BACK TO BASICS: REVISITING THE FUTURE
(AND REMINISCENCES)

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the 26th Bertil Aldman Lecture

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Clinical Professor of Neurosurgery George Washington University, USA

IRCOBI, September (the 7th Roman Month) 11, 2019
Firenze, Italy

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How did we get to now?

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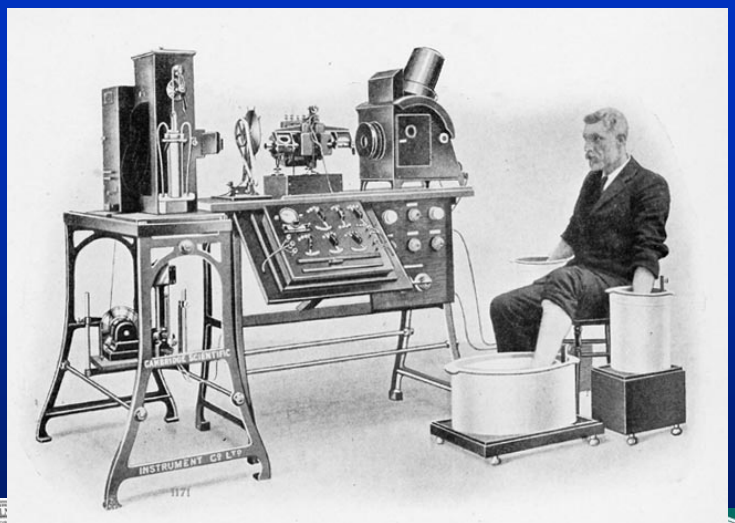
When I started….



PHOTOGRAPH OF A COMPLETE ELECTROCARDIOGRAPH, SHOWING THE MANNER IN WHICH THE ELECTRODES ARE ATTACHED TO THE PATIENT, IN THIS CASE THE HANDS AND ONE FOOT BEING IMMERSED IN JARS OF SALT SOLUTION

An early Electrocardiograph

To now

JOURNAL OF NEUROTRAUMA 35:1–6 (XXXX XX, 2018)
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DOI: 10.1089/neu.2018.5836

Original Article

Association of Acute Increase in Plasma Neurofilament Light with Repetitive Subconcussive Head Impacts: A Pilot Randomized Control Trial

Angela Wirsching,[1] Zhongxue Chen,[2] Zachary W. Bevilacqua,[1] Megan E. Huibregtse,[1] and Keisuke Kawata[1,3]

detecting proteins at Sub-femtomolar concentrations

To now

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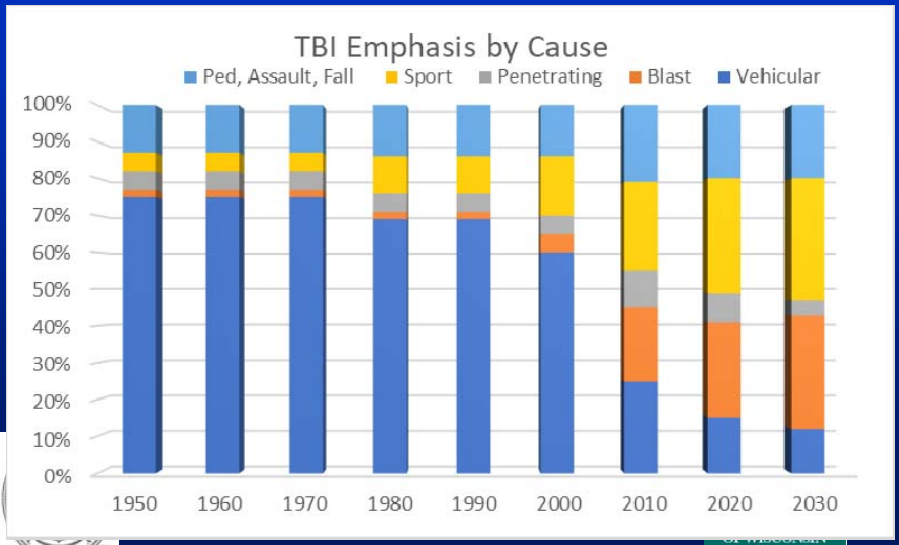
detecting proteins at Sub-femtomolar concentrations

10^{-15}

What we think we know about TBI

What we study changes with time



Purpose of this presentation

- To review aspects of team Gennarelli-Thibault research
- To appreciate data analysis techniques and their influence on head injury tolerances
- To modify conceptual paradigms of brain injury after re-analysis of data

Subtitle:

Don't forget the "bio" side of biomechanics

It still allows for fruitful biomechanical research

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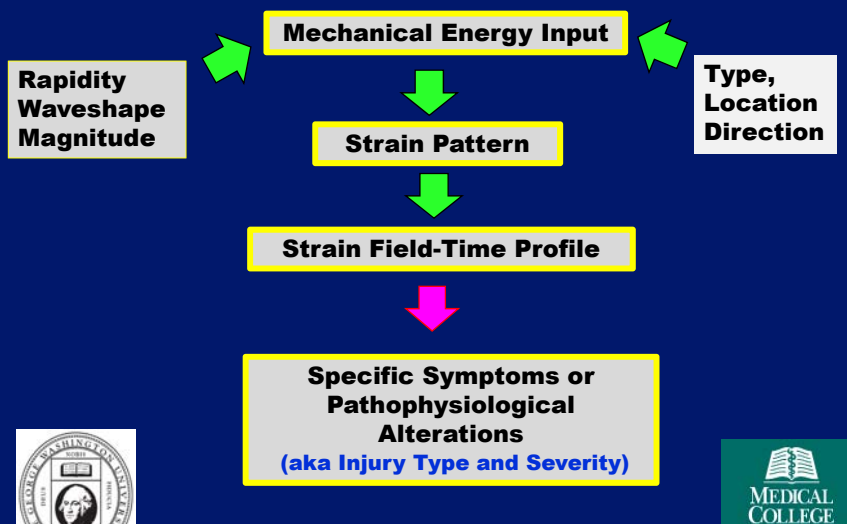
Injury Pattern Depends on Brain Strain Pattern



Strain in the Brain: our mechanistic concept

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Strain in the Brain

- Until recently, brain strain could not be measured (or computed) so surrogate measures were used (acceleration, velocity)
- Unfortunately, WE have studied only a few of sets of input variables and thus, very few of the many possible "strain field-time profiles"

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Phase 1: 1970-1974 HAD-II:
Were all types of head motion equally important in producing concussion?

- Modified an existing apparatus (HAD-I) to constrain, single, non-impact, AP planar head movement to either translational or angular sagittal motion
- Delivered equivalent accelerations
- Result: ***only angular motions produced concussion (as then defined)***

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Conclusions of HAD-II

- "Rotation of the head is more likely to produce cerebral concussion than translation."
- "translation alone can produce visible brain lesions."
- "at the levels of translation studied, concussion does not occur.
- "We cannot say that concussion will not occur in translation at higher acceleration levels"

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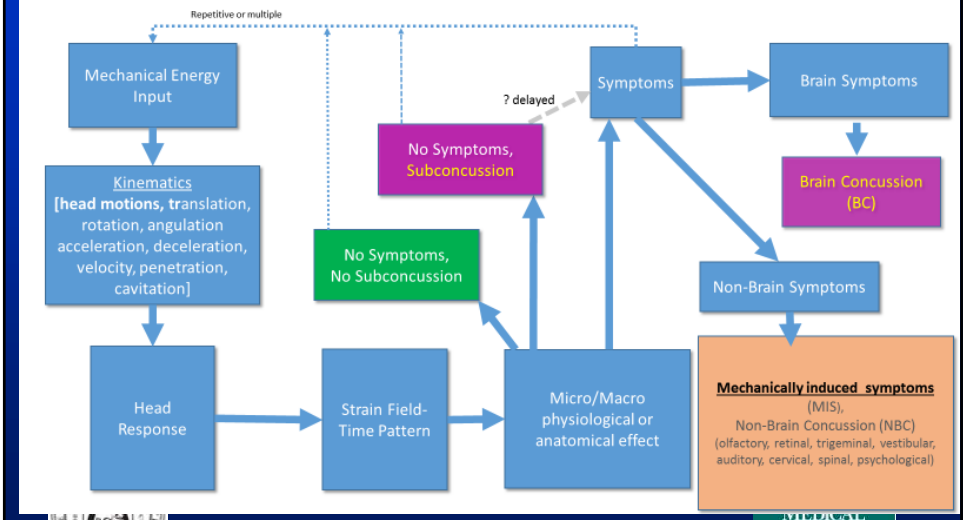
Concussion in 2019



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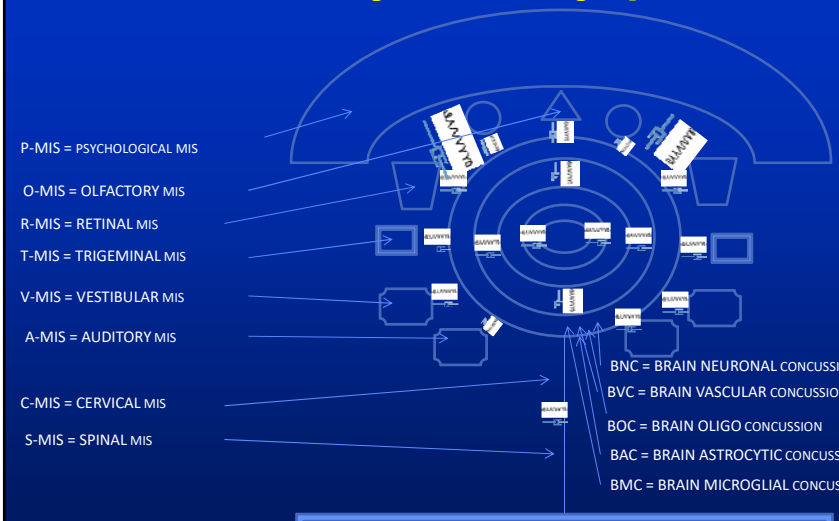
Symptomcentric Concept of the Concussions: Mechanically Induced Symptoms



Gennarelli IRCOBI 2015

These can occur singly or in any combination

Surely, these are not all due just to angular head movements

The Concussions 2018

Bromeliad analogy

Phase 2: 1976-1980, Penn I:

Can prolonged coma (DAI) be produced by raising angular acceleration higher than concussion levels?

- Building from the HAD-II results, a programmable piston (HYGE) was developed to move a subject head in the sagittal plane by non-impact angulation
- Once concussion was achieved, higher accelerations were used in an attempt to produce prolonged coma (now DAI)
- **Result**: ***DAI was not achieved, but ASDH due to bridging vein rupture were***

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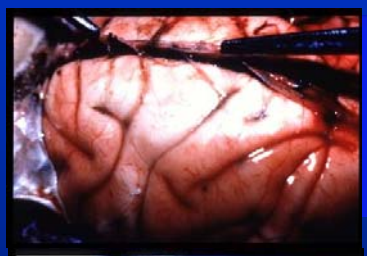
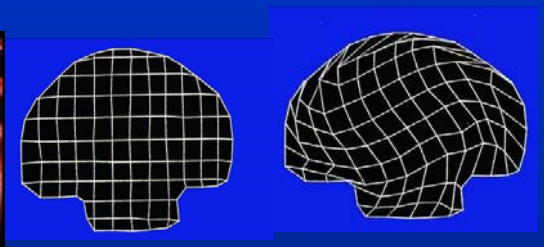
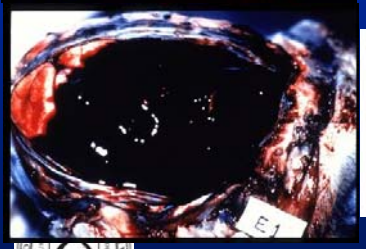
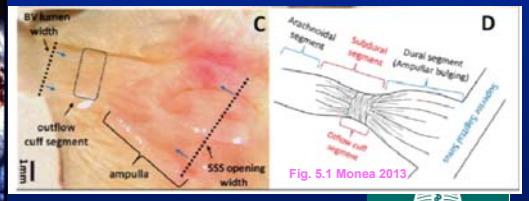
BRIDGING VEIN RUPTURE → SDH









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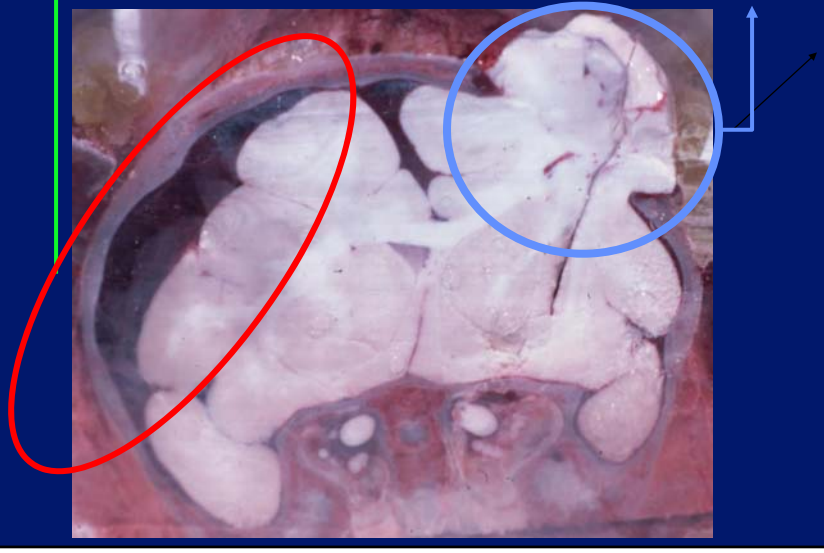
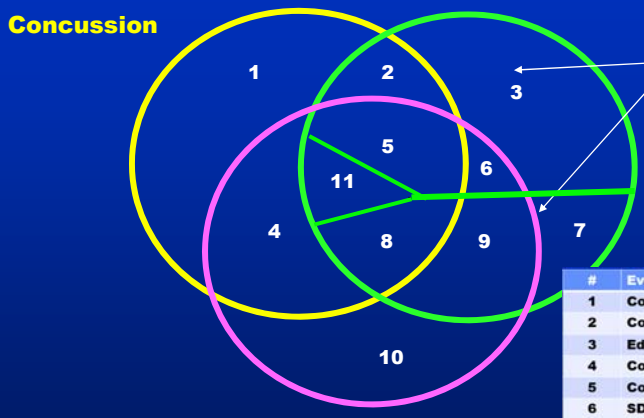
ASDH and Brain Swelling



Consequences of a sporting impact



#	Event(s)
1	Concussion
2	Concussion + Edema
3	Edema
4	Concussion + SDH
5	Concussion + SDH + Edema
6	SDH + Edema
7	Hyperemia
8	Concussion + SDH + Hyperemia
9	SDH + Hyperemia
10	SDH
11	Concussion + SDH + Edema + Hyperemia

Phase 3: 1980-1985, Penn II

Can prolonged coma be produced by altering input dynamics?

- Many believed that prolong coma was a human phenomena and would never be produced in non-human species
- Penn II was configured to
  - Increase the pulse duration
  - Provide coronal plane motions
- **Result**: ***prolonged coma was produced when longer duration coronal motions were used.***

Penn- II Conclusions

- importance of input direction on brain response
- blood vessels (ASDH) were more susceptible to injury at short pulse durations and that axons (DAI) were more susceptible to injury at longer pulse durations, and
- implicated the axon as a locus of brain damage due to these input conditions.

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Penn- II Conclusions

- However, we never concluded that the axon was the only site of injury.
- Nonetheless, many researchers, including our own team, began to focus on what happed to the axon and neurons after injury

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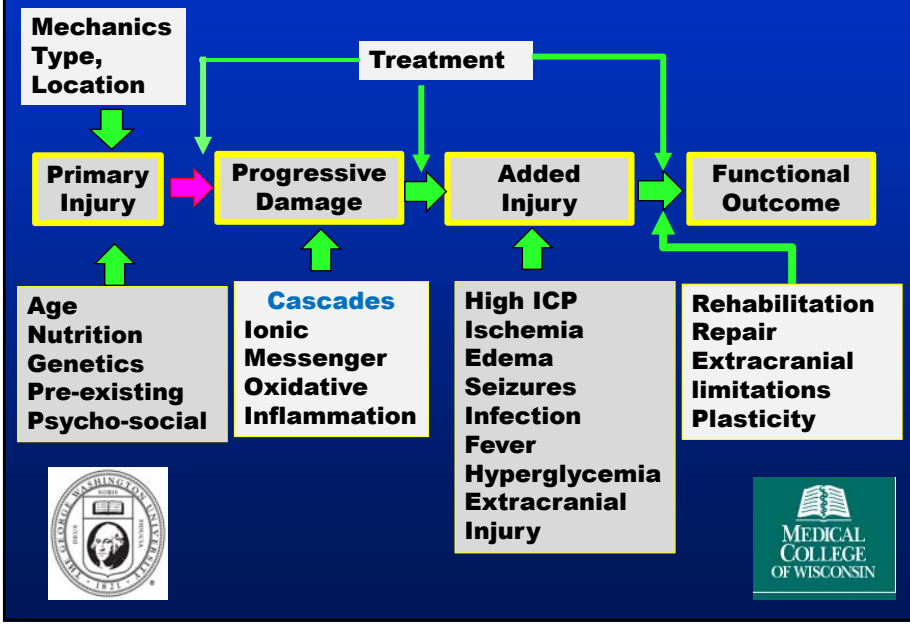
Influences on Head injury Outcome



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TBI Damage Progression

Is this link mechanical or biological???

Primary Injury → **Progressive Damage**

What is the initiator of deleterious cascades?:

- **I**onic/Calcium damage:
- **O**xidative damage:
- **M**essenger Dysfunction:
- **I**nflammation:

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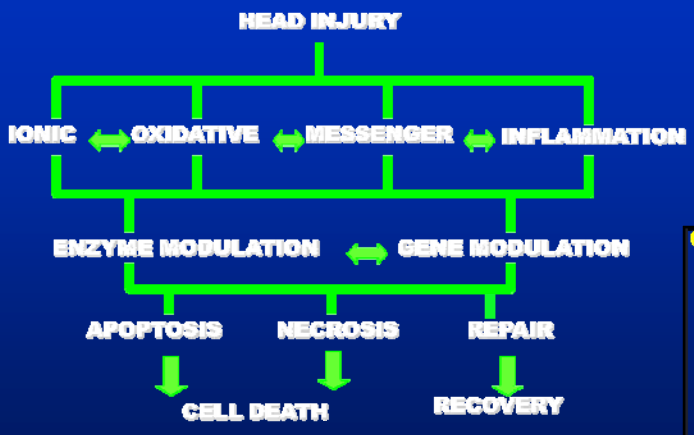
CELLULAR DAMAGE AFTER HEAD INJURY



Proportion changes in different types of brain injury and magnitude modulates over time

Can affect

-Vascular,

-Neural,

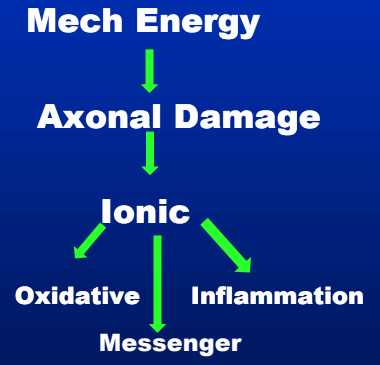
-Mitochondrial

-Glial

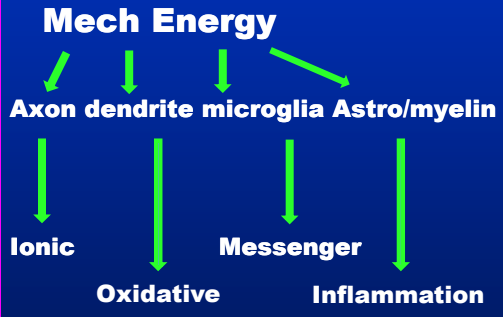
elements

Possible Mechanisms for Mechanisms of Damage

- **Serial**



- **Parallel**



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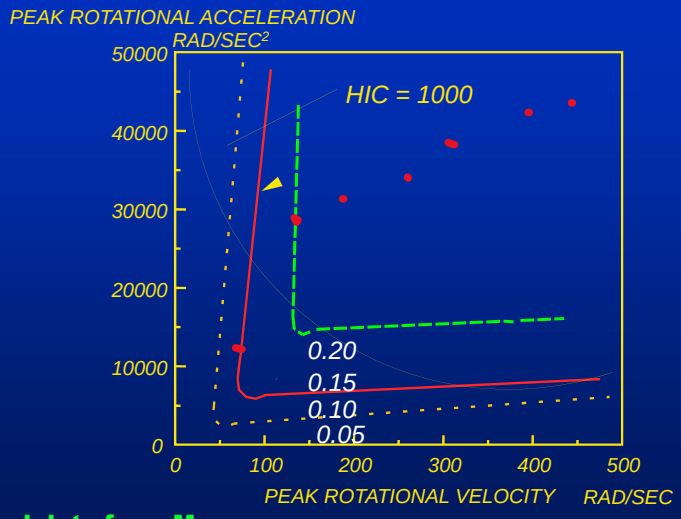
Phase 5: Re-analysis

- What is the error in relating experimental data to humans?
- The pure experimental situation is rarely seen in human TBI (pure planar, non-impact, uniform acceleration, etc.)
- What is effect of waveform shape on strain field?
- Is there too much focus on the axon?

Phase 5: Transferring animal data to human tolerances

- Effect of wave shape
- Conceptual relation between angular velocity (aka pulse duration and brain response
- Quantitative relations

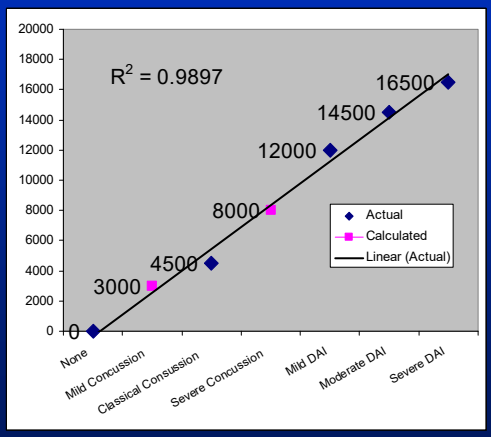
DAI THRESHOLDS FOR VARIOUS STRAINS



-Red dots from Meaney
-L curves from Margulies

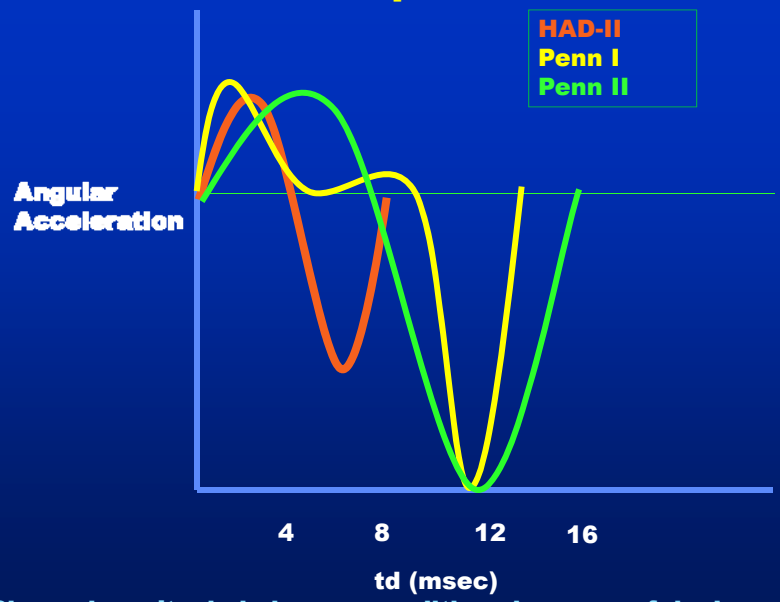
Relation of Tolerances to Adjectival Descriptors of Diffuse Brain Injury

Results of using scaled tolerances values from Margulies to equivalent AIS



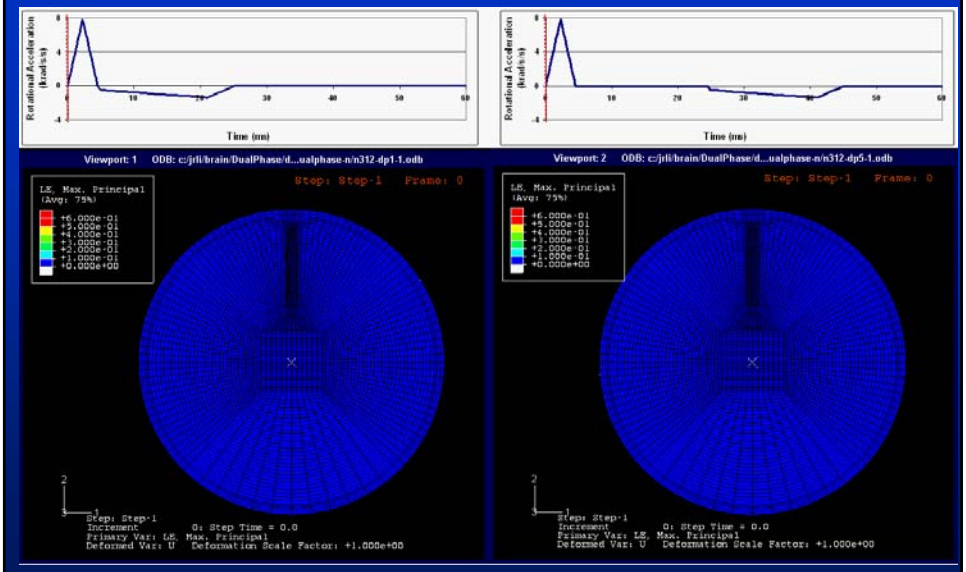
Gennarelli, AAAM, 1993

Waveshape effects

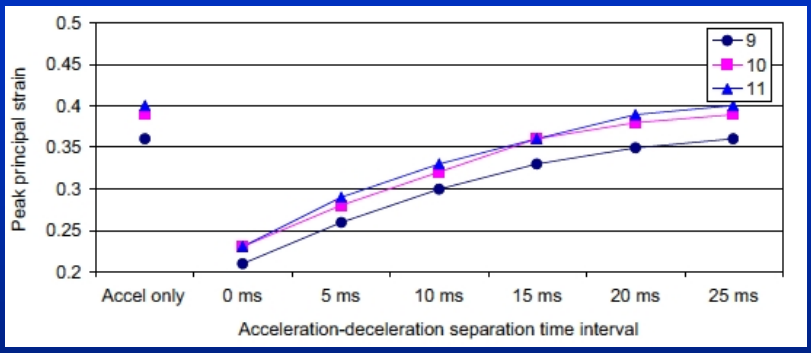


Shape doesn't mimic human conditions because of lack of separation of accel and decel

Brain Strain: no separation vs long separation

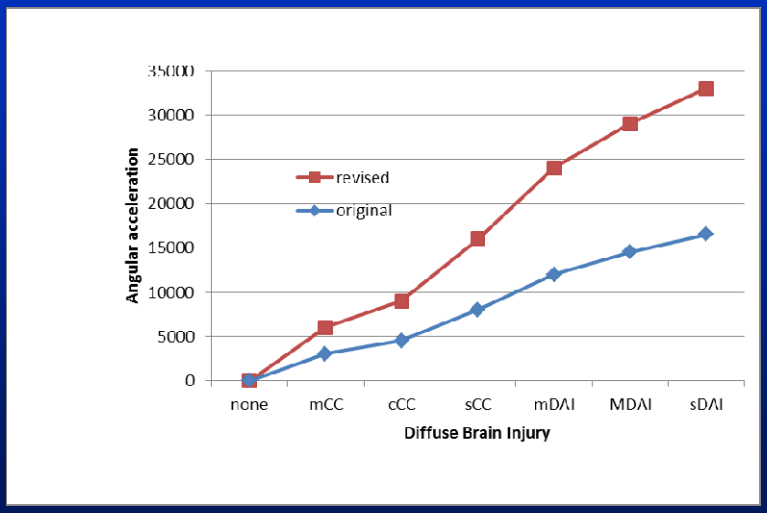


Implications

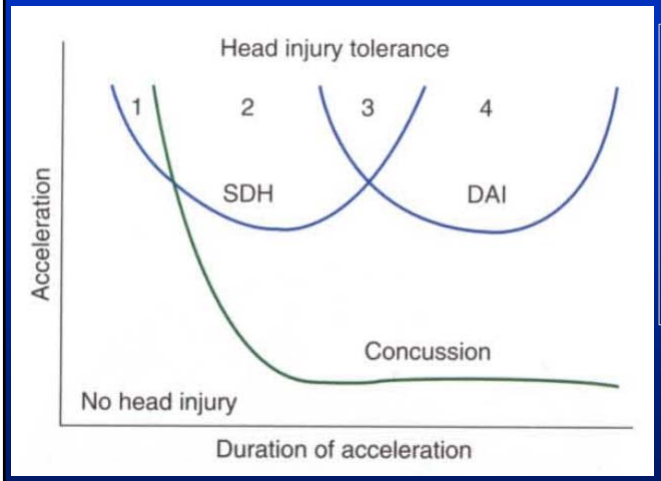


- **Brain strain increases with separation interval to 20-25msec, after which it is same as single pulse**
- **At zero separation strain is half that of single pulse**
- **THUS, if single pulse or widely separated pulse is more realistic in humans, our initial tolerances are half as high as they should be!**

Revised Concept of Diffuse Brain Injury due to strain field induced by angular acceleration



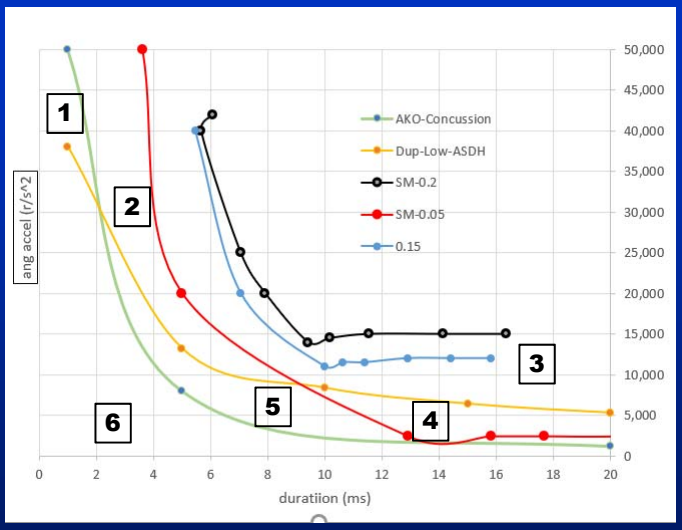
Hypothetical Qualitative Construct of Injuries Due to Angular Acceleration



Zones:

1: SDH without concussion
2: concussion and SDH
3: SDH and DAI
4: DAI
5: Concussion
6: No Injury

Quantitative Construct of Injuries Due to Angular Acceleration



Zones:

1: SDH without concussion
2: concussion and SDH
3: SDH and DAI
4: DAI
5: Concussion
6: No injury

The approximate formulae that describe the tolerance curves are:

Concussion: $\alpha = 43900d^{-1.04}$ (R^2=0.9596)
ASDH: $\alpha = 38040d^{-0.658}$ (R^2=0.99)
DAI (strain=0.20): $\alpha = 578.79d^2 - 14758d + 104465$ (R^2=0.8901) or $19570*d^{-1.019}$ (R^2=0.7189)

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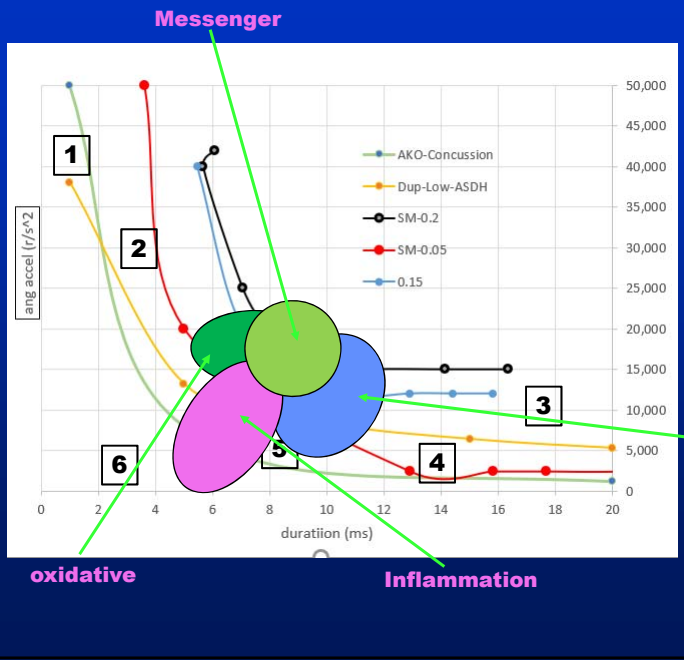
Head Injury Tolerances: the Future



Zones:

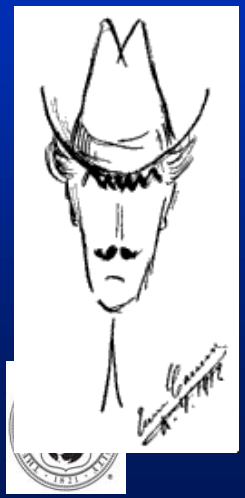
1: SDH without concussion
2: concussion and SDH
3: SDH and DAI
4: DAI
5: Concussion
6: No injury

SO,

Expect Changes:

Arturo Toscanini (drawn by Caruso)

born Parma March 25, 1867 – died NYC January 16, 1957



LaScala, Met, etc then NBC Orchestra , "Live from Studio 8H" (Zubin Mehta)

To

"Live It's Saturday Night"

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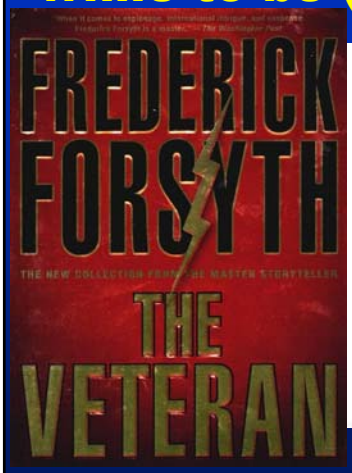
Expect your discoveries to take a while to be (mis)understood



There was certainly no fresh haematoma to account for the continuing coma. The blood vessels he had tied off remained leak-proof. No blood was pressing on the brain. It had expanded quickly to its full and usual size. No fresh leaks had developed to create pressure from a different source.

And yet, intra-cranial pressure remained too high, and blood pressure was the same. He began to fear the neurosurgeon's nightmare. If there had been catastrophic and diffuse axonal injury inflicted by those kicks, it would not show up, even on the scan. But if the brain stem or cortex was damaged beyond self-repair, the man would remain in a permanent vegetative state until the life-support system was switched off, or he would simply die. He resolved to do brain-stem tests after the weekend. Meanwhile, his wife was much looking forward to

2001: DAI first published 1982

Conclusions

- **You are never too wise that you can't still learn from your own experiments**
- **Hopefully, others will as well**

Humble thanks to my many collaborators over the years

- **Medical School**: 1968 Tony Raimondi, Don Matson
- **NIH**: 1970-72 Ayub Ommaya
- **Univ Pennsylvania**: 1976-1995
  - Larry Thibault, Dave Meaney, Susan Margulies, Tina Duhaime
  - Tom Langfitt, Walter Obrist, Wayne Alves, Gerri McGinnis
  - many residents, students and faculty
- **Glasgow University**: 1976-2006
  - Hume Adams, David Graham, also Graham Teasdale, Brian Jennett
- **UVA**: John Jane, Rebecca Rimel
- **Trauma folk**: Howard Champion, Elaine Wodzin-McKay
- **MCW**: 1999-2011
  - Narayan Yoganandan, Frank Pintar, Jianrong Li, Jiangyue Zhang
- **AND SO MANY OTHERS!!!**

Now, the rest is in your hands!

All you have to do is put the pieces together

Thanks
for your attention