Disclosure

- No disclosures
- Alas, no financial conflicts
Framing a disease

- We create a frame for a disease (biology, cause, clinical picture, danger, prognosis, costs to person, society etc)

- How we frame a disease determines
  - how we do our research
  - How we treat our patients

- And this effects how our patients experience their disease

We have differing frames

- ADHD
- Autism
- Post traumatic stress disorder (PTSD)
- Alcoholism
- Fibromyalgia
- Drug addiction
Neurological cases before 1868

Saint Lidwina
Bleeding for Neurological Disease

Treatment of nervous diseases
(Neill and Smith) 1852

- **Sedatives**: foxglove, tobacco, Indian tobacco, aconite, hemlock, hydrocyanic acid

- **Stimulants**: musk, castor, asafoetida, valarian, garlic, oil of amber, skunk cabbage, coffee, tea

- **Cerebral stimulants**: alcohol, ether, Hoffman anodyne, chloroform, opium, camphor, hops, bittersweet, henbane, thornapple, deadly nightshade, extract of hemp

- **Other**: Restricted diet; open, draining wounds with setons, blisters, vigorous rubbing, electricity, moxibustion, hydrotherapy, horseback riding
Charcot’s Tuesday Clinic

Charcot’s View on therapy

- After what precedes need I detain you long ... the time has not yet come when such a subject can be seriously considered.
Therapy at the Salpêtrière

- Arsenic; mercury; ergot of rye
- Strychnine and nitrate of silver
- Suspension for ataxia

William Moxom’s Therapy

1870

- Meat diet
- Bleeding
- Cooling with sponges
- Galvanic stimulation
- Farradic stimulation
- Mist. Effervescens
- Iron preparations
- Strychnine
- quinine

- Belladonna
- Calumbae
- Potassium iodide
- Arsenic
- Nux vomica
- Silver nitrate
- Hyocynamide
- Atropine
- ergot

The results were [most unsatisfactory]
[No approach to cure has been made]
Every decade someone discovers the cause and cure for MS

- **Pierre Marie** (1884)
- MS is due to infection
- A vaccine will soon make MS disappear
- Anyone who disagrees with me hasn’t read my papers

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**Edwards ☆ Review of MS Therapy 1895**

- Drugs to be used in toxic doses: solanine, veratrum, IM hyoscynamine, IM arsenic, IM curare
- Suspension apparatus
- Electricity and magnetism
Other approaches

- Rest cure
- Sanatorium for 3-6 months
- Avoid stress and worry
- Limit wine and excess eating
- Horseback riding
- Control over menstruation
- Fever box

Julius Wagner-Jauregg

- 1927 Nobel Prize for malaria therapy of syphilis, followed by quinine and salvarsan
- Anti-semitic; Nazi
- Used for MS patients
  - Transfusion of malaria to a case of neurosyphilis
**Period of Polypharmacy 1930s**

- Brickner listed 159 therapies for MS
- MS experts at the time felt half were beneficial (Putnam)

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**Sober Second Thought**

- 1930 Review
- "The multiplication of remedies is eloquent of their inefficacy"
Cause and Cure of MS Found!

- Sir James Purves Stewart
- Kathleen Chevassut
- Lancet (1930) 2 papers
- Isolation of *Spirula insularis*
- Vaccine given to 128 patients - benefit in the 40 of the 70 assessed

The pharmacopoeia has been ransacked for nerve tonics which flatter only to deceive.

- Arsenic; fibrolysin; TAB vaccine sodium cacodylate injections, Intravenous salicylate; pyrexial therapy; malaria; whole liver, quinine; colloidal metals, mercury; iodides; lecithin, massage; electrical therapy, Lowenthal lymphoid serum
Taking Action

- Sylvia Lawry was concerned about progression of her brother Bernard's MS and the lack of information and support. She put an ad in the New York Times (1945)

- Multiple Sclerosis. Will anyone recovered from it please communicate with patient. T272 Times
The Era of Clinical Trails

- Henry Miller
- Steroids

John Kurtzke
Isoniazid

Classifying MS

- Charcot’s clinical criteria
- Schumacher Criteria
- Poser Criteria
- McDonald Criteria
- Modified McDonald Criteria
1970-1993 Failed Trials

- But much was learned about the nature of the disease
- Trial design continually improved
- More MS clinics began
- MRI available in the 1980’s

Unproven Therapies

- Le Gac anti-Rickettsial therapy
- Histamine desensitization of Horton and Jonez
- Swank diet
- Forced CSF drainage
- Fever therapy
- Cervico-dorsal sympathectomy
- Ganglionectomy
- Laiguel-Vasastine-Karessios sera
- Stransky sera
- Alexander regimen of steroids
Recent claims of therapy

- Cari Loder Therapy
- Super-resonant Wave Energy
- Calcium ethylamino-phosphate (ca-EAP)
- Snake venom therapy
- Hydrogen peroxide therapy
- Alphasal (formerly Chlororazone or Vitamin X)
- Low Dose Naltraxone
- Coral calcium therapy (Robert Barefoot infomercials stopped)

Zombies*

- Russian vaccine
- Histamine desensitization
- Procarin (histamine and caffeine)
- Dental amalgam toxicity
- Bee venom
- Chelation therapy
- Hyperbaric oxygen
- Magnets
- High colonic detoxification therapy

*David Sackett
Randomized Clinical Trial (RCT)

Quality of evidence
- The placebo effect is not imaginary
- The placebo has no effect: it is your mind that has the effect
- Different placebos have different effects

**Placebo**

- Placebo has greater effect if:
  - Color (Red for stimulant, blue for sedation)
  - Expensive
  - Larger
  - Capsule rather than pill
  - Injection
  - Number (2 vs 1)
  - Anecdotal support
We are coming to the end of placebo trials in multiple sclerosis

The Power of the Anecdote

- Celebrity endorsements
- Human interest stories
- Media reports
- Belief trumps evidence

My aunt said she heard on Oprah that a lady got out of her wheelchair by eating kale three times a day.
Myelin protein therapy for MS

- Logical theory
- Safe
- Cheap

- An impressive open trial – 50% improved

Myelin protein therapy for MS

- Logical theory
- An impressive open trial – 50% improved

- Randomized trial, blinded
- 50% of patients treated improved
- 50% of placebo group improved
Approved Drugs for MS

- Aubagio (teriflunomide)
- Avonex (interferon beta-1a)
- Betaseron (interferon beta-1b)
- Copaxone (glatiramer acetate)
- Extavia (interferon beta-1b)
- Gilenya (fingolimod)
- Lemtrada (alemtuzumab)
- Novantrone (mitoxantrone)
- Plegridy (peginterferon beta-1a)
- Rebif (interferon beta-1a)
- Tecfidera (dimethyl fumarate)
- Tysabri (natalizumab)

A History of Breakthroughs

- 101 studies suggesting promising therapy or technology 1979-1983
- 25 years later, only 5 had been marketed, only 1 was in common use (ace inhibitors)
- 200 “breakthroughs” in cancer in recent years failed
Medical Talk Show recommendations (BMJ Dec 17, 2014)

- **Dr. Oz show**
  - supporting evidence 46%
  - no evidence 39%
  - contradictory evidence 15%

- **The Doctors**
  - supporting evidence 63%
  - no supporting evidence 24%
  - contradictory evidence 14%.

Conclusion: the public should be skeptical of recommendations given on medical talk shows.

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**Alternative Therapies**

- 78% using one or more
- Often conflicting philosophies
- Switch therapies often
- Many don’t tell their physicians
A personal view

- We should not have two solitudes:
  - Scientific medicine and alternative medicine
- There should be just medicine that works
- To go forward we should design tests that show what works

CCSVI
- Dr. Paolo Zamboni
- Cardiovascular surgeon
- His wife has MS
- Reported the liberation therapy
Small open trial on 65 patients

Stenosis
Images courtesy

After treatment
of Paolo Zamboni
What did the Zamboni paper report?

CCSVI in 100% of MS patients
CCSVI in 0% of normals and other CNS diseases

- 65 MS patients treated by balloon angioplasty
  - 35 relapsing remitting MS patients (duration 1-7 yrs)
  - 20 secondary progressive MS patients
  - 10 primary progressive MS patients.


- Zamboni - 50% relapse free at 18 mo
  Cladribine study 60.5% in placebo group

- No response of CCSVI in secondary progressive or primary progressive patients

- (these are the patients going for therapy!)
Studies of CCSVI

- None have substantiated Zamboni’s results
- 14 negative studies
- 2 negative controlled trials
- 2 negative prospective studies of CCSVI pts

- It is following the trajectory of other claims of miraculous breakthroughs in MS
The Promise for the Future

- New agents under study
- Learning from DMTs in the long term
- Combination studies
- Bone Marrow Transplantation
- Basic research