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Hungry brains- trialling creatine in Huntington's disease

Huntington's Disease

THE

MEDICAL AND SURGICAL REPORTER.

No. 789.] PHILADELPHIA, APRIL 13, 1872. [Vol. XXVI.—No. 15.

ORIGINAL DEPARTMENT.

Communications.

ON CHOREA.

By George Huntington, M. D.,
Of Pomeroy, Ohio.

Essay read before the Meigs and Mason Academy of Medicine at Middleport, Ohio, February 14, 1872

Chorea is essentially a disease of the nervous system. The name "chorea" is given to the disea-e on account of the *dancing* propensities of those who are affected by it, and it is a very appropriate designation. The disease, as it is commonly seen, is by no means a dangerous or serious affection, however distressing it may be to the one suffering from it, or to his friends. Its most marked and char-

The upper extremities may be the first affected, or both simultaneously. All the voluntary muscles are liable to be affected, those of the face rarely being exempted.

If the patient attempt to protrude the tongue it is accomplished with a great deal of difficulty and uncertainty. The hands are kept rolling—first the palms upward, and then the backs. The shoulders are shrugged, and the feet and legs kept in perpetual motion; the toes are turned in, and then everted; one foot is thrown across the other, and then suddenly withdrawn, and, in short, every conceivable attitude and expression is assumed, and so varied and irregular are the motions gone through with, that a complete de-cription of

1872

Huntingtin 1993

- Pre 1993
  - Familial Nature of Disease
  - Anticipation
  - Anatomical studies of brain
  - Some information about the chemical abnormalities
- Post 1993
  - Triplet Expansion
  - Anticipation confirmed and explained
  - Genetic Counselling

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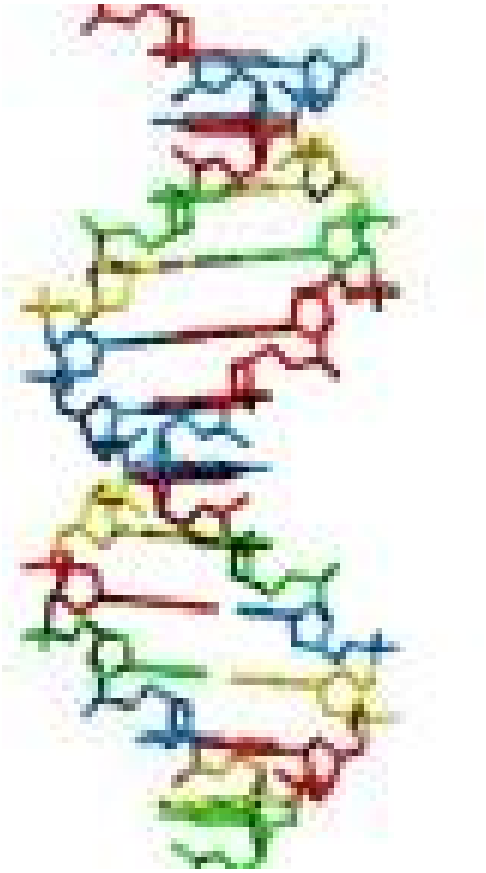
  - *How does gene expansion cause disease?*
  - *What can be done about it?*

DNA

- Double Helix
- 4 bases

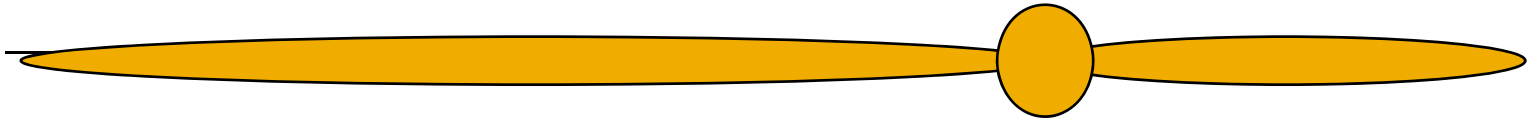
  A - - T

  G - - C
- 2, 300, 000, 000 in humans



Chromosome

Triplet Repeat Disease: What is it?



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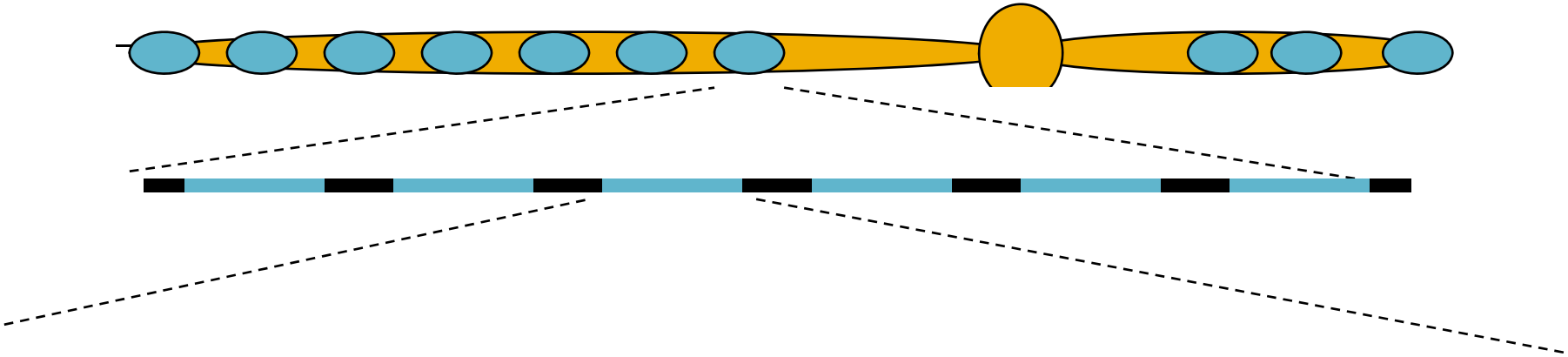

…TAGCTCAGCAGCAGCAGCAGCAGCAGCAGCAGTAAC …

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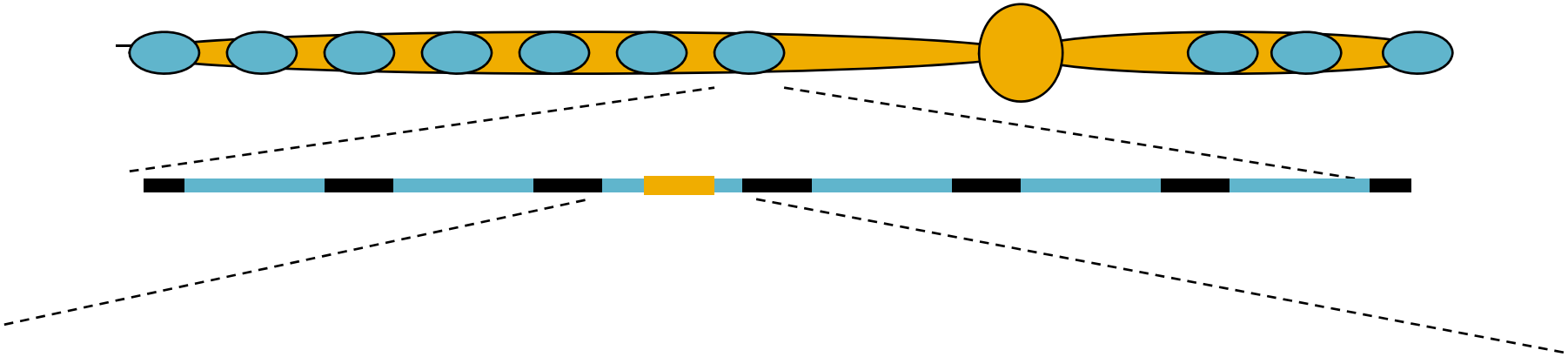

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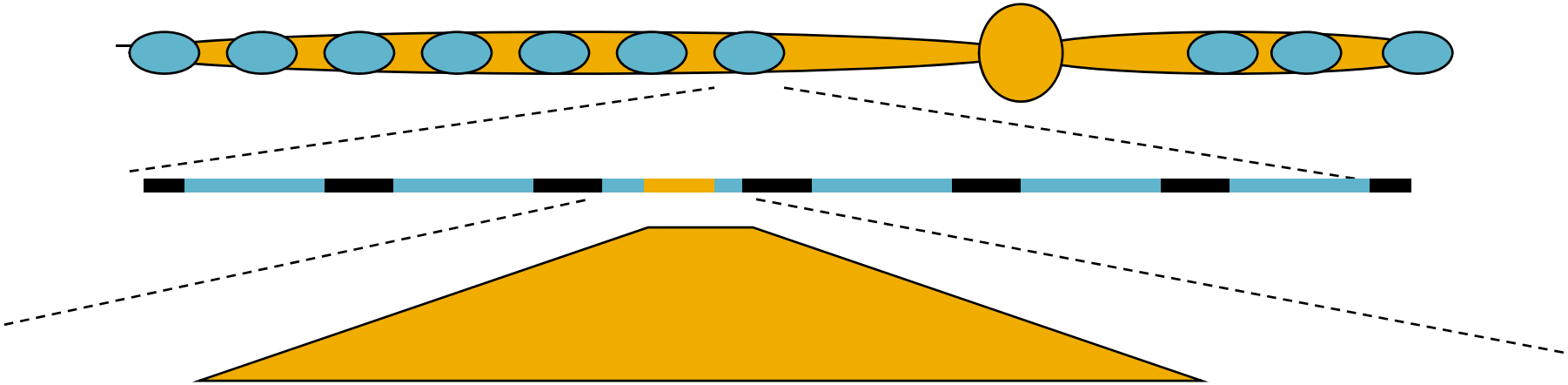

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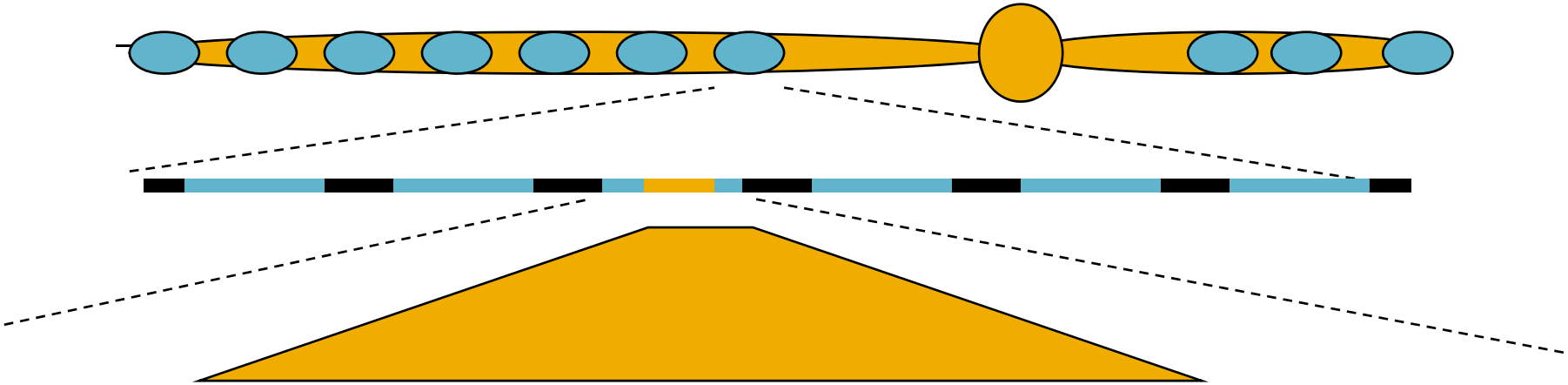
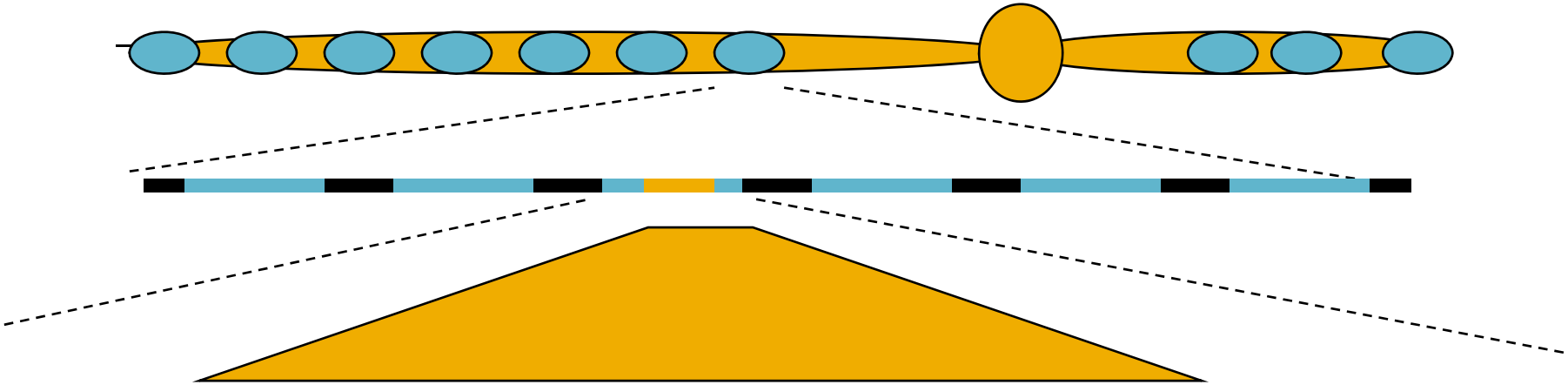


... TAGCTCAGCAGCAGCAGCAGCAGCAGCAGCAGCTGTAAC ...

↓

Protein

Triplet Repeat Disease: What is it?



... TAGCTCAGCAGCAGCAGCAGCAGCAGCAGCTGTAAC ...

... Ala-Leu-Gln-Gln- Gln-Gln- Gln-Gln- Gln-Gln- Tyr-Pro-Ile ...

Triplet Repeat Disease: What is it?

... GCTCAGCAGCAGCAGCAG ... CAGCAGCAGCTAC ...

Normal 5-35 Repeats

Pathological Expansion

... GCAGCAGCAGCAGCAG ... CAGCAGCAGCAGCAGTAC ...

>40 Repeats

Modelling – The advantage of studying genetic disease

... GCTCAGCAGCAGCAGCAG ... CAGCAGCAGCTAC ...

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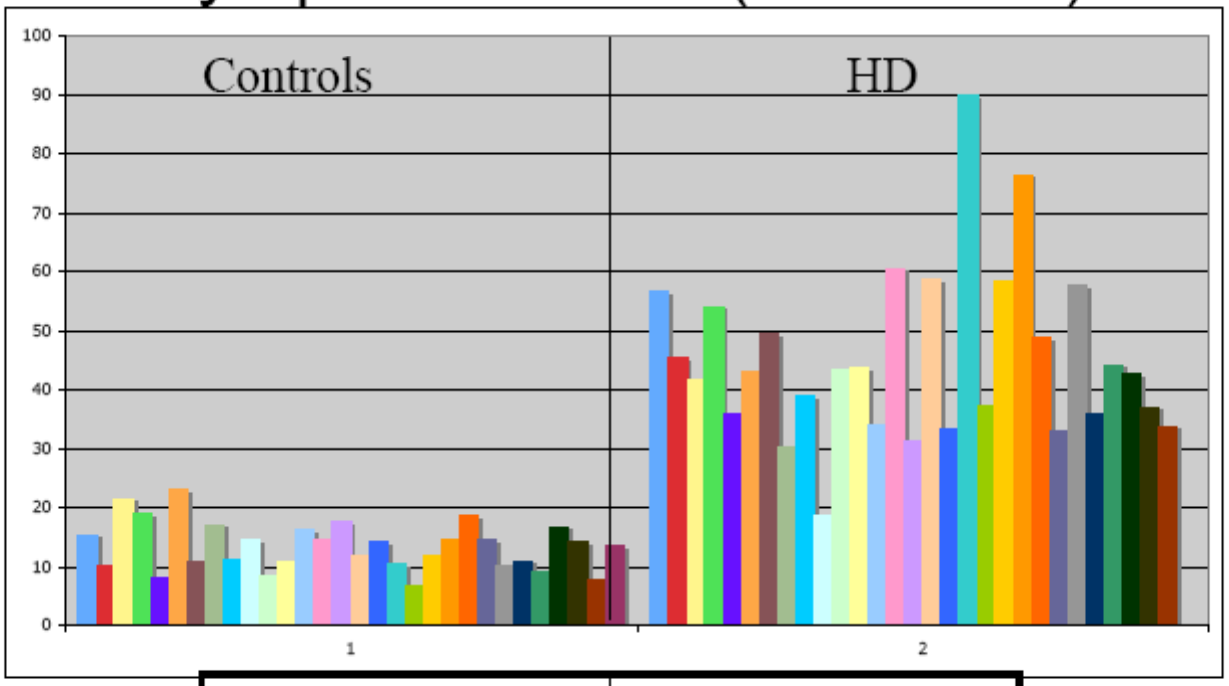
Human Studies

What have we learned?

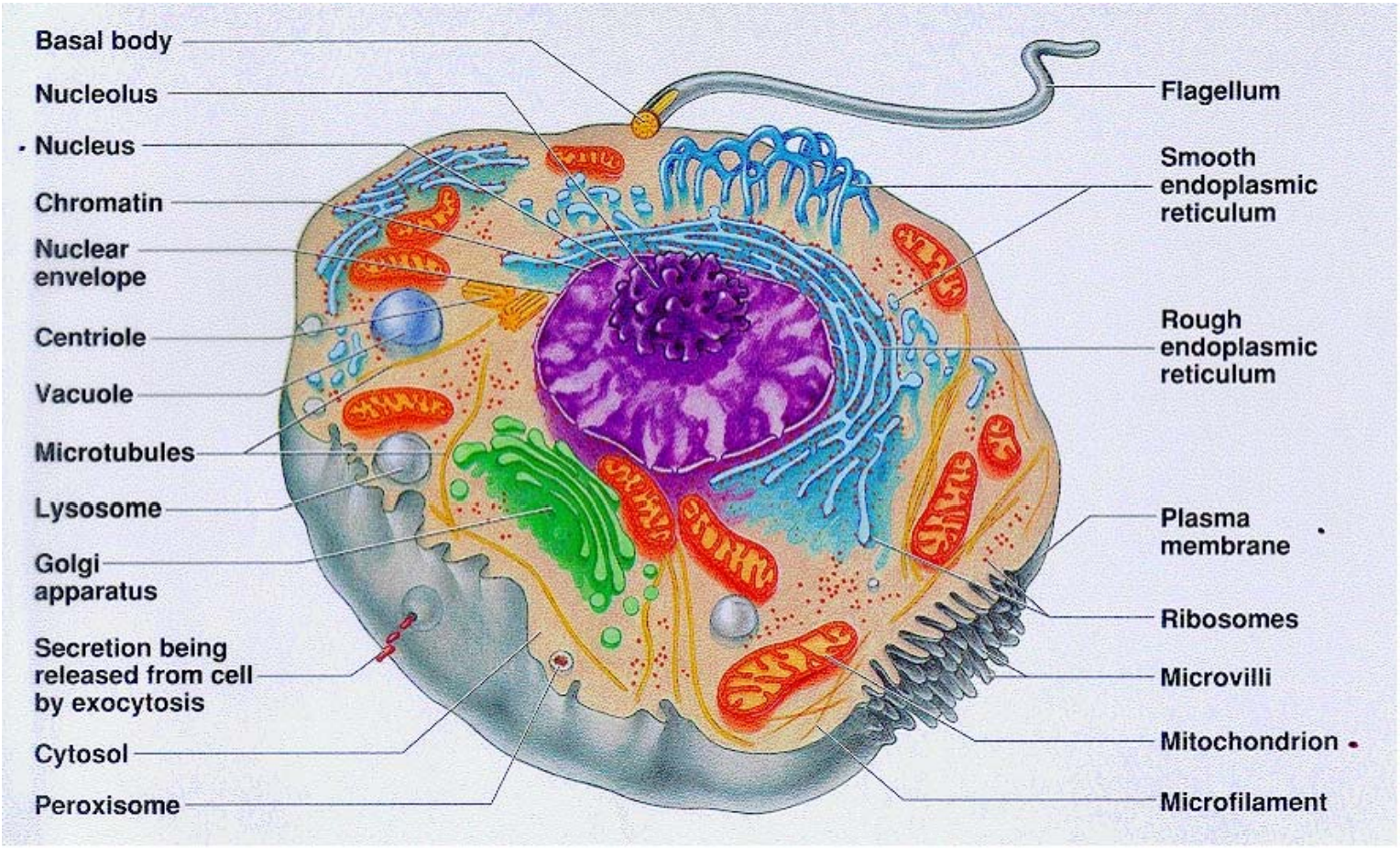
Huntington's Brains are under Stress

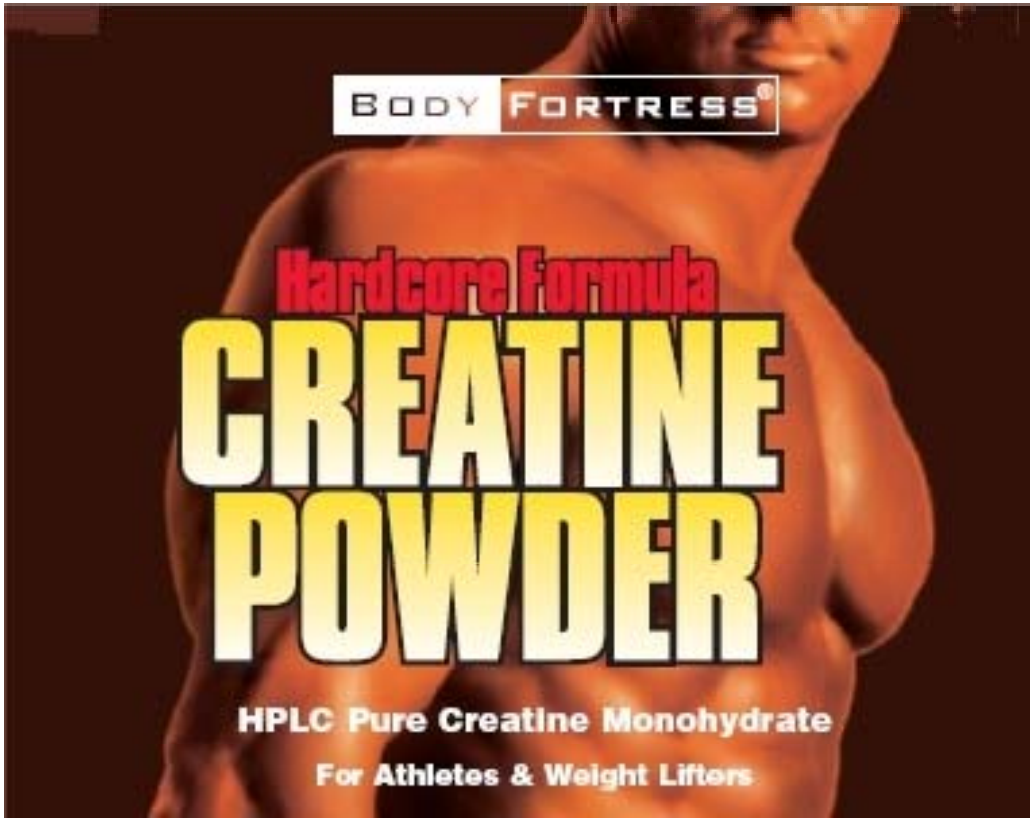
8OH2'dG is Elevated in Early Symptomatic HD (TFC 13-7)



Mean=13.5	Mean=45.3
SD=4.04	SD=14.62

Huntington's Mitochondria are unstable



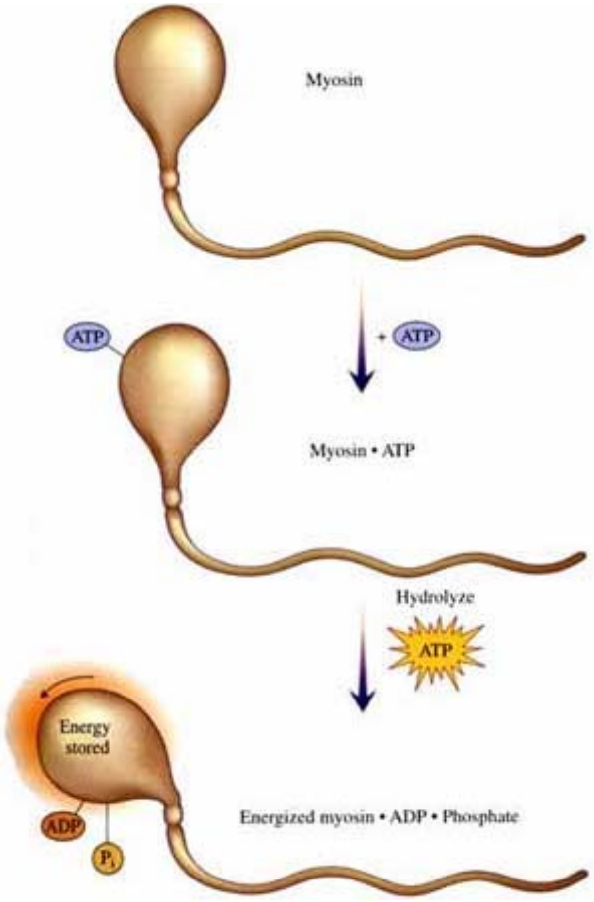

BODY FORTRESS®
Hardcore Formula
CREATINE
POWDER
HPLC Pure Creatine Monohydrate
For Athletes & Weight Lifters

Creatine - What is it

- Found in animal tissues
- (Almost) Immediate Energy Source

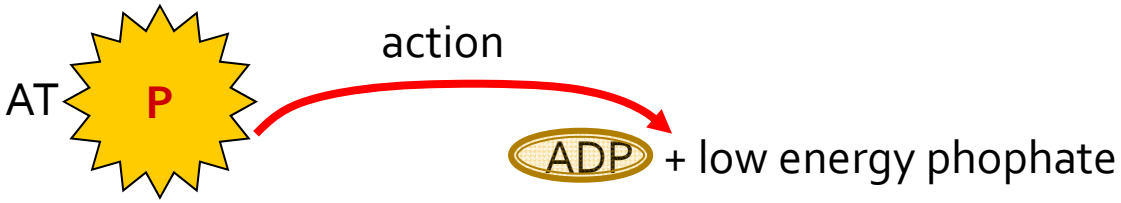
Slow	Fast	Recharge	Immediate
Fat	Glucose	Creatine P	ATP

Creatine - What is it



Creatine: Instant Recharge

ATP = Adenosine triple Phosphate ADP = double phosphate



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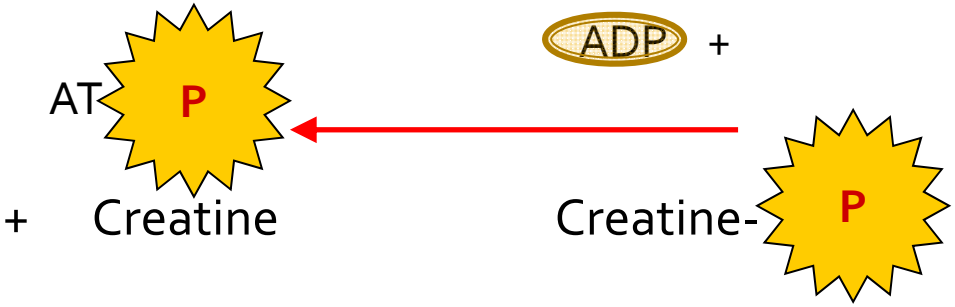

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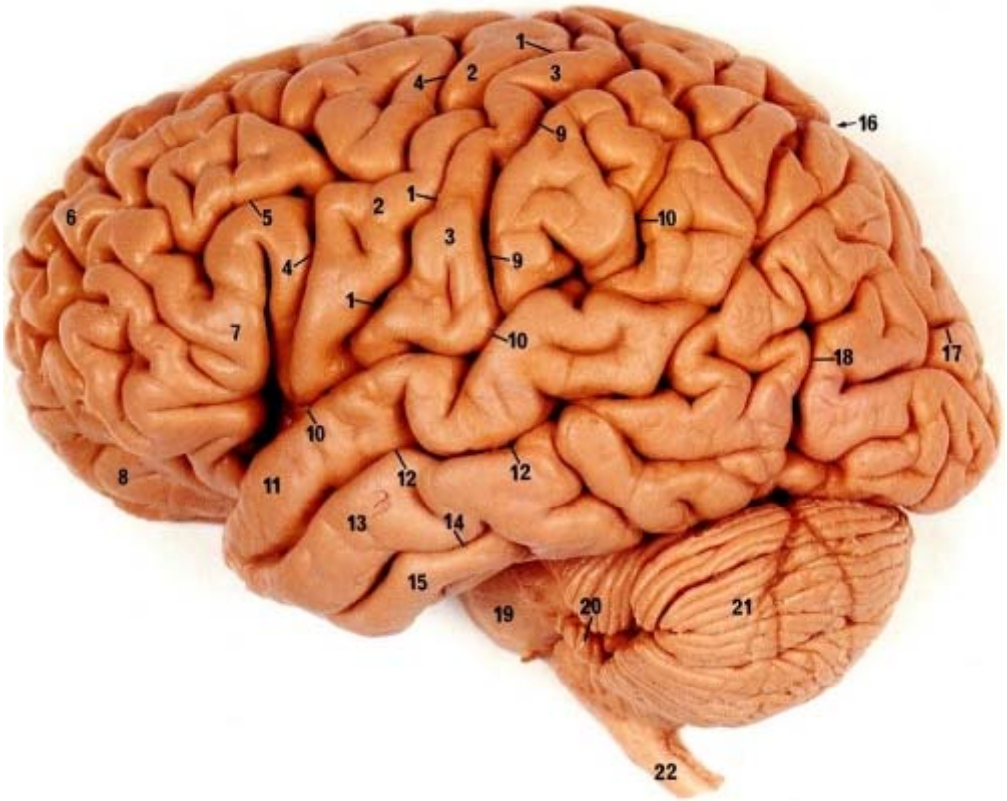
Brains use Energy too!



Creatine in Huntington's Disease

- 2000/1 Transgenic Huntington's Mice given creatine
  - live longer
  - show less damage in the brain
  - prevents diabetes
  - interferes with aggregate formation

Creatine Trials in Humans

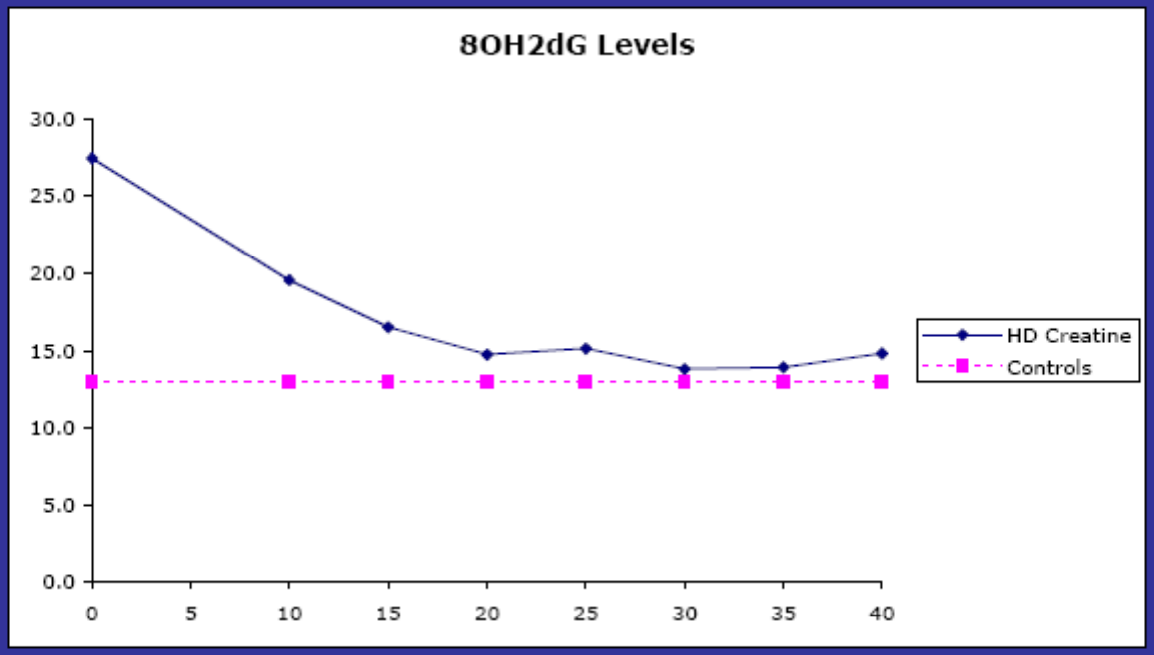
- 2001 small trial Belgium 52 patients
  - 5 g/day
  - Exercise fitness, coordination improved
  - Neuro exam no difference

2006: Creatine Safety Trial

- 64 patients
- Either creatine or placebo
- 16 weeks
- 8 g creatine
- No difference in side effects
- Measure of cell stress markedly reduced

Creatine reduces cell stress

Dose Dependent Suppression of 8OH2'dG by Creatine in Symptomatic HD (CREST-UP)



2007 Creatine Dose Ranging Study

- World Congress on Huntington's Disease
- Patients tolerate up to 40 g / day
- Slowing of cognitive changes
- Slowing of brain atrophy

CREST-E Study

- Huntington's Study Group
- National Institutes of Health funded
- Randomized, double blind placebo controlled trial.
- 650 participants from over 40 HSG centres
- 3 years
- Very high dose (up to 40 g/day)

CREST-E Study

- Outcome measures
  - total functional capacity (TFC)
  - Physical and cognitive tests
  - Quality of life
  - Markers in blood

CREST-E Study

- Study Timetable
  - 3 years
  - Weekly, then monthly phone calls
  - Visits to Auckland Hospital
    - monthly for four months
    - then six monthly for to 3 years
  - MRI scans at yearly intervals

CREST-E Study

- Eligibility
  - Disease severity
    - Motor symptoms
    - Largely Independent
  - Age
  - Other illnesses

CREST-E Study

- Progress in NZ
  - Personnel
    - Virginia Hogg Study Coordinator
    - Richard Roxburgh Primary Investigator
  - Recruitment
    - First Patient next Wednesday

Acknowledgements

- Prof Richard Faull
- Prof Steve Hersch and Diana Rosas
- Dr Lynette Tippett
- Virginia Hogg
- Jo Dysart and Jane Devine
- Dr Greg Finucane
- Dale Kerr
- Prof Don Love and Elaine Doherty
- Prof David Christie