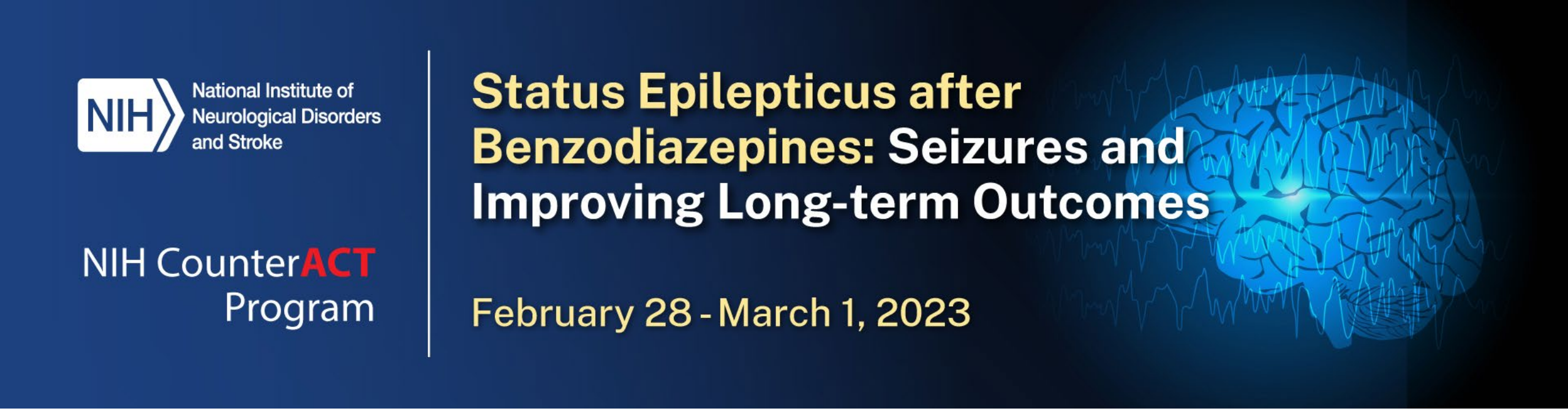

From terrorists, without love: nerve agent-induced status epilepticus and its treatment

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Status Epilepticus after Benzodiazepines: Seizures and Improving Long-term Outcomes

Disclaimer

This certifies that the views expressed in this presentation are those of the author and do not reflect the official policy of the National Institutes of Health, the Department of Veterans Affairs, the Department of Defense, or the Commonwealth of Virginia.

Disclosure

This certifies that I, Jonathan Newmark, have no financial relationship that is relevant to the subject matter of the presentation.

Status Epilepticus after Benzodiazepines: Seizures and Improving Long-term Outcomes

Disclaimer

I am a contractor employed by Kelly Government Services Inc., supporting NIH, not a Federal employee.

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NIAID has the lead role in biodefense MCM research and development across the NIH.

From terrorists, without love: nerve agent-induced status epilepticus and its treatment

- Status epilepticus in everyday clinical practice usually results from established but poorly controlled epilepsy, alcohol withdrawal, structural CNS lesions, and/or previous head trauma. Status epilepticus due to exposure to organophosphate nerve agents differs in some key respects, in pathophysiology and appropriate treatment protocols. This presentation attempts to place nerve agent-induced status epilepticus, for which an ethical prospective human trial is impossible, in context, and to highlight why the Department of Defense and civilian medical chemical defense communities need to exploit synergisms between this clinical entity and other forms of refractory status epilepticus.

FTX, Camp Doha, Kuwait AUG 02

Fritz Dreifuss, MD
1926-1997
Chair, neurology
University of Virginia

Two audiences

- Those who deal with community-acquired SE, its mechanisms and treatments
- Those who deal with nerve agent exposure and nerve agent-induced SE, almost entirely in animal models
- My purpose today is to introduce these people to each other. As Fritz Dreifuss demonstrated, they tend not to communicate regularly.

What is “normal” status epilepticus? International League Against Epilepsy definition (2015):

" Status epilepticus is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures (after time point t_1). It is a condition, which can have long-term consequences (after time point t_2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.

What causes “normal” SE?

Huge differential diagnosis. Most common:

Drugs and drug withdrawal

(Especially known epileptics who are non-compliant with anticonvulsant drugs)

Alcohol (mostly withdrawal)

Infections, including herpes and other encephalitides

Autoimmune conditions

Specific syndromes, especially paediatric (example: Lennox-Gastaut, Rasmussen’s encephalitis, FIRES)

[Head trauma or history of head trauma]

Structural lesions including tumors, stroke

NORSE = new onset refractory status epilepticus

NB: You don’t have to be epileptic to go into SE!

“Normal” SE: how do we approach it clinically? (acknowledgement: William Theodore MD, NINDS)

When we encounter a patient in continuous seizures, we usually don’t know what the cause was.

We have a generic boilerplate sequence of treatments which has not enormously changed in the past 40 years.

Here’s the general recipe. If any treatment stops seizures, we stop treatment; if not, we go to the next treatment.

1. Benzodiazepine (lorazepam, diazepam, most recently midazolam)
2. Repeat benzodiazepine if an initial dose is ineffective
3. Breathing support, intubation if required, draw bloods for metabolic parameters

   (EEG, neuroimaging)
4. Thiamine (never a bad idea)
5. Choice of second anticonvulsant:

   fosphenytoin

   levetiracetam

   valproic acid
6. (Paraldehyde), barbiturate, phenobarbital, consider midazolam drip and/or general anaesthesia
7. A second drug from the list in #5 above (third line anticonvulsant)
8. Steroids, anakinra (empiric, non-standard)

“Normal” SE: Second anticonvulsant after benzodiazepines

Kapur J et al. **Randomized Trial of Three Anticonvulsant Medications for Status Epilepticus.**

N Engl J Med 2019, 381(22):2103-2113

Showed that levetiracetam, fosphenytoin, and valproic acid used in benzodiazepine-refractory SE each were basically EQUIVALENT in terms of efficacy and adverse side effects.

Using any of these three drugs had a 45-47% chance of seizure cessation and increased alertness after 60 minutes.

We do not have ideal treatment for SE!

The NEW ENGLAND JOURNAL of MEDICINE

Trial of Three Anticonvulsant Medications for Status Epilepticus

MULTICENTER, RANDOMIZED, DOUBLE-BLIND TRIAL

384
Children and adults with benzodiazepine-refractory status epilepticus

	Levetiracetam	Fosphenytoin	Valproate
	60 mg/kg	20 mg/kg (phenytoin equivalents)	40 mg/kg
Absence of clinically evident seizures and improved responsiveness at 60 min	47% (68/145)	45% (53/118)	46% (56/121)

No significant difference in rates of seizure cessation or in safety

J. Kapur et al. 10.1056/NEJMoa1905795

ESETT results

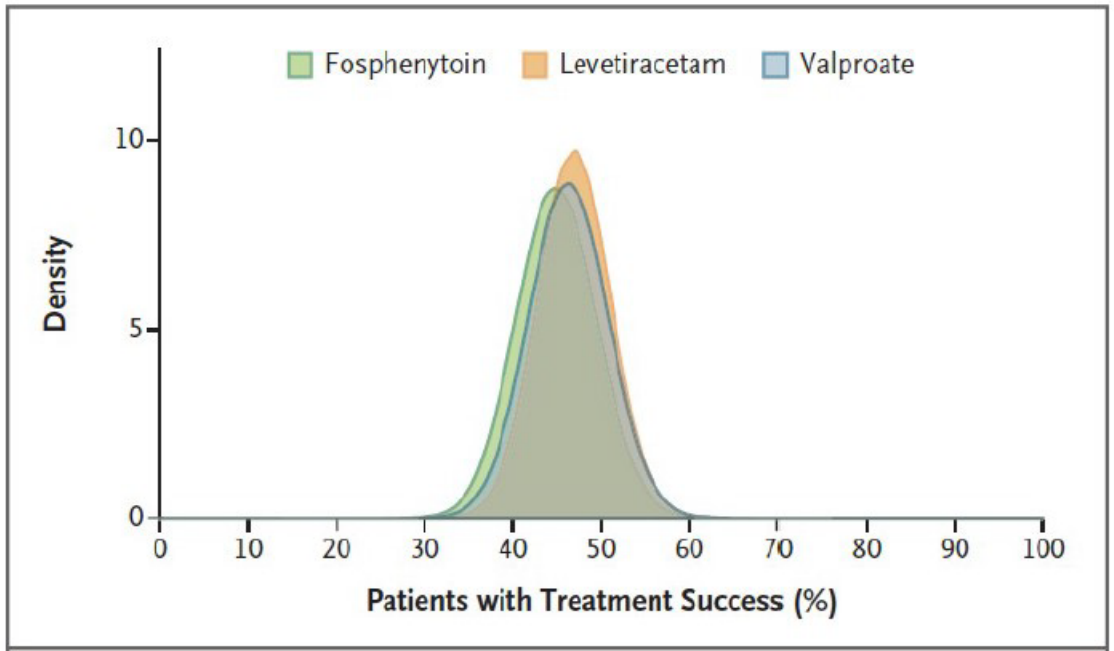


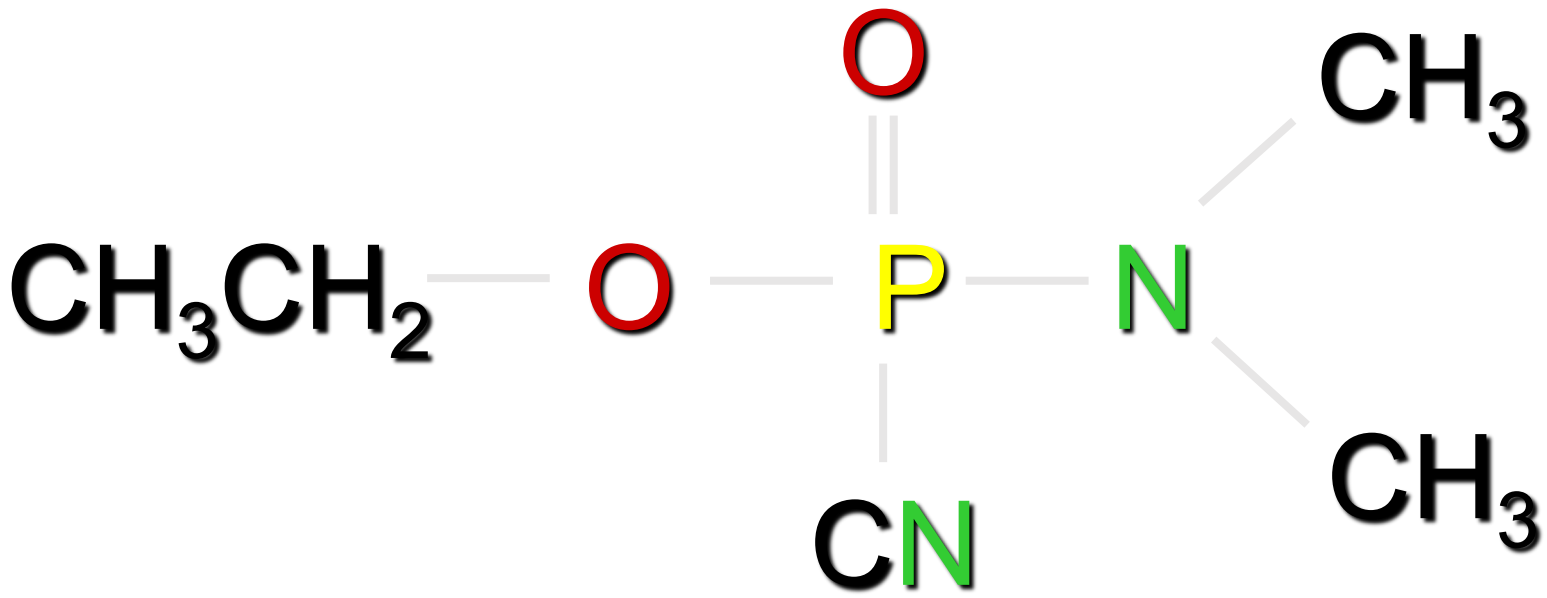
Figure 2. Posterior Probabilities of Success According to Treatment Group for the Primary Outcome of Cessation of Status Epilepticus at 60 Minutes.

The relative posterior probabilities of treatment success with regard to the primary outcome for each drug are shown. The percentage of patients with treatment success was 47% (95% credible interval, 39 to 55) in the levetiracetam group, 45% (95% credible interval, 36 to 54) in the fosphenytoin group, and 46% (95% credible interval, 38 to 55) in the valproate group.

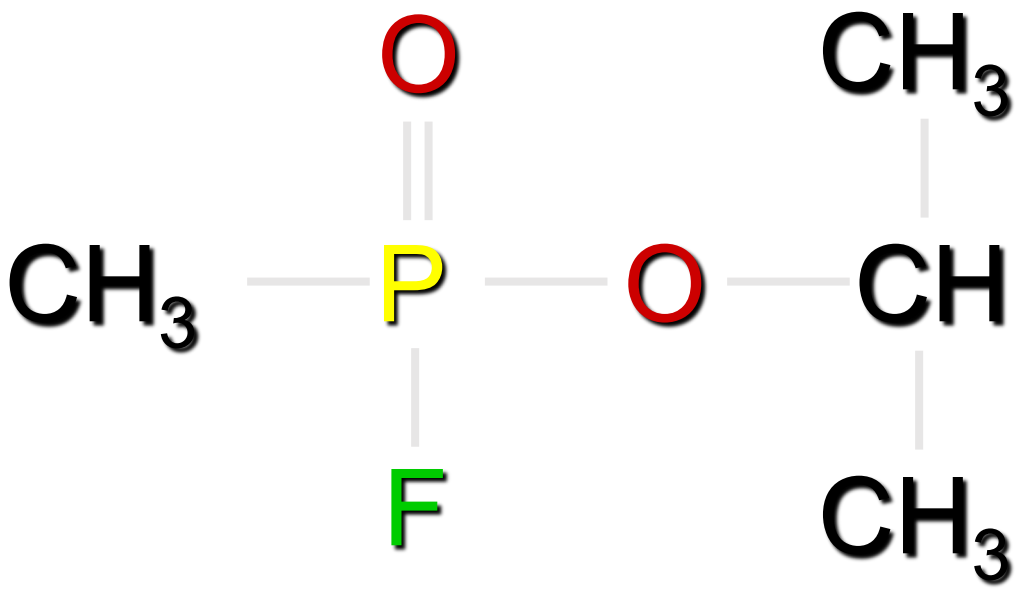
Nerve agent: DEFINITION

- A substance that causes biological effects by inhibiting acetylcholinesterase
- Acetylcholinesterase, therefore, is the target of nerve agents
- Acetylcholine accumulates
- Effects are due to excess acetylcholine

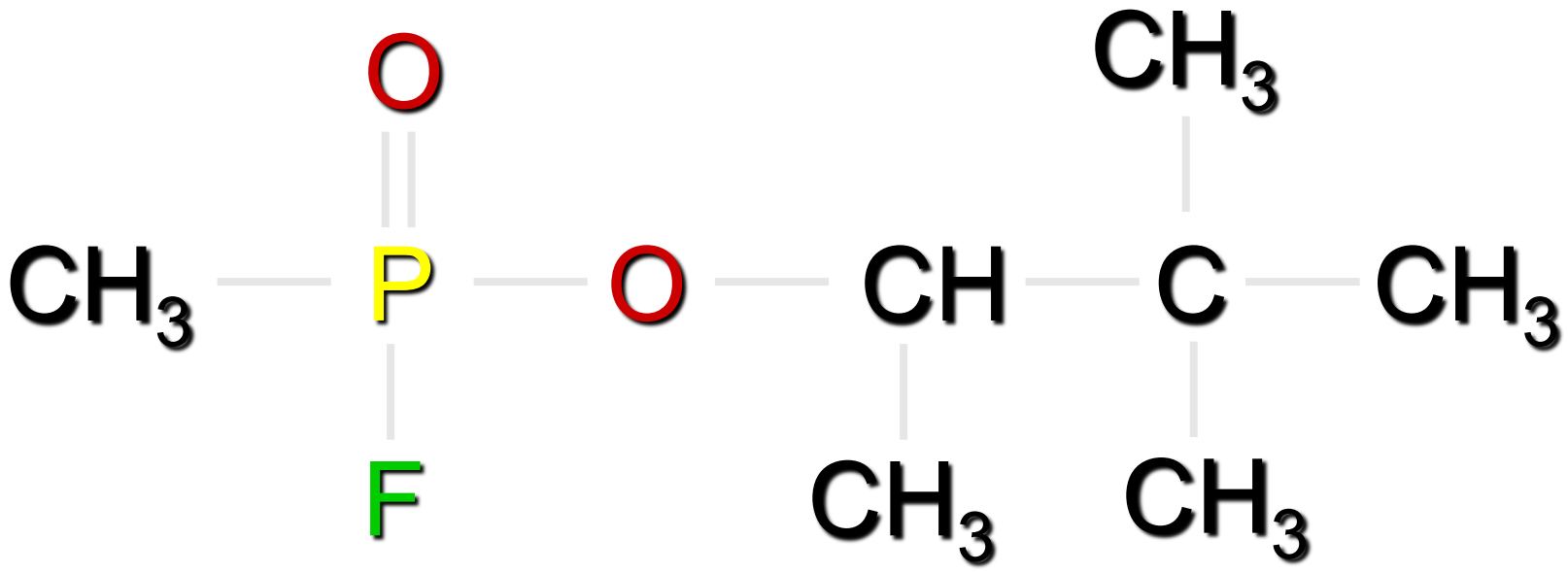
GA (tabun)



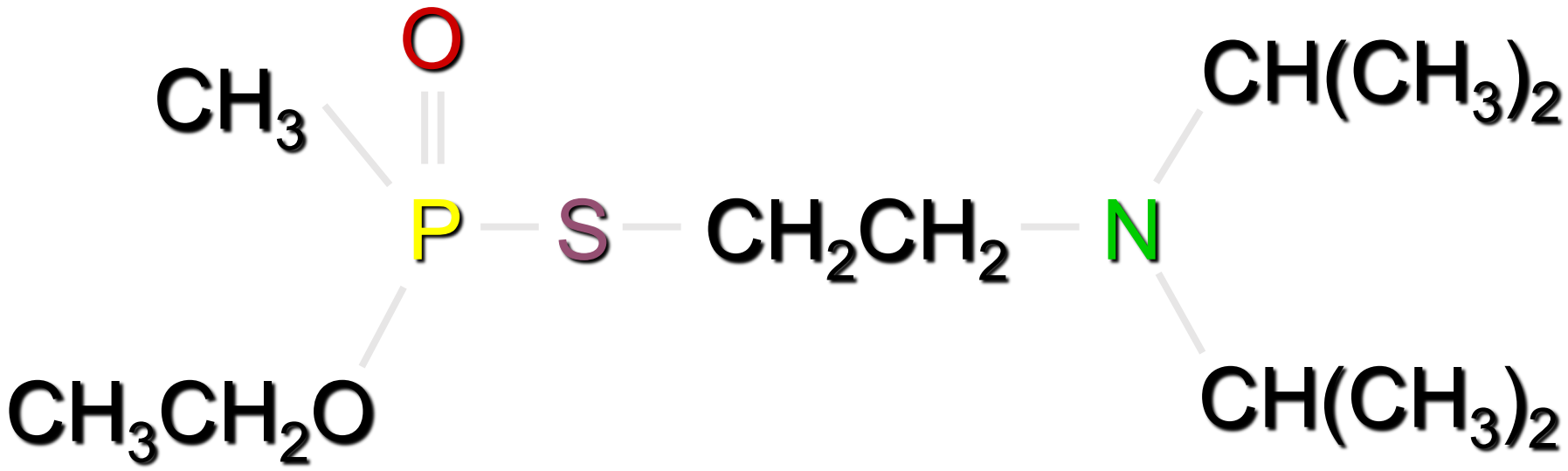
GB (sarin)



GD (soman)



VX



HISTORY

- First synthesized by Gerhard Schrader, IG Farben, Germany, 1936-1938
- Weaponized and stockpiled by Germany in WWII but never used
- Manufactured and stockpiled in quantity by USA, USSR, Iraq, others
- First used on the battlefield by Iraq, 1984-1987
- Biggest terrorist attack: Aum Shinrikyo in Tokyo, 1995
- *First documented US battlefield casualties, Iraq, 2004*
- Biggest recent use: Syrian civil war, 2013-
- Assassinations/attempts: Kim Jong Nam, Sergei Skripal, Alexei Navalny

PHYSICAL PROPERTIES

- Clear, colorless liquids (when fresh); not “nerve gas”
- Tasteless, most are odorless
- Freeze/melt <0º C
- Boil >150º C
- Volatility GB>GD>GA>GF>>>VX
- Penetrate skin, clothing

TOXICITY

	LCt_{50} mg-min / m^3	LD_{50} mg / 70 kg
GA	400	1,000
GB	100	1,700
GD	70	50
GF	50	30
VX	10	10

LD50 of VX

Nerve agents cause cholinergic crisis

- Non-neurologic:
  - Miosis, dim vision
  - Increased secretions of exocrine glands, upper airway and oral cavity
  - Bronchorrhoea, bronchospasm, dyspnoea
  - GI discomfort, nausea, diarrhoea
  - Variable heart rate abnormalities
- Neurologic:
  - Mild exposure: malaise, visual obscurations, headache
  - Next: twitching, fasciculations
  - Severe exposure (ACUTE): seizures, loss of consciousness, central apnoea, flaccid paralysis, death

Military personnel and first responders are all trained to recognize this syndrome!

Roll-ins

Nerve agent poisoning: clinical approach (Army FM 8-285 and derived doctrine for civilians)

- Atropine, first via IM autoinjector and then via IV prn
- Oxime, via IM autoinjector (in the United States, 2-PAM Cl)
- If any question, anticonvulsant via IM autoinjector
  - Diazepam moving to midazolam, largely due to RAMPART trial

Military personnel and first responders are trained to institute this protocol immediately if they suspect cholinergic crisis syndrome.

The only documented US military nerve agent casualties diagnosed themselves due to their training (Baghdad, Iraq, 2004).

Sadr City, Iraq
This is close to where the only US nerve agent battlefield casualties were exposed

Refractory nerve agent-induced SE

- Animal data shows that NASE can be refractory to benzodiazepines.
- Recent anecdotal human cases suggest this can happen in people too.
- Morgan JE et al. Refractory and super-refractory status epilepticus in nerve agent poisoned rats following application of standard treatment guidelines. Front Neurosci 2021, 15:732213
- Tested second line anticonvulsants in a NASE (soman) rat model – “ICU on a lab bench”
- IM and IV benzodiazepines were insufficient to stop SE
- Ketamine and propofol were ineffective and had high levels of mortality
- Valproic acid terminated SE in 35% and required an anaesthetic
- Phenobarbital terminated SE in 56%, 19% remaining seizure-free x 24 h
- We don’t have particularly good treatment for this form of SE!
- Not even as effective as Kapur et al. data on second anticonvulsant in “normal” human SE.

Why are these two forms of SE different?

- We can't study NASE in people. All medical countermeasures for NASE will have to go via the Animal Rule unless they are for ALL forms of seizures (like midazolam).
- "Normal" SE occurs in individuals. NASE often will occur in a mass casualty event (war or terrorism). So logistics are key to NASE planning.
- "Normal" SE often occurs in individuals with CNS lesions and/or pre-existing illness. NASE occurs most often in previously completely normal people.
- "Normal" SE often has a neurology (localization): stroke, tumor, focal epilepsy, old head trauma. NASE is basically global due to the wide distribution of cholinergic transmission.
- "Normal" SE does not show signs of cholinergic crisis (miosis, wet, SLUDGE). Cholinergic crisis is the hallmark of NASE.

What are the commonalities?

- In both “normal” SE and NASE, we want to stop seizures in order to save neurons and thus save neurological function. The longer you seize, the less well you do.
- In both, we pay attention to long-term effects of SE. These include cognitive impairment and, at least in theory, greater tendency to epilepsy (theoretic in human NASE).
- We treat both conditions aggressively, but suboptimally.
- Those working on each condition should leverage work done by those working on the other.

طرق الوقاية من غازات الحروب الكيماوية
Safeguards against chemical war gases.

إذا كنت داخل السيارة (ورأيت بعض الطيور على الأرض) افعل مايلي :
If you are inside your car (and see birds dropping)

a. Close all windows. أ. أغلق كافة النوافذ. قف على جانب الطريق
b. Switch off the air-conditioning unit. ب. اطفئ جهاز التكييف
c. Pull off the road. ج. اطفئ المحرك
d. Turn engine off. د. استمع الى جهاز راديو السيارة. وتلقى تعليماتك منه

مع تحيات: البنك الأهلي التجاري و قيادة الدفاع المدني بالمنطقة الشرقية

e. Make that last breath a deep one.

Instructions courtesy of Dennis Roach, Dhahran, Saudi Arabia.