

## Neurodegenerative Diseases

CNS neurons can not be regenerated.

Hard to analyze because:

effects of old age or accumulated damage, so long latency to onset.

hard to reproduce in animal models (age, human specific).

affect many cells, but predominately a particular groups of neurons that leads to symptoms

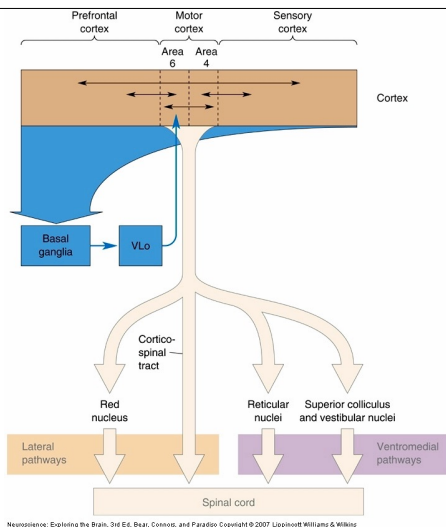
gain of function or loss of function?

caused by interactions of proteins, and we don't have tools to analyze protein interactions.

## Neurodegenerative Diseases

	Number of cases (in US)	Time course	Brain regions	Cellular pathology
<b>Cerebrovascular disease</b>	1.5 million new cases per year; third commonest cause of death	Acute, often persistent disability	Grey matter/white matter	Ischaemia/infarction; death of neurons; damage to axons
<b>Epilepsy</b>	~2.5 million cases	Paroxysmal	Neocortex, hippocampus, thalamus	Neuronal hyperexcitability
<b>Alzheimer's disease</b>	>5 million cases	Chronic, progressive	Neocortex, hippocampus, subcortical nuclei	Hyperphosphorylated tau in tangles; extracellular Ag deposits; degeneration of subsets of neurons in specific brain regions
<b>Parkinson's disease</b>	>500,000 cases	Chronic, progressive	Substantia nigra	Degeneration of dopaminergic neurons; $\alpha$ -synuclein inclusions (Lewy bodies)
<b>Multiple sclerosis</b>	300,000 cases	Acute, subacute, remitting, chronic	White matter	Demyelination; loss of oligodendroglial cells
<b>Huntington's Disease</b>	30,000	chronic	striatum	huntingtin inclusions

## Basal Ganglia





## Basal Ganglia (BG)

Modulate voluntary motor movements **by inhibiting CPGs.**

1. inputs from cortex, outputs -> motor areas
2. activity of BG neurons correlated with movement (during or after movement)
3. Lesions of BG -> severe movement disorders

No direct inputs from peripheral sensory systems  
No direct outputs to spinal motor circuits

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## Basal Ganglia Lesions

If BG modulates by inhibition of voluntary movement, then:

**provocative lesion:** complete inhibition of movement  
*hypokinetic Parkinsons disease*

**ablative lesion:** excessive, uninhibited movement  
*hyperkinetic Huntingtons disease*

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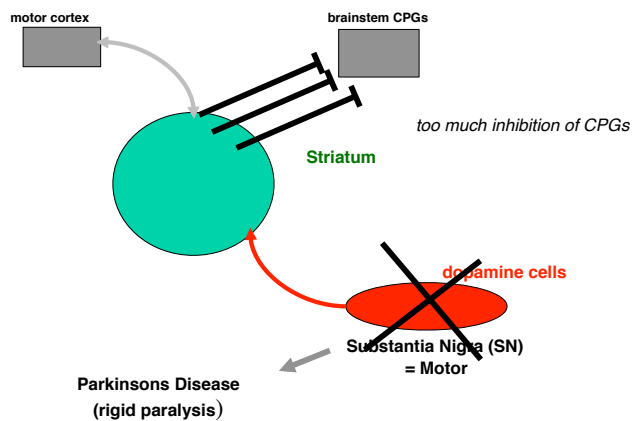
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## Basal Ganglia Lesions



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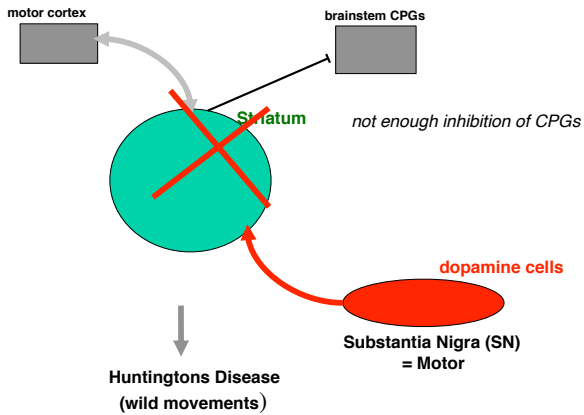
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## Basal Ganglia Lesions



## Huntington Disease or Chorea (dance)

Random excessive involuntary movements that look like voluntary movements.

**Hereditary** – characterized in Long Island families.

**Late onset** in life, but age of onset can be variable.

**Loss of neurons** in the striatum – not clear which ones.

**Loss of inhibition** of involuntary movements, or no negative feedback to cortex and brainstem.

**Molecular mechanism** is accumulation of mutant **huntingtin** protein (HD).

## The HD gene and CAG repeats

Mutation isolated from Venezuelan lineage.

Large gene - 170 kb long with 67 exons.

**CAG repeat** in exon 1 -> polyglutamine residue (polyQ)

Normally 6-30 repeats, but in Huntington Disease the CAG repeat undergoes **expansion** to 36-180 repeats.

## Gain of Function mutation:

*Note: striatal loss of inhibition, but molecular gain of function*

1. deletion of normal gene causes prenatal death in transgenic mice – so can't be a loss of gene function.

*(need to put 100s of repeats to give a mouse huntingtons within its lifespan)*

2. mutation is dominant, so only one copy of mutant gene causes HD
3. Conclusion: mutant protein adds an unintended, toxic component to cells expressing huntingtin.

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## Mechanism of Expansion Mutation

Originally spontaneous addition of a few repeats, but above a certain threshold (e.g. 30 repeats) replication becomes unstable and many more repeats can be added.

Repeats added during meiosis in sperm generation – so each generation gets a few more repeats.

Number of repeats predicts age of onset.

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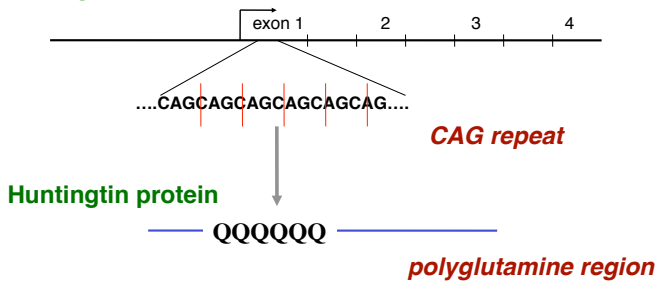
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## Mechanism of Expansion Mutation

*huntingtin gene*



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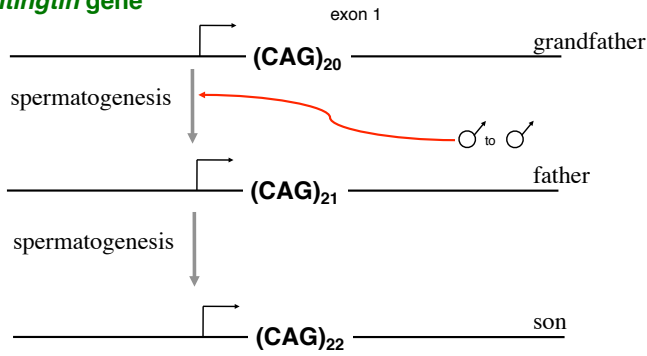
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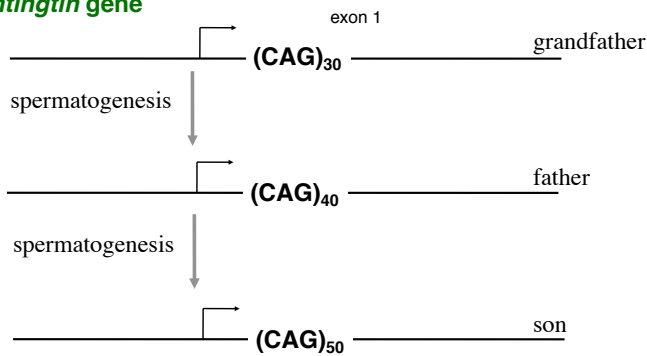
## Mechanism of Expansion Mutation

*huntingtin* gene

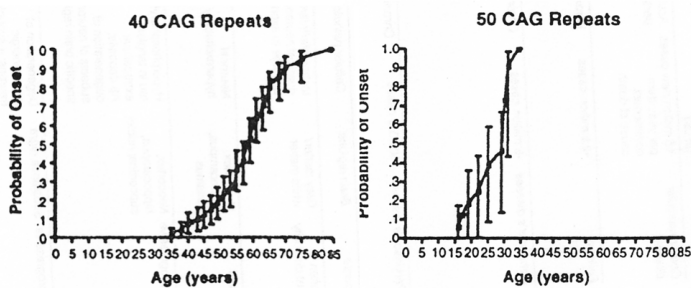


## Expansion less stable above (CAG)<sub>30</sub>

*huntingtin* gene



## Number of repeats predicts age of onset:



Accumulation of mutant protein?

Accumulation of neuronal damage by protein?

Combination of other insults + mutant protein?

## Repeat size predicts onset

CAG Repeat Size	Median Age at Onset* (95% CI) (years)
39	66 (72-59)
40	59 (61-56)
41	54 (56-52)
42	49 (50-48)
43	44 (45-42)
44	42 (43-40)
45	37 (39-36)
46	36 (37-35)
47	33 (35-31)
48	32 (34-30)
49	28 (32-25)
50	27 (30-24)

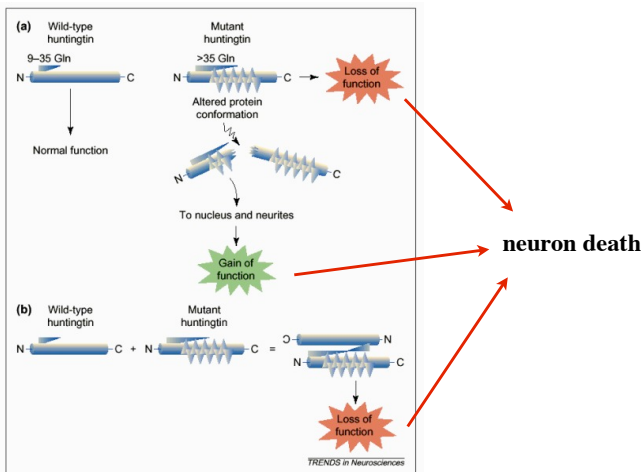
\* Age by which 50% of individuals will be affected.

## Repeat size predicts Penetrance

Estimation of Penetrance of CAG Expansion in HD Gene,  
by CAG Repeat Size

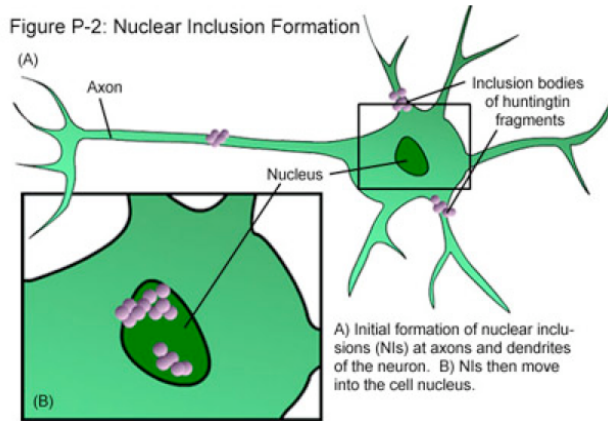
CAG Repeat Size	No. of Affected Individuals	No. of Unaffected Individuals, Age >75 Years (Males) or >80 Years (Females)	Total
<29-35	0	9	9
36	1	2	3
37	4	0	4
38	2	1	3*
39	8	1	9*
40	64	1	65
41	74	1	75
>41	575	0	575

## Huntingtin toxicity:



## Huntingtin Toxicity:

**Inclusions** of huntingtin and other filament proteins form in nucleus of striatal cells and muscle cells.



## Diagnostic tests

PCR first level screen for expansions. Vast majority of HD expansions will amplify. PCR primers which only flank the CAG region should be used for accurate sizing of repeats. In cases which result in a single band, a primer pair which also includes an adjacent 3' polymorphic CCG repeat can be used.

In small number of cases involving an unamplifiable expansion (>70 repeats) probe 4G6P1.8 can be used in a Southern blot which binds to a 1.8kb Pst1 fragment in normals which is expanded to 2.2kb in HD individuals.

Linked polymorphic microsatellite markers can still be used for exclusion testing.

- UK MRC18

## CAG repeat diseases

CAG repeat diseases are **common**, because of instability of CAG repeat expansion.

**Inclusions** form when a protein is expressed with too many CAG repeats.

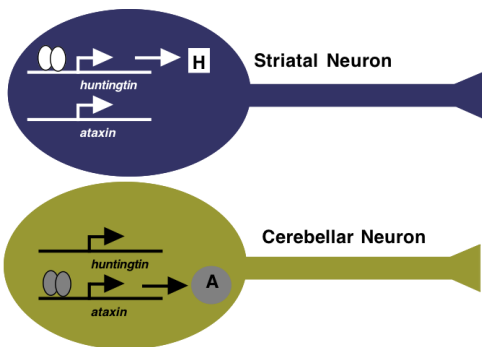
**Tissue specific:** System affected depends on which protein is expressed in what cells. (e.g. spinocerebellar ataxia -> inclusions in cerebellar cells).



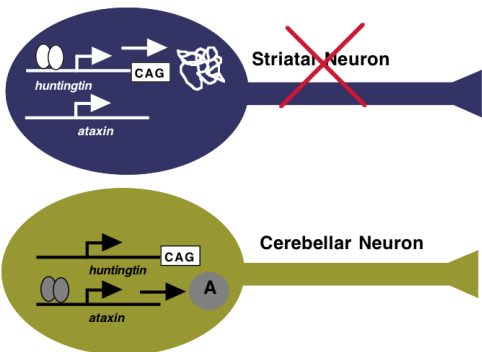
## Repeat diseases

Disease	Protein	Normal/Disease Repeats	Normal CAG sequence	Disease CAG sequence	Aggregates
Huntington	Huntingtin	6-35/38-180	Penultimate CAA interrupt	Penultimate CAA interrupt	Nuclear
Huntington 2	Junctophilin-3	6-27/35-57	?	Pure CAG	?
SCA1	Ataxin-1	6-39/40-88	1-3 CAT interrupts	Pure CAG	Nuclear
SCA2	Ataxin-2	14-32/33-77	CAA interruptions	Pure CAG Anticipation-20 yrs	? Cytoplasmic
SCA3	Ataxin-3	12-40/55-86	1 GGG or CGG polymorphism	1 CGG (90%) polymorphism	Nuclear
SCA6	P/Q Ca <sup>++</sup> Channel	4-18/21-31	?	?	?
SCA7	Ataxin-7	7-17/34-200	?	?	Nuclear
SCA12	PPP2R2B	7-32/55-93	?	Purer CAG	?
SBMA	Androgen Receptor	9-36/38-65	Pure CAG	Pure CAG	Nuclear
DRPLA	Atrophin-1	3-36/49-88	Pure CAG	Pure CAG	Nuclear
Ataxia & Intellectual Δ	TATA-binding protein	25-42/45-63	CAA interruptions	CAA interruptions	?
Schizophrenia	KCNN3	12-28/Long alleles over-represented			

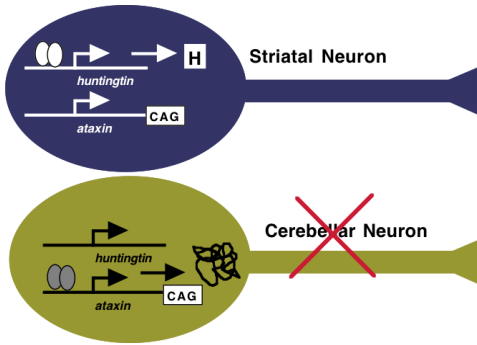
## Neuron-specific Gene Expression



## Huntingtons



## Spinocerebellar Ataxia



**Ultimate cause known,  
but no treatment, no cure.**

## Parkinsons Disease

Loss of Dopamine Cells in the Substantia Nigra

### Causes of Parkinsons

- Encephalitis Lethargica
- MPTP

### Treatments for Parkinsons

- L-DOPA
- Dopamine Agonists
- Cell Transplants
- Chronic Electrodes

## Causes of Parkinsons Disease

### Loss of Dopamine Cells in the Substantia Nigra

#### Shaking Palsy (*Paralysis Agitans*)

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured.

James Parkinson, 1812

He was a member of several secret political societies, including the London Corresponding Society for Reform of Parliamentary Representation.

In 1794 his membership in the organization led to his being examined under oath before the Privy Council to give evidence about a plot to assassinate King George III. He refused to testify regarding his part in "The Pop-Gun Plot", until he was certain he would not be forced to incriminate himself.

The plan was to use a poisoned dart fired from a "pop gun" to bring the king's reign to a premature conclusion. Fortunately for Parkinson, the whole affair was soon forgotten, and no charges were ever brought against him

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## Subjects: 3 patients, 3 passerbys on the street

#### Case II.

The subject of the case which was next noticed was casually met with in the street. It was a man sixty-two years of age; the greater part of whose life had been spent as an attendant at a magistrate's office. He had suffered from the disease about eight or ten years. All the extremities were considerably agitated, the speech was very much interrupted, and the body much bowed and shaken. He walked almost entirely on the fore part of his feet, and would have fallen every step if he had not been supported by his stick. He described the disease as having come on very gradually, and as being, according to his full assurance, the consequence of considerable irregularities in his mode of living, and particularly of indulgence in spirituous liquors. He was the inmate of a poor-house of a distant parish, and being fully assured of the incurable nature of his complaint, declined making any attempts for relief.

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## Encephalitis Lethargica

### sleeping sickness with Parkinsons years later

Usually associated with the influenza epidemic that claimed more than 30 million lives, tens of thousands of cases of encephalitis were reported during and after the first World War.

The prodromal phenomena consists of general discomfort, shivering, headache, and slight pharyngitis. The temperature is generally only a little raised to slightly above 98°C.... Within the next few days, somnolence begins to predominate. The patients left to themselves fall asleep in the act of sitting and standing, and even while walking, or during meals with food in the mouth.... if aroused, they wake up quickly and completely, are oriented and fully conscious ... but soon drop back to sleep. Sleep in this form may last for weeks or even months but frequently deepens to a state of most intense stupor or even a comatose condition which may terminate fatally after some days or weeks.

[news.bbc.co.uk/2/hi/health/3930727.stm](http://news.bbc.co.uk/2/hi/health/3930727.stm)  
[www.balllement.com/lettres/vonecononmo.html](http://www.balllement.com/lettres/vonecononmo.html)

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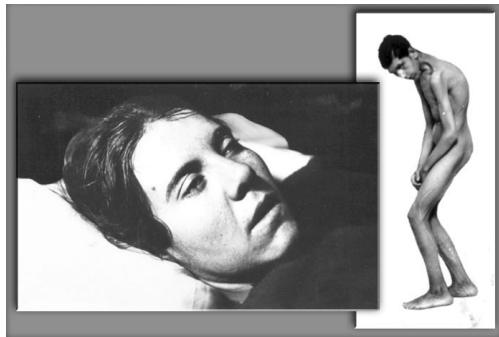
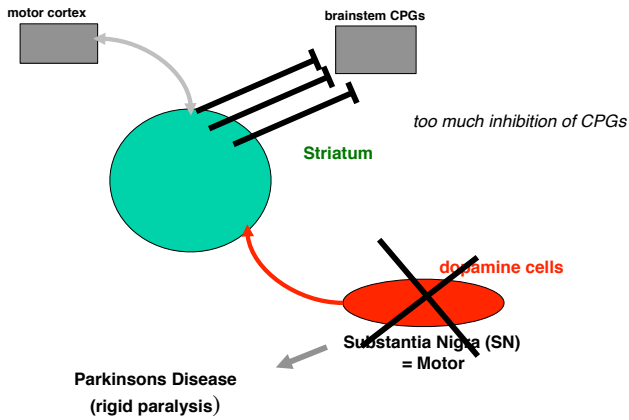
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## Basal Ganglia Lesions



Von Economo wrote in 1918: It seems strange when sleep appears as a symptom of an illness. "Sleeping sickness", where people fall asleep while eating or working was first described in two cases in our clinic in Vienna in 1916. Usually headache, nausea and fever were followed, often within one day, by sleeping that frequently occurred in the most uncomfortable positions."

Among the late sequelae, post-encephalitic parkinsonism was particularly common. Von Economo wrote, "the amyostatic-akinetic form... characterized by a rigidity, without a real palsy and without symptoms arising from the pyramidal tract.... To look at these patients one would suppose them to be a state of profound secondary dementia. Emotions are scarcely noticeable in the face, but they are mentally intact." Photograph (right) from Barcelona clinic of L. Barraquer Ferré (c. 1930, 1919).

[www.aneuroa.org/html/c20html/1910\\_1919.htm](http://www.aneuroa.org/html/c20html/1910_1919.htm)

## Encephalitis Lethargica

sleeping sickness with Parkinsons years later

As early as 1920 von Economo began observing cases that had apparently recovered fully, only to be stricken with parkinsonian features months, or even years, later.

"Parkinsonism may develop in immediate sequence after the amyostatic form ... as well as 4 or 5 years after an apparently complete recovery from acute encephalitic lethargica. The acute stage may have been slight or serious; it is of no importance in indicating the probable development of later symptoms. Often we see cases where such sequelae develop with no history of a previous acute phase."

[www.bailllement.com/lettres/voneconomo.html](http://www.bailllement.com/lettres/voneconomo.html)











## Mirapex and other dopamine agonists: compulsive gambling, sex, shopping

When Wayne Kanuch received a diagnosis of Parkinson's disease in 1993, the last thing he imagined was that the drug prescribed to treat his illness would turn him into a compulsive gambler and put his libido into overdrive. Kanuch's marriage ended in divorce, partly as a result of the sexual pressures he placed on his wife, and he began losing fortunes at the racetrack. He was fired from his job at Chevron for trolling for dates on the Internet while at work, and he quickly went bankrupt. "I contemplated suicide a couple of times," he said in an interview last week. "Everyone was blaming and I was looking at the mirror and blaming myself and asking why I could not stop."

Source: Washington Post  
Date: 19 March 2006

## Mirapex and other dopamine agonists: compulsive gambling, sex, shopping

New evidence unearthed by scientists at the Food and Drug Administration, Duke University and other centers suggest the reason Kanuch could not stop is that the drug being used to treat Parkinson's boosted the level of dopamine in his brain. Researchers are looking into the possibility that dopamine, which is associated with a host of addictive behaviors, may turn some Parkinson's patients into obsessive pleasure seekers.

Source: Washington Post  
Date: 19 March 2006

Barbara Hermansen, 52, of Winnetka, Ill., said she was prescribed Permax in 1996 for restless-leg syndrome, in which patients feel electrical impulses crawling under their skin when they lie down to sleep -- and causing debilitating bouts of insomnia.

The drug worked like a charm, and her physician steadily increased the dose, which tends to be necessary -- by 2001, she was on 40 times her original dose. On a weekend visit to Las Vegas with her sister, Hermansen dropped \$300, which surprised the Sunday-school teacher because before that she had been in a casino twice before and could not wait to get out.

On returning home, the financially conservative lawyer began gambling over the Internet. She maxed out her credit cards, emptied her retirement accounts and sold jewelry to fuel the gambling. When she confessed to her husband after losing about \$15,000, she said he was incredulous because she had been so staid when it came to finances.

...

When Hermansen asked her neurologist if the drug might be the problem, he said he did not know of a connection. At a Gamblers Anonymous meeting, the theory was booted down and she was told she needed to take responsibility for her actions. A therapist suggested she was testing her husband's love because she felt she didn't deserve to be happy; a psychiatrist told her to make a list of all the reasons she was trying to sabotage her life.

When an expert in pathological gambling finally took her off the drug, the urge to gamble vanished. The restless-leg syndrome came back with a vengeance, but Hermansen swears that she would rather "suffer from insomnia for the rest of my life rather than go through that gambling hell."

Source: Washington Post  
Date: 19 March 2006

