- a definitive test does not exist

- The physician should first make sure that information presented is pertinent to the specific decision. Patients should understand the relevant information, manipulate it rationally, appreciate the situation and consequences, and communicate stable choices.
- A sliding-scale model has been proposed that applies increasing stringent standards to different medical decisions, depending on complexity.

Institutional care issues

Abuse

I sit on a committee at CLSC Rene-Cassin which provides consultations to CLSCs from all over Quebec about cases of elder abuse. It meets monthly, and includes a family doctor, 2 lawyers, a representative from the Public Curator's office, someone from the Human Rights Commission, as well as social workers.
The committee deals mostly with cases of financial abuse, physical or emotional abuse, or neglect suffered by dementia patients at the hands of family members or other caregivers. However, we don't deal with the systematic abuse that goes on in public institutions such as nursing homes or long term care hospitals.
We know that some nursing home residents are physically and even sexually abused by staff. Severely demented individuals, of course, are unable to complain. But even those who are able to do so, may be fearful of further abuse as revenge for blowing the whistle.
Much more common and more insidious, I think, is the institutional abuse of residents with restraints and medication.

Restraints

Last year, I was part of a working group at the Corporation des Medecins du Quebec, whose mandate was to revise the guidelines on the use of restraints. We reviewed all the deaths of restrained patients for the past several years; most had been patients with dementia, who had been kept restrained while in bed, and had gotten strangled by the restraints.
As a consultant for six years at a large nursing home, I learned that two different units with the same types of patients and the same staffing patterns could have greatly different rates of putting patients into restraints. I can tell you that the use of restraints has much more to do with staff attitudes and habits, and institutional policy, than with patient characteristics.
If you want to prevent patients from falling out of bed, just put the mattress on the floor. For frail patients who are at risk of falling, an effective way to prevent them from getting out of a geriatric chair without using lap belts or chair tables, is to place a triangle of foam rubber under the thighs. I have never seen these modalities actually being used.

Medication

In the U.S., standards of care in nursing homes are defined by the federal government. Use of restraints, including chemical restraints (medications given to control disruptive behaviour), is severely restricted, and nursing homes must find alternative ways to deal with problem behaviours. No such standards exist in Canada.

One frequently occurring situation has to do with sleep. As people age, their sleep needs decrease, and over 65's generally need only 6 hours of sleep or less. However, in nursing homes, it's highly unusual to find staffing which is adequate for keeping the residents active and occupied for 18 hours every day. Instead, residents are frequently put to bed or encouraged to nap after breakfast, then again after lunch, and then by 8 o'clock in the evening everyone is expected to be asleep. Of course these people cannot sleep so many hours; when they start to waken at night, the staff will ask the doctor to prescribe sleeping medication. But sleeping medication has side effects: besides increasing the risk of falling and worsening memory problems, it can also cause depression. Falling is bad enough: 25% of elderly who fall and break a hip never walk again; of this group, half will be dead withing 2 years. But depression worsens dementia, weakens the immune system, and makes family members feel helpless.

Changing attitudes

Several years ago, when I was Director of Psychogeriatrics at Douglas Hospital, I had the opportunity to visit a centre d'acceuil in the Ville Emard area of Montreal. This nursing home was run by a gentleman whose own mother had had Alzheimer's and had been institutionalized. He had been appalled by the care she received, and resolved to do things differently.
For the five years that he had been Director General, he made it a point to personally interview all the staff who applied to work, regardless of whether it was the director of nursing or a floorsweeper. He hired only those individuals who he felt genuinely related to elderly and demented patients as real people worthy of the same dignity and respect as anyone else. It had taken five years for enough of the staff with old attitudes to quit or retire, for a critical mass of employees with the respectful attitudes he wanted, to be in place. And it worked! Residents had their own rooms; they controlled who came in. If a resident refused to let a staff enter their room, that refusal was respected. Resident rooms even had chains on the doors! There were no locked units. In the basement, there was a depanneur, a bank, and a daycare for the neighbourhood children. There was even a pub! All this, within the same budget as every other public nursing home received.

consequences of apolipoprotein E testing

(Mayeux & Schupf 1995) It is now possible to enter genetic information contained in an individual's DNA into widely accessible computerized databases. This raises novel privacy issues, as this data provides information about future risks for the individual and also for other family members. Employers might require apoE testing as a prerequisite of employment. This testing does not benefit the individual, as there is little known about effective ways to reduce risk or treat AD. However, it might be used by employers to deny health care insurance; other insurers will then also deny insurance. The information might also be used to deny employment or insurance coverage to the person's offspring.