Stroke Milestones: Past, Present, Future

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Oregon Stroke Network
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Disclosures

None

Except that my wife is a MUCH better golfer than I am.
Knowledge Doubling Curve

1973: started Neurology Residency at UVA
We will be using the audience response system for this presentation.
Audience Response Question

The earliest written document that describes what we now call acute stroke is by:

A. Hippocrates
B. Thucydides
C. Herodotus
D. Thomas Willis
Hippocrates (c 460 – c 370 BCE)
apoplexy (n.)

...from Greek apoplexia [αποπληξία], from apoplektos ..."to strike down and incapacitate," from PIE root *plak- (2) "to strike" (source also of plague, which also has a root sense of "stricken").
“A Person in health is suddenly seized with a pain about the head, the voice is immediately intercepted, he snores and gapes, and if spoken to or moved, he only sighs; is insensible, and makes a great deal of water without knowing it. If he becomes mute and snores, he dies within seven days, unless a fever comes on, and then he generally recovers...”
The 31st metope from the south side of the Parthenon in Athens. On display in the British Museum, the southern aspect metopes depict the battle between the centaurs (left) and the Lapiths (right) at the wedding of Peirithus, the king of the Lapiths. The left carotid artery of the Lapith is here being intentionally compressed to induce unconsciousness.

Photograph courtesy of Colin Howley. Used with permission.
Galen of Pergamum (129-201 CE)
Galen’s theory of Apoplexy:
- “Vital Spirits” were formed in the heart & transformed in the *rete mirabile* and transported to the ventricles, the center of neurologic function. Apoplexy was caused by a failure of flow of these “animal spirits” caused by accumulation of thick phlegm within the ventricles.
Nothing much changed for 1500 years
Vascular theory of Apoplexy

- Began in 16\textsuperscript{th} century with some opposition to Galen’s views.
- 1664 Thomas Willis described his eponymous circle, described collateral circulation in the brain, coined the term “neurologia” and believed that intracerebral hemorrhage was the cause of apoplexy.
- 1761 Morgagni identified “sanguineous” and “serous” apoplexy on autopsy.
Vascular theory of Apoplexy

- 1847 Virchow introduced the terms “embolus” and “thrombosis”
- Late 1800’s It was generally accepted that:
  - patients with sudden explosive onset had had a cerebral hemorrhage with associated LVH and arterial disease.
  - Those with cerebral softening had occlusive arterial disease, thrombotic or embolic.
Charles Foix (1882-1927)
The First Modern Stroke Neurologist (Caplan, 1990)
Charles Foix Salpêtrière

• Described in detail anterior and posterior circulation.
• Focused on clinical, anatomical, and pathological correlation of various stroke syndromes.
• Proposed 4 possible mechanisms:
  – Arterial occlusion
  – Embolism
  – Insufficiency (proximal circulatory failure)
  – Vasospasm
• After his premature death in 1927, vasospasm became the favored mechanism.
Audience Response Question

Egas Moniz, Portugese neurologist, won the 1949 Nobel Prize in Medicine for:

A. Pneumoencephalography
B. Cerebral Angiography
C. Frontal lobotomy
D. Carotid endarterectomy
Egas Moniz (1874-1955)

Although best remembered for developing cerebral angiography (1927), he won the 1949 Nobel Prize in Medicine for his work on frontal lobotomy.
A Brief History of Clinical Trials
Evolution of Clinical Trials

• Book of Daniel ~562 BCE.
  – King Nebuchadnezzar ordered a diet of meat & wine but allowed several young royals to eat only legumes as they wished.
  – After 10 days the legume lovers were healthier and the king allowed them to continue that diet.
Evolution of Clinical Trials

- Ambroise Paré 1537
- Barber Surgeon
  - ran out of standard burning oil to cauterize battlefield wounds and substituted a mixture of egg yolk, oil of roses & turpentine.
  - The next day these wounds were healthier and pain-free.
Evolution of Clinical Trials

• James Lind 1747
  – First physician to intentionally conduct a controlled trial.
  – 12 patients at sea with scurvy “lay together” with identical diets plus:
    • 2 each cyder, elixir vitriol, vinegar, sea water, 2 oranges and 1 lemon, or a surgeon-recommended diet.
    • After 6 days the two sailors with the citrus fruits were recovered.
  – It took 50 years for the British Navy to require citrus as part of the seafarer’s diet.
Randomized Controlled Trial (RCT)

- Hooper’s Medical Dictionary 1811
  - Placebo: “an epithet given to any medicine more to please than to benefit the patient.”

- Austin Flint, MD 1863
  - 13 patients with rheumatism were treated with placebo herbs instead of usual treatment and did well.

- Patulin (penicillium derivative) 1943-44
  - First double blind controlled trial.
  - alternation not randomization of subjects.
  - No benefit shown for the common cold.

- First Randomized Controlled Trial, BMJ 1948
  - Streptomycin for pulmonary tuberculosis.
  - Benefit shown.
THREE LETTER ACRONYM (TLA)

Good Science Requires a Good TLA

• Acronym (old definition): RADAR, NASA, CAT Scan.
• Abbreviation: MRI, Mrs., Ave., CTA, RCT.
  – Modern usage considers MRI, CTA, TIA, RCT acronyms too.
• Initialism: MRI, CTA, RCT.
Two Important Discoveries

• Heparin isolated in 1916 by McLean & Howell while looking for compound to enhance clotting.
  – human clinical trials in 1935 confirmed effectiveness & safety as an anticoagulant.

• Dicumarol: from “sweet clover hay” accidental cow poison in the 1920’s in Canada, to a rat poison, and finally a clinical treatment in the early 40’s.
C. Miller Fisher (1913-2012)
C. Miller Fisher

• Drew attention in 1951 to the extracranial carotid artery as a potential cause of stroke.
  – Previously mentioned by Chiari, 1905, & Ramsay-Hunt, 1914, Moniz, 1937 (but ignored).

• Studied angiographically “puzzling cerebral symptoms, especially transient episodes of blindness, aphasia, paresthesia and paralysis”.
  – The concept was not new, Hippocrates wrote “attacks of numbness and anesthesia are signs of impending apoplexy”.

• The term “Transient Ischemic Attack” was born
Vasospasm was the suspected predominant mechanism but Fisher suggested an alternate mechanism: *thromboembolism*, and wrote:

- *It is even conceivable that some day vascular surgery will find a way to by-pass the occluded portion of the artery during the period of ominous fleeting symptoms.*

- *Since the pathological substrate of carotid disease is atherosclerosis, the fundamental approach to therapy must be directed at the prevention or cure of that disorder.*
Origins of Stroke Treatment

Surgery for carotid occlusive disease:

- Denton Cooley also claimed first CEA case.
- Patient with left pulsatile tinnitus.
- Post-op, his tinnitus was cured but he was aphasic with a right hemiparesis.
Knowledge Doubling Curve

1973: started Neurology Residency at UVA
Diagnostic Tools for Stroke & TIA 1973

- History & Physical
- Plain Skull X-ray
- Midline Cranial Ultrasound (A mode)
- Doppler ophthalmosonometry
- Isotope Brain Scan
- Catheter or direct puncture Angiography
Lateral & Towne’s View Skull X-ray
Check Position of Calcified Pineal
Fig. 1. Preoperative scalp echoencephalogram of hypertensive intracerebral hemorrhage. This 71-year-old man was admitted with disturbance of consciousness and hemiplegia on the left side. Examination made on the 3rd day after attack showed a hematoma echo with a midline shift. (HE = hematoma echo; ME = midline echo.)
Doppler Ophthalmosonometry
Isotope Brain Scan
Carotid Angiography 1973
At that time, still many anatomical unknowns

Time for another Audience Response Quiz

Which of the following early neurologists wrote a frequently cited paper locating the pyramidal tract in the internal capsule?

A. Charcot
B. Babinski
C. Dejerine
D. Englander
E. A & B
F. C & D
Location of human pyramidal tract in the internal capsule
Anatomic evidence

RAYMOND N. ENGLANDER, MARTIN G. NETSKY, LESTER S. ADELMAN

First published September 1, 1975, DOI: https://doi.org/10.1212/WNL.25.9.823
List of Acute Stroke Interventions

• IV Heparin
## List of Secondary Stroke Preventions

<table>
<thead>
<tr>
<th>Surgical</th>
<th>Medical</th>
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<tbody>
<tr>
<td>• Carotid Endarterectomy</td>
<td>• Treat Diabetes</td>
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<tr>
<td>• EC-IC Bypass</td>
<td>• Treat Hypertension</td>
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<tr>
<td></td>
<td>• Stop Smoking</td>
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<tr>
<td></td>
<td>• Warfarin especially in valvular heart disease</td>
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<td>• Treat SBE</td>
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<td>• (Non-Valvular AF was not thought to cause stroke)</td>
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</table>
Major Milestones Since My Residency: *my top 10*

**The Stories I Will Tell**
- Advanced Digital Imaging
- Surgery Comes of Age
- Smoking Reduction
- Aspirin
- Cholesterol
- Non-valvular Atrial Fibrillation
- Thrombolysis
- Endovascular treatments
- Public Education
- Neuroprotectants?

**Won’t Discuss (honorable mention)**
- Stroke Rehabilitation
- ICH
- Spontaneous SAH
- Dissection
- PFO
- Rare Causes of Stroke
- Decompressive Craniectomy
Advanced Digital Imaging
CT / CAT Scan

Allan M Cormack, Tufts physicist, developed the mathematics of a two-dimensional function describing X-ray attenuation in each part of a slice knowing the mean absorption in 1963 & 1964.

Godfrey N Hounsfield, Electric and Musical Industries, engineer & Chief of Medical Research Division, described a complete system for medicine in a 1968 patent application.

They shared the Nobel Prize in Physiology & Medicine 1979
First Commercial EMI Scanner, 1971

- Each slice took 160 parallel readings through 180 angles $1^\circ$ apart with each slice taking 5 minutes to record with a total scan reconstruction time of 2.5 hours
Subsequent Enhancements
CT or CAT Scan

• Processing Speed
• Helical
• Multi-slice
• CT Angiography
• Perfusion scanning
• Portable
• Reduced Radiation
• Now over 80 million CT scans annually in USA
MRI Scan

• Nuclear Magnetic Resonance observed in 1930’s.
• 1973 Paul Lauterbur used NMR to produce images.
• Peter Mansfield developed the math processes.
• They received the Nobel Prize in Medicine 2003.
• NMR scanning was renamed MRI because “nuclear” was off-putting to patients.
• Ubiquitous in USA by mid-1980s.
• Now over 40 million MRI scans annually in USA.
Duplex Scan

B-Mode Ultrasound

Pulsed Range-Gated Doppler
Two High-Volume Surgeries of the 1960’s and 1970’s Finally Studied in Controlled Trials

Symptomatic Carotid Endarterectomy

- NASCET 1991: High grade symptomatic stenosis (>70%) = ARR 17%.
- NASCET 1998: Moderate symptomatic stenosis (50-69%) = ARR 7%.
- ECST 1998: stenosis measured against presumed original lumen: (>70-80%) = 12% ARR.

Fox Method for % Stenosis

ICA bulb: anatomic speculation
- NASCET %
  N/D x 100 = % stenosis
Two High-Volume Surgeries of the 1960’s and 1970’s Finally Studied in Controlled Trials

Asymptomatic Carotid Stenosis Endarterectomy

- VA Cooperative, 1991: >50%
- ACAS, 1995: > 60%
- More recently Spence & Barnett advise surgery only for “high-risk” Stenoses.
  - Persistent TCD microemboli.
  - Progressive stenosis despite best medical management.
Two High-Volume Surgeries of the 1960’s and 1970’s Finally Studied in Controlled Trials

Extracranial-Intracranial Bypass

• Popular operation in 70’s and early 80’s presumably to restore brain function and prevent stroke.

• EC/IC Bypass Study Group, NEJM 1985: Failure of Extracranial-Intracranial Arterial Bypass to Reduce the Risk of Ischemic Stroke—Results of an International Randomized Trial.

• 2 years later CMS, VA, Private insurers stopped paying for it for this indication.
Smoking Reduction

Percentage of U.S. Adults Who Are Smokers: 1944-2018

Have you, yourself, smoked any cigarettes in the past week? (% yes)

<table>
<thead>
<tr>
<th>Year</th>
<th>% National adults</th>
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<tbody>
<tr>
<td>1948</td>
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<td>2008</td>
<td>21</td>
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<td>2013</td>
<td>16</td>
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GALLUP

1966

Cigarette Labeling
The Aspirin Story

• Hippocrates noted benefits of willow bark.
• Galen recorded anti-inflammatory & antipyretic effects of willow leaves.
• 1891 Binz recorded mucosal bleeding from salicylic acid.
• 1950 Craven (ENT) reported 400 patients taking aspirin had no MI’s. Later 8,000 patients.
• 1967 Weiss identified that ASA inhibited platelet aggregation.
The Aspirin Story

• 1971 John Vane reported aspirin inhibited prostaglandin synthetase as the mechanism and won the 1982 Nobel Prize

• 1971 Harrison et al found that aspirin reduced amaurosis fugax events in 2 patients

• Canadian Collaborative Trial
  – Factorial design with sulfinpyrazone, ASA (1300 mg daily), & placebo.
  – Only ASA groups showed benefit: 19% reduction in TIA, stroke & death. Women did NOT benefit.

• Warfarin remained popular for non-cardioembolic strokes.
The Aspirin Story

WARSS Trial

A Comparison of Warfarin and Aspirin for the Prevention of Recurrent Ischemic Stroke

J.P. Mohr, M.D., J.L.P. Thompson, Ph.D., R.M. Lazar, Ph.D., B. Levin, M.D., et al., for the Warfarin–Aspirin Recurrent Stroke Study Group

November 15, 2001
DOI: 10.1056/NEJMoa0111258

WASID Trial

Comparison of Warfarin and Aspirin for Symptomatic Intracranial Arterial Stenosis

Marc I. Chimowitz, M.B., Ch.B., Michael J. Lynn, M.S., Harriet Howlett-Smith, R.N., Barney J. Stern, M.D., et al., for the Warfarin–Aspirin Symptomatic Intracranial Disease Trial Investigators

March 31, 2005
DOI: 10.1056/NEJMoa043033
The Cholesterol Story

• Major early statin trials showed significant benefit for cardiac disease but conflicting or insignificant results for stroke.
  – Scandanavian Simvastatin Survival Study (4S) 1994
  – Heart Protection Study (HPS) 2002
  – PROVE IT 2004

• Entry for these trials was a cardiac event
Is elevated cholesterol a risk factor for stroke? While the evidence is mostly indirect for stroke, it is not disputable for coronary heart disease. This must be remembered when patient management is addressed, since the prevention of atherothrombotic events should be a global effort.

In summary, the prevailing evidence is not supportive of the hypothesis that cholesterol is an important risk factor for stroke. This is based on the observation that the association between cholesterol and stroke is weak, inconsistent, and that lowering cholesterol levels does not necessarily result in a reduction in the risk of stroke. It is clear that this issue has been clouded by the observation of a reduced risk of stroke with use of statins.
The Cholesterol Story

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)

- Randomized, double-blind trial in 4731 patients with stroke or TIA in past 1 to 6 months
- Randomized to atorvastatin 80 mg daily or placebo
- Mean follow-up 4.9 years
- Primary endpoint: Stroke

RRR: 15%
P < 0.001
ARR: 1.9%
NNT: 53

The Atrial Fibrillation Story
as told by Lew Caplan, 2018

• Late 19th Century: RHD & SBE known as embolic stroke causes.
• 1949 C. Miller Fisher suggests that AF even in non-RHD/SBE patients could cause embolic stroke (based on 3 autopsy cases).
• 1977: Hinton et al (Am J Cardiol) reported autopsy findings that lone AF increased systemic embolic infarcts including brain.
The Atrial Fibrillation Story
as told by Lew Caplan, 2018

• 1978: Framingham Heart study confirmed a high rate of stroke from AF over 24 years.
  – 17.6 fold stroke risk increase with RHD & AF
  – 5.6 fold stroke risk increase with AF alone (“lone A Fib”)

• 1979 Fisher published a plea for anticoagulation in patients with persistent or paroxysmal AF before brain ischemia occurs.

• 1986: Cerebral Embolism Task Force wrote:
  – “Nonrheumatic nonvalvular atrial fibrillation is the most common cardiac condition associated with presumed embolic stroke, accounting for almost half of cardiogenic embolic strokes...”
The Thrombolysis Story

• 1981: 22/29 successful IA streptokinase reperfusion of 22/29 acute MI patients.
• 1986: ISAM reports early IV streptokinase limits size of myocardial infarction.
• Streptokinase trials in stroke produced excess hemorrhagic conversion & lack of efficacy.
• 1979 Recombinant Tissue Plasminogen Activator (rtPA) first produced.
• 1995 NINDS trials for rtPA in acute stroke published.
• Tenecteplase has longer half-life & more fibrin specificity. Still undergoing trials.
Endovascular Treatment of Acute Stroke

- Mechanical Embolus Removal in Cerebral Ischemia (MERCI) retriever
- FDA Cleared 2004 for removing foreign body (clot is a foreign body)
- Then MULTI-MERCI
Endovascular Treatment of Acute Stroke

- Penumbra System FDA cleared in 2007
- Trevo cleared 2012
- Solitaire FR cleared 2012
Public Education

**BALANCE**: Does the person have a sudden loss of balance?

**EYES**: Has the person lost vision in one or both eyes?

**FACE**: Does the person’s face look uneven?

**ARMS**: Is one arm weak or numb?

**SPEECH**: Is the person’s speech slurred? Does the person have trouble speaking or seem confused?

**TIME**: Call 9-1-1 now!

Duke Stroke Program
The Very Short Story of Successful Acute Stroke Neuroprotection Trials

• At least 1,026 agents/methods have been tried in animal models.
• At least 114 of these have been tested in human clinical trials so far.
• Essentially none has succeeded yet!*
  — *Except hemicraniectomy & maybe citicoline.
Oscar Wilde

Might have said this about the next neuroprotectant trial: 
*It is the triumph of hope over experience.*

Actually he said:

*MARRIAGE* is the triumph of imagination over intelligence.  
*SECOND MARRIAGE* is the triumph of hope over experience.

And:

*BIGAMY* is having one wife too many.  
*MONOGAMY* is the same.
Present

I won’t cover this so that the other speakers have something to talk about
It is difficult to make predictions, particularly about the future.
### Stroke Prevention

#### Stroke Risk Factors

**You Can’t Control:**
- Age
- Race
- Gender
- Prior Stroke or TIA
- Family history of stroke

**You Can Control:**
- Atrial Fibrillation
- Diabetes
- High Blood Pressure
- High Cholesterol Levels
- Obesity
- Physical Inactivity
- Smoking
Future Directions in Prevention

• There will be continued incremental improvements in:
  – Anti-thrombotics
  – essential hypertension management
  – Diabetes management
  – LDL-C management

• But there are a couple of “next big things” that I hereby predict and that you are hearing here for the very first time!
The First Big Thing: A Convergence
Heat Trapping Greenhouse Gases Produced by Cattle and Automobiles

Average amount of methane produced by two cows each year

Average amount of carbon dioxide produced by one car each year

200 kg (440 lbs.) methane

2 cows

4,600 kg (10,120 lbs.) carbon dioxide

1 car driven 21,000 kilometres (15,000 miles)

BCFarmsandFood.com
Ownership trends. The US publisher Ward's estimates that as of 2010, there were 1.015 billion motor vehicles in use in the world.

Currently, there are approximately 1.3 to 1.5 billion cows living on Earth. Jun 25, 2018.
110 kg methane produced annually by

- 1 dairy cow
- 2 beef cows
- 14 sheep
- 22 goats
- 74 pigs
BEYOND MEAT BEAST BURGER 2.0

NO GMOS
SOY FREE
GLUTEN FREE

23G OF PLANT PROTEIN
EXCELLENT SOURCE OF IRON, B12, VITAMIN B, ANTIOXIDANT VITAMINS A, C & E

SERVING SUGGESTION
ENLARGED TYPE: SERVE WARM

NET WT. 8 OZ. (226G)
100 CALORIES

KEEP FROZEN
PLANT-BASED BURGER PATTY WITH PEA PROTEIN
Second Big Thing for Prevention
Gene Therapy
## Stroke Risk Factors With Gene Therapy

<table>
<thead>
<tr>
<th>You Can’t Control:</th>
<th>You Can Control:</th>
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<tbody>
<tr>
<td>Age</td>
<td>Atrial Fibrillation</td>
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<td>Race</td>
<td>Diabetes</td>
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<td>Gender</td>
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<td>High Cholesterol Levels</td>
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<td>Obesity</td>
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<td>Physical Inactivity</td>
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<td>Smoking</td>
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<td>Family history of stroke</td>
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</tbody>
</table>
Your great great grandchildren will all be GMOs
Future Acute Stroke Treatment
Ubiquitous for Cardiac Arrest
Coming Soon

Emergency Brain Fixer Device
Slight Modification

- Balance: Does the person have a sudden loss of balance?
- Eyes: Has the person lost vision in one or both eyes?
- Face: Does the person’s face look uneven?
- Arms: Is one arm weak or numb?
- Speech: Is the person’s speech slurred? Does the person have trouble speaking or seem confused?
- Time: Call 9-1-1 now!

And get the Nearest BFD!
Proper BFD Net Application on Victim
BFD Precision Targeting of Cortical and Subcortical Ischemic Cells & Tracts with pinpoint tDCS Slowing Ischemic Cascade
Nearest Mobile Stroke Unit Dispatched
CT & Thrombolysis En Route
Better Thrombolytics?

• Tenecteplase (TNK)
• Desmoteplase
• Reteplase

• True Biologics
Introducing My New Company

Happy Leeches, Inc

“our business really sucks”

Larry Leech
Happy Leeches, Inc
“our business really sucks”

Currently in development:

The PeaceHealth Apoplexy Leech (PAL)
• Targets intra-arterial clots
Happy Leeches, Inc
“our business really sucks”

The PAL is currently undergoing animal testing to identify the best administration route. So far it looks like “Up Your Nose With A Rubber Hose” is most effective.
Happy Leeches, Inc

“our business really sucks”

Not to be confused with our LipoLeech
Happy Leeches, Inc
“our business really sucks”

LipoLeech: Precision Body Sculpting

Before LipoLeech

After LipoLeech
Happy Leeches, Inc

“our business really sucks”

PeaceHealth Apoplexy Leech 2.0 (PAL 2.0)

Hybrid between PAL & LipoLeech
Seeks and destroys thrombus AND plaque
Happy Leeches, Inc

“our business really sucks”

• The other major advantage of the PAL system is that endovascular fellowships will no longer be needed.
• Replaced with a weekend course in the Cayman Islands.
Rumor has it

in the 60’s & 70’s college guys carried a foil packet in their wallets

Those guys are older now
And will soon start carrying a different foil packet

- The Oral Apoplexy Reverser (OAR)
- Put your OAR in the water, swallow, and the first successful oral neuroprotectant goes to work.
- There is a suppository form: The Apoplexy Reversal Suppository (ARS).
• A second foil pack will contain a miniaturized BFD headnet.
• It will connect via Bluetooth to the iPhone XXV.
• The **BRAIN Fast Apoplexy Reversal Tool (BRAINFART)** App will initiate tDCS replacing the wall-mounted BFD’s which will become as rare as phone booths are today.
• It will also automatically call 911.
The Amazon Drone with Do It Yourself PeaceHealth Apoplexy Leeches will be Automatically Deployed.
Or maybe we will just go for a drive-through replacement
Thank you for
Your kind attention