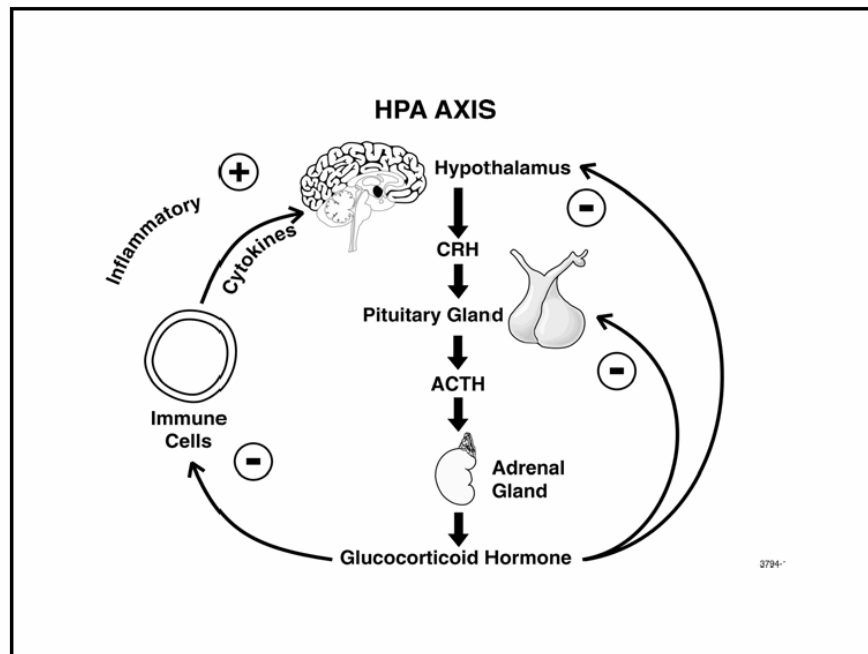


### Presentation 6 – Mohan Sopori

- Brain and the immune system communicate bidirectionally.
- Many neuroactive substances have the potential to affect the immune system through the CNS.
- Two established pathways by which the brain affects the immune system:
  1. Activation of the Hypothalamus-pituitary-adrenal (HPA) axis.
  2. Through sympathetic cholinergic innervations.

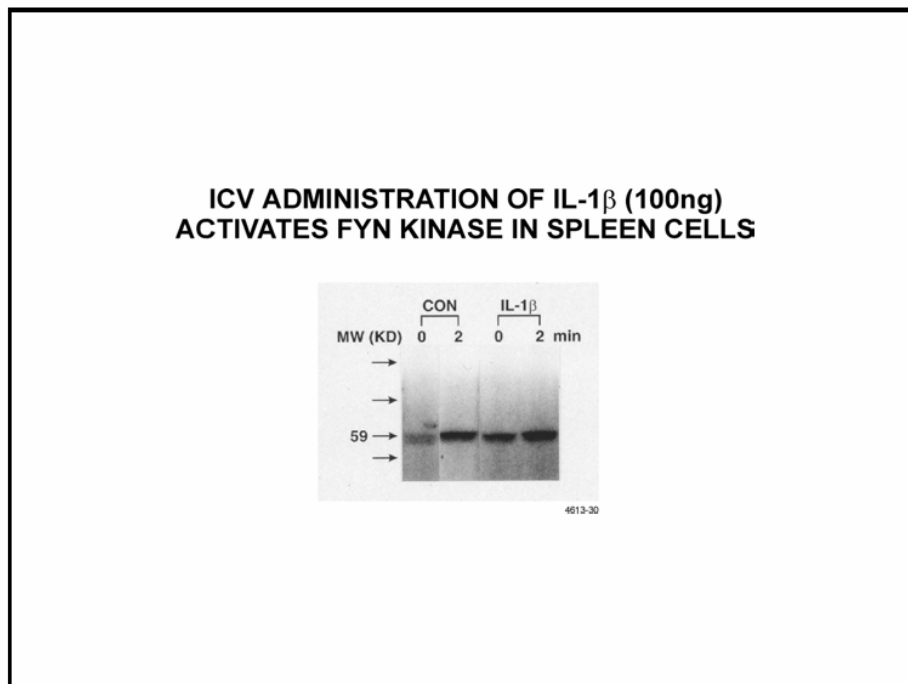
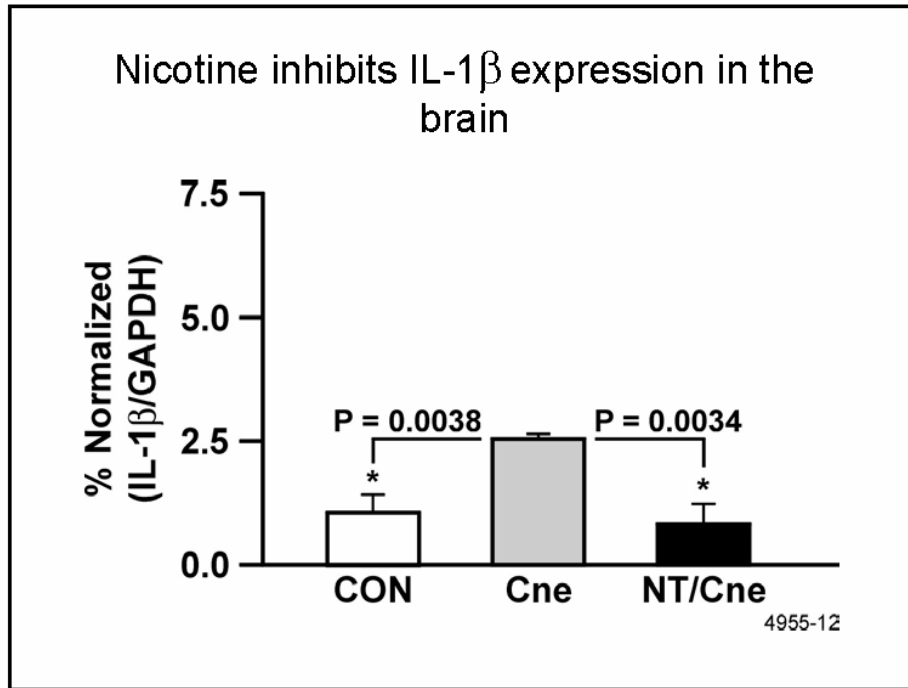


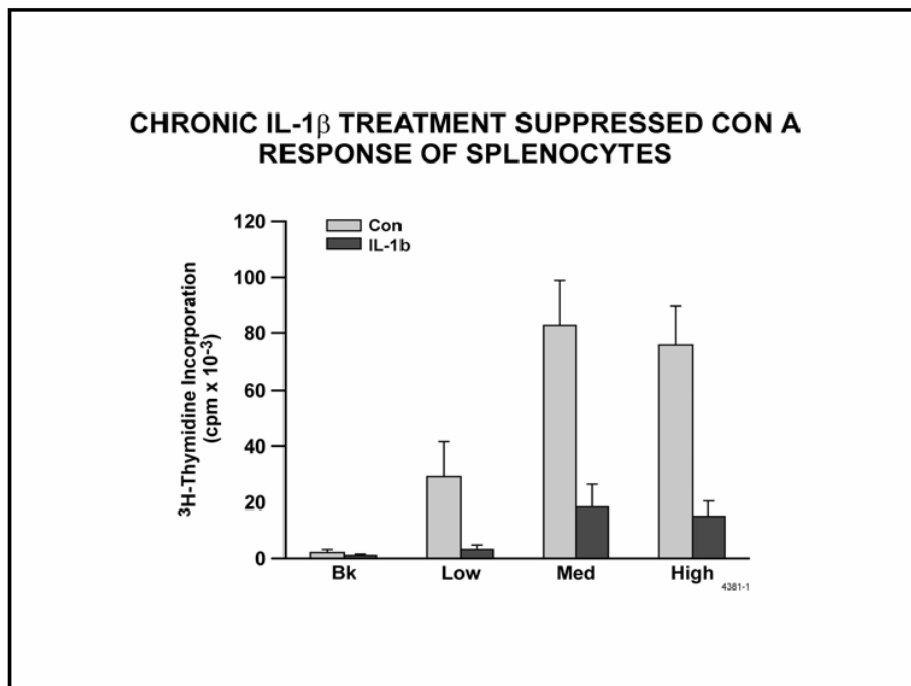
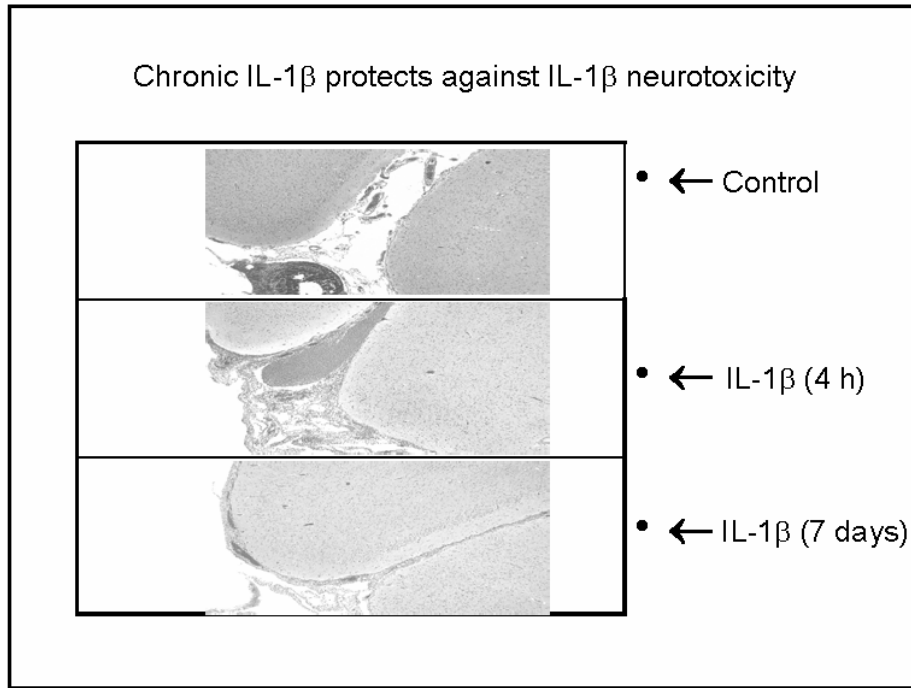
## Cytokine Effects

- Cause sickness behavior (e.g., malaise, listlessness, fever, pain, loss of interest in social activities) ....Keith Kelly, Suzzane Broussad et al.
- Correlation between acute viral infection (e.g., EBV, Q fever) and the levels of IL-1 $\beta$  and IL-6 in serum and produced by PBMC in culture (Ute Vollmer-Conna et al.).
- There is lack of tight correlation between serum and brain cytokine levels (LPS-tolerance, Sulie Chang).
- How does a cytokine signal reach the brain? Vagal afferents sense peritoneal cytokines, but not IV or subcutaneous cytokines.

## Cytokine Effects

- Pyrogenic effects of cytokines are critical for survival of cold-blooded animals from infections (M. Kluger).
- Use of antibodies against proinflammatory cytokines has adverse effects on human sepsis patients (C. Dinarello).
- Ischemic brain injury is more severe in TNF- $\alpha$  and IL-6 KO animals.
- Chronic nicotine treatment blunts inflammation, but increases viral, bacterial, and viral load (Razani-Boroujerdi et al.; Tom Klein et al.).
- Tolerance: sublethal exposures to endotoxin or TNF- $\alpha$  protects against subsequent lethal infections (Hymie Anisman).



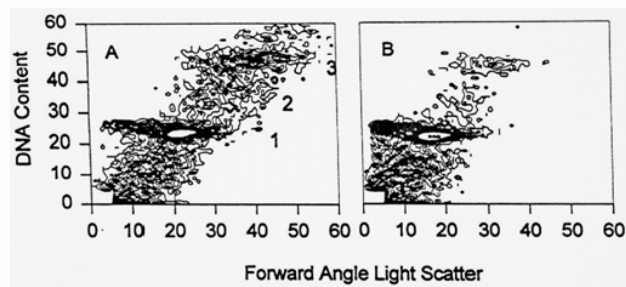


## Cholinergic compounds and neuroimmune interaction

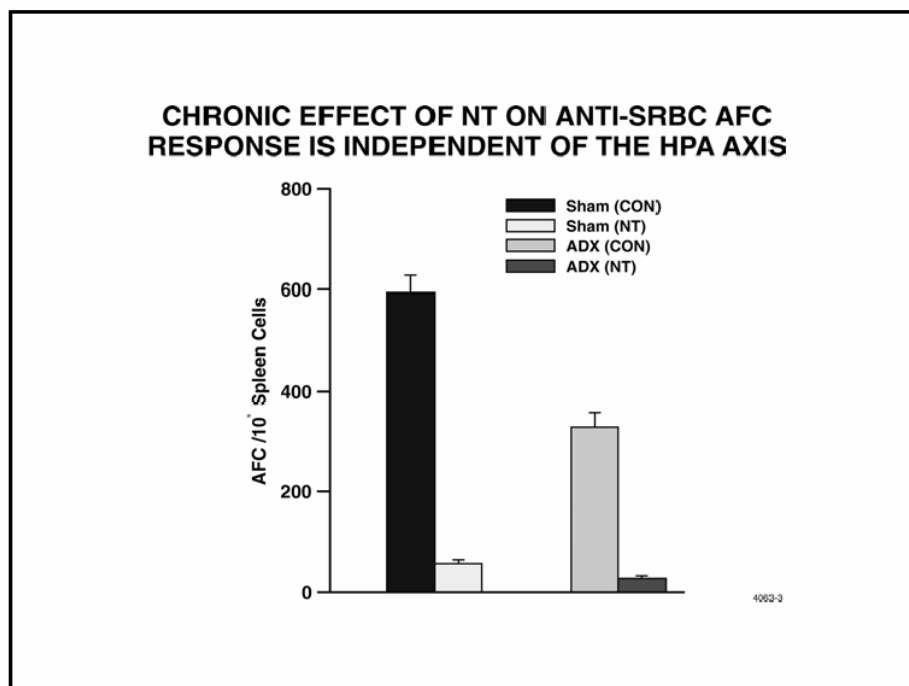
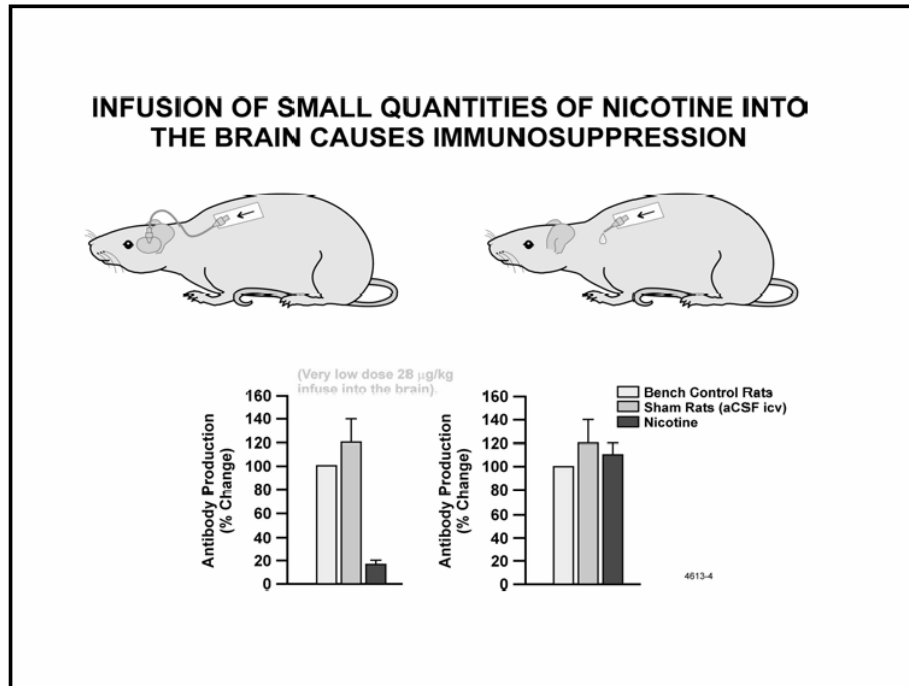
- Lymphocytes contain both muscarinic and nAChRs.
- Sarin - a powerful acetylcholine esterase inhibitor, in high doses causes cholinergic shock -respiratory failure and death.
- Nicotine –a neuroactive substance. It is an established immunosuppressive and anti-inflammatory.

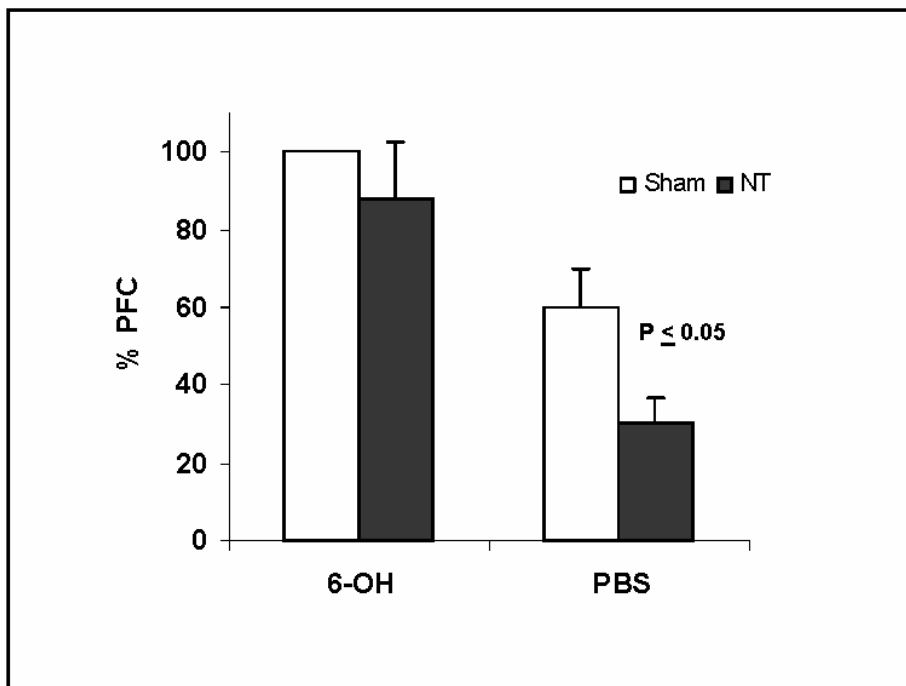
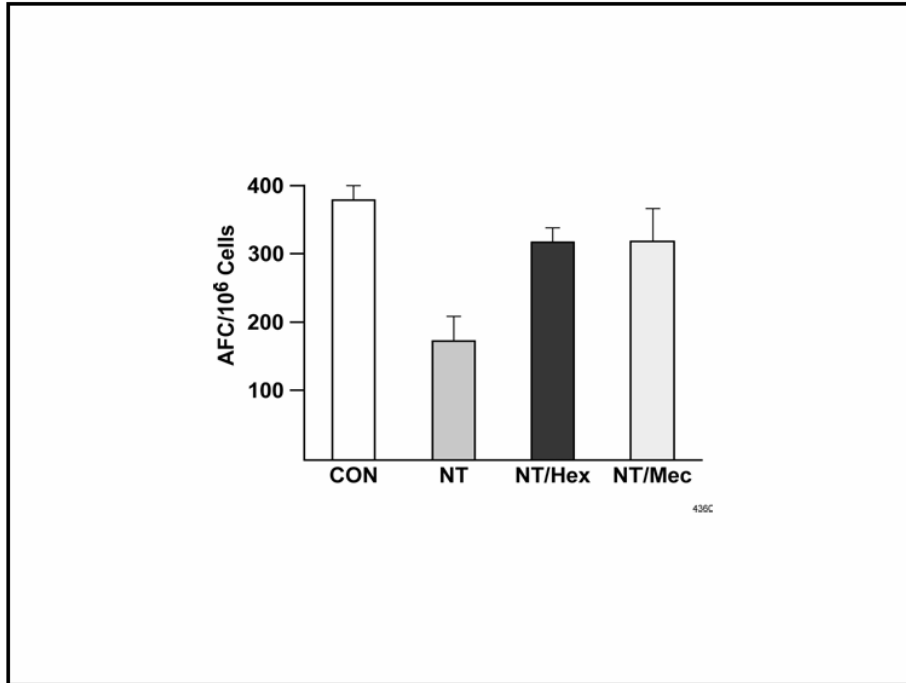
- Lymphoid tissues have dense sympathetic innervations.
- Leukocytes, including lymphocytes and dendritic cells also have beta-2-adrenergic receptors .
- The sympathetic neurotransmitter norepinephrine (NE) binds beta-2-adrenergic and suppresses immune and inflammatory responses.

## EFFECTS of NICOTINE



4613-2E







### TCR-Mediated Signaling for Ca<sup>2+</sup> response

**ANTIGEN**

↓

**Protein Tyrosine kinases  
(PTK)**

↓

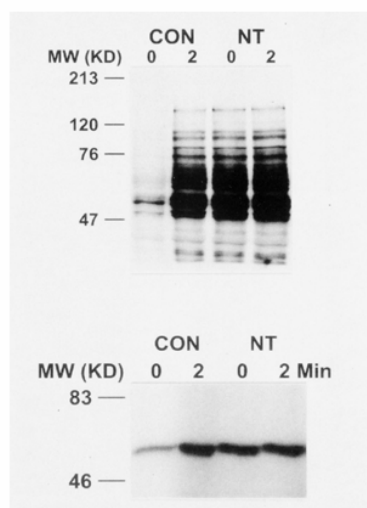
**IP3 (PLC- $\gamma$ 1)**

↓

**Calcium from stores**

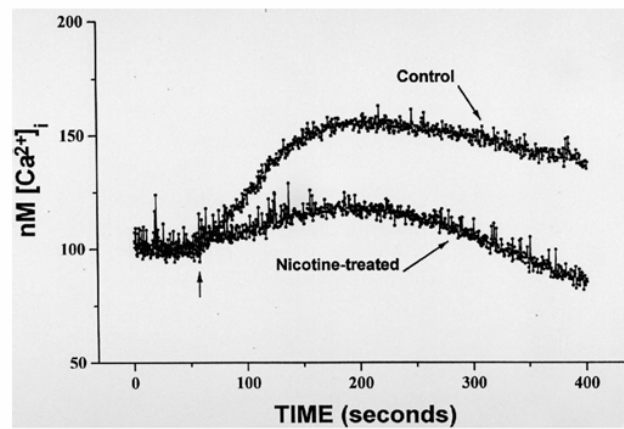
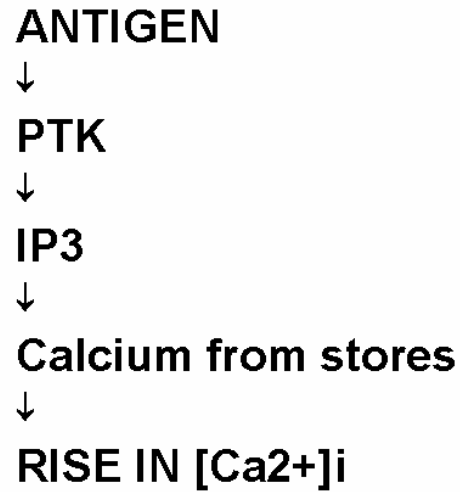
↓

**RISE IN [Ca<sup>2+</sup>]<sub>i</sub>**



4613-32

### TCR-Mediated Signaling for Ca<sup>2+</sup> response



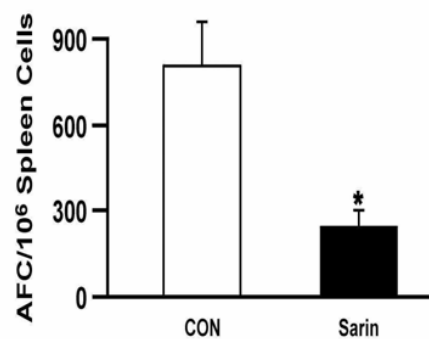
4613-2B

## Health effects of low-doses sarin

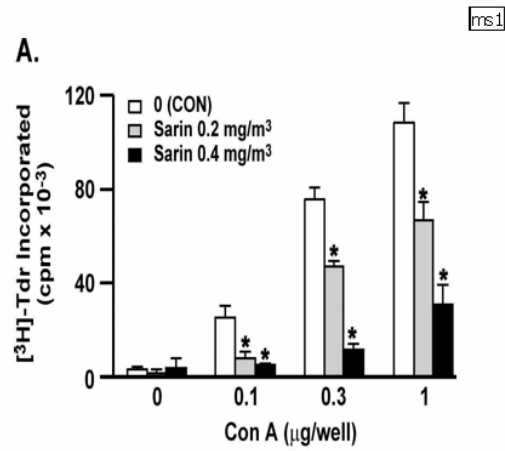
- The possibility that some GW-I veterans were exposed to sarin, engendered the possibility that some symptoms of the GWS might be related to low-dose exposure to sarin.
- The health effects of low-dose sarin are not known. Some survivors of the 1994 subway sarin attack in Japan have exhibited chronic neurological problems.
- Some of the survivors died from opportunistic infections, such as Legionella, indicating sublethal doses of sarin might have long-term effects on the immune system.

DOES SARIN AFFECT THE IMMUNE SYSTEM?

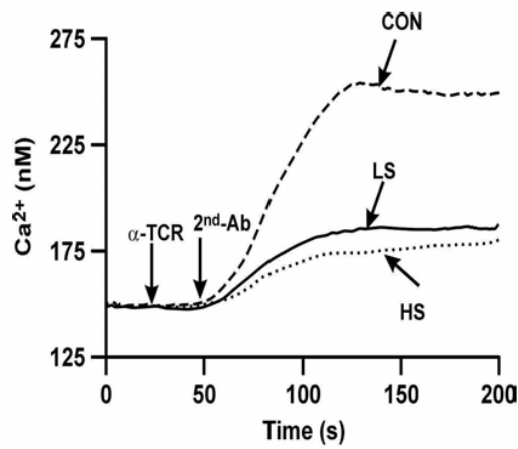
## Sarin inhibits antibody response



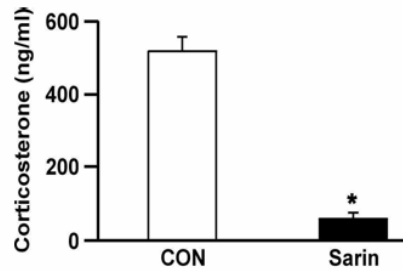
### Sarin suppresses T cell mitogenesis



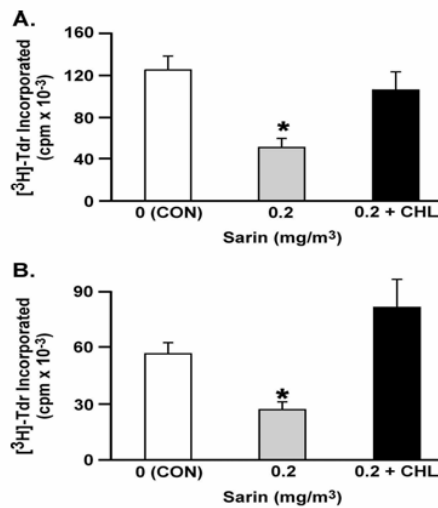
### Sarin impairs T cell signaling (calcium response)

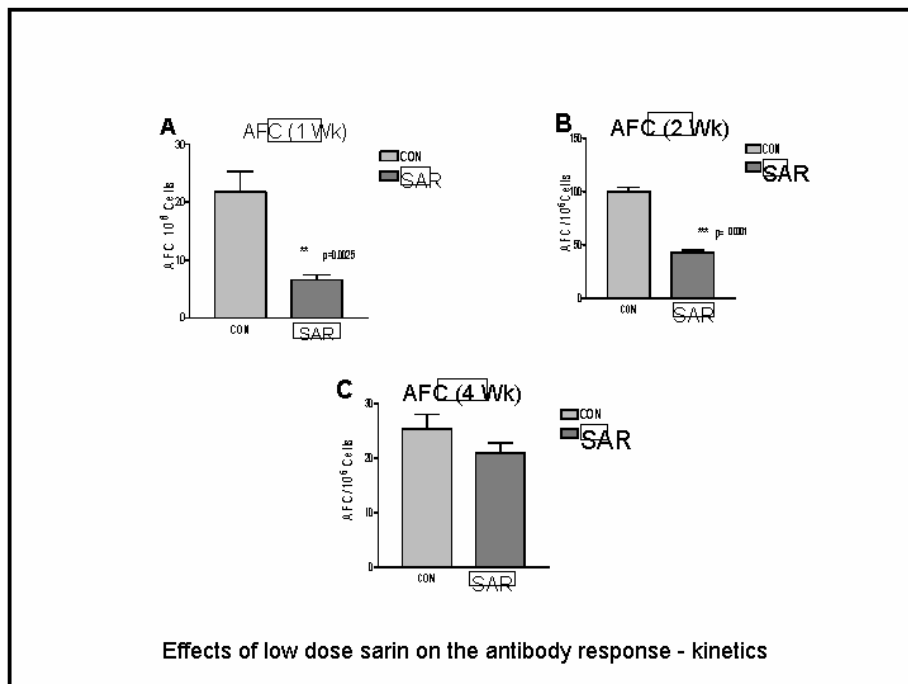
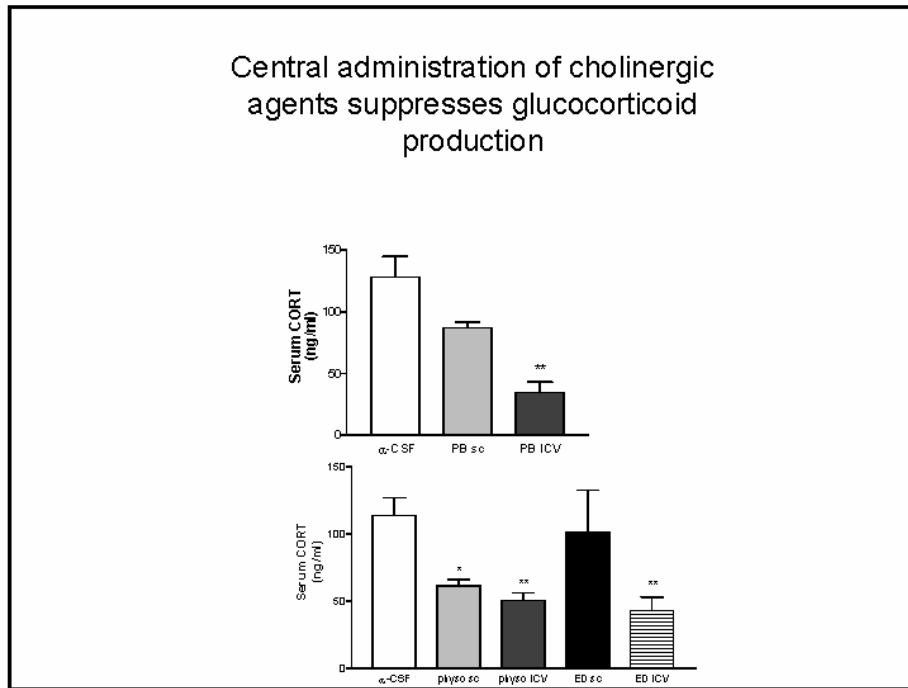


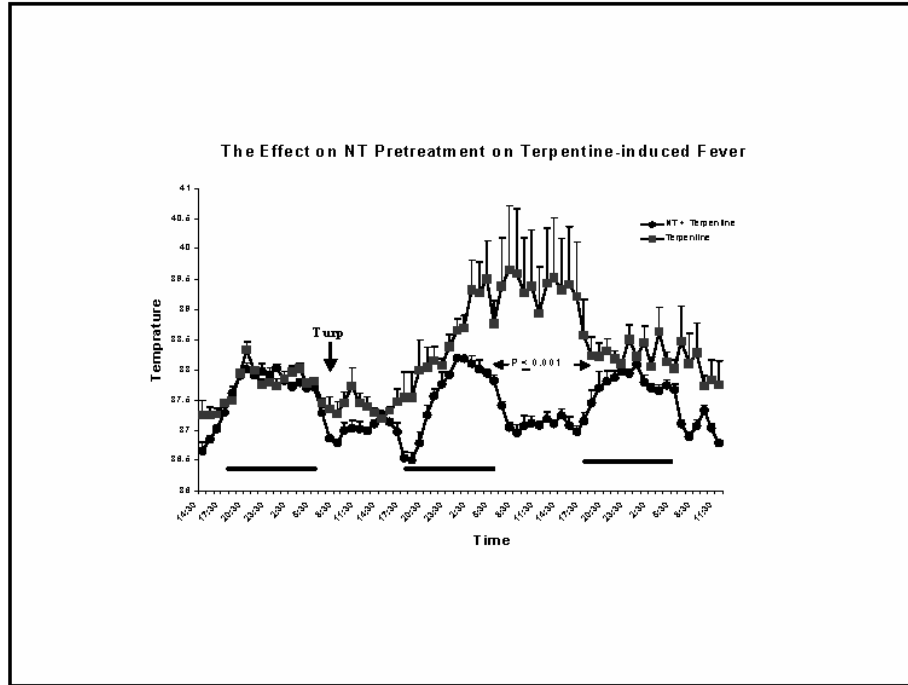
### Sarin suppresses corticosterone production



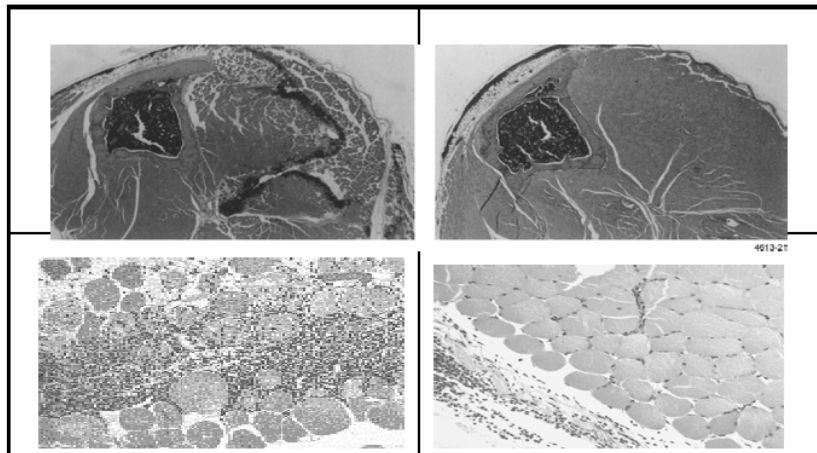
### Chlorisondamine blocks sarin-induced immunosuppression (A: Con A; B: anti- $\alpha\beta$ TCR)

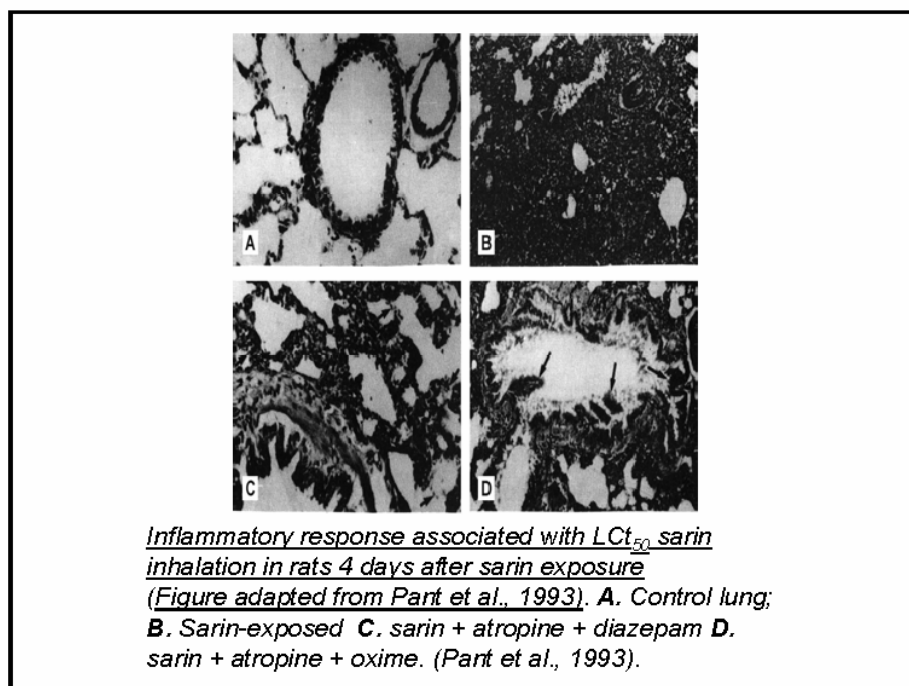
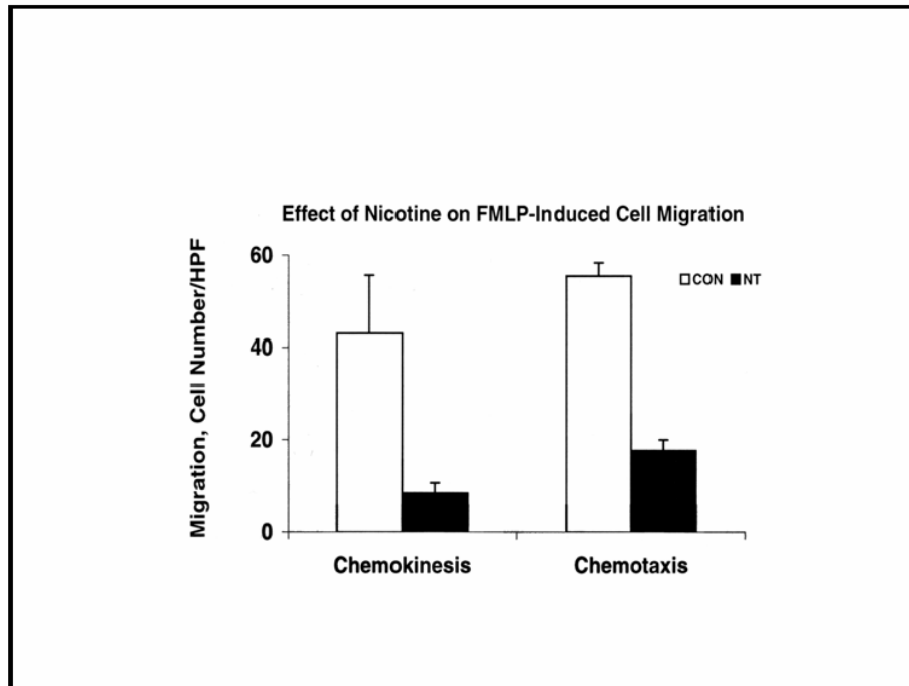




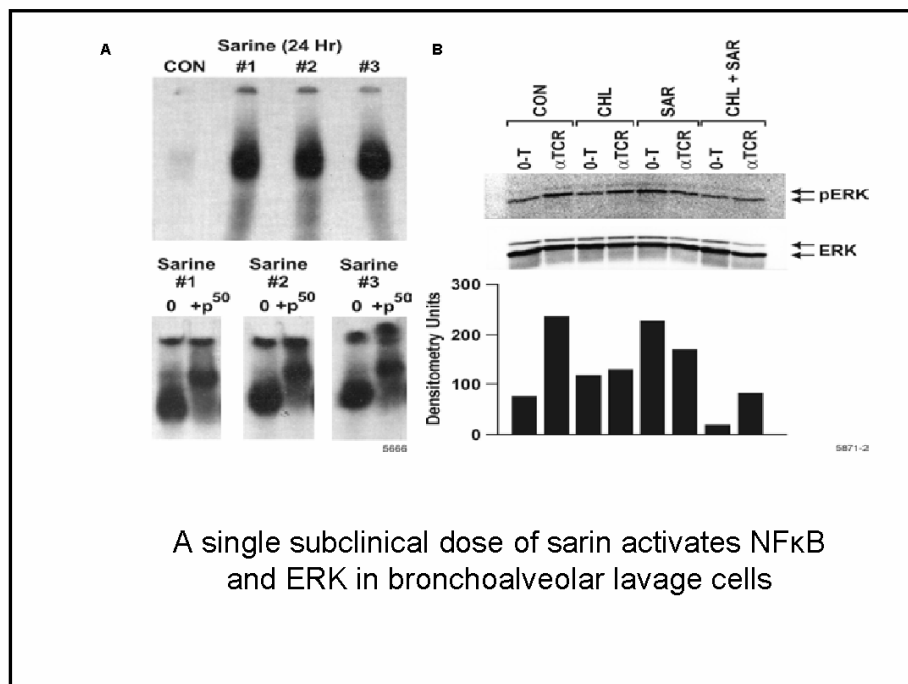
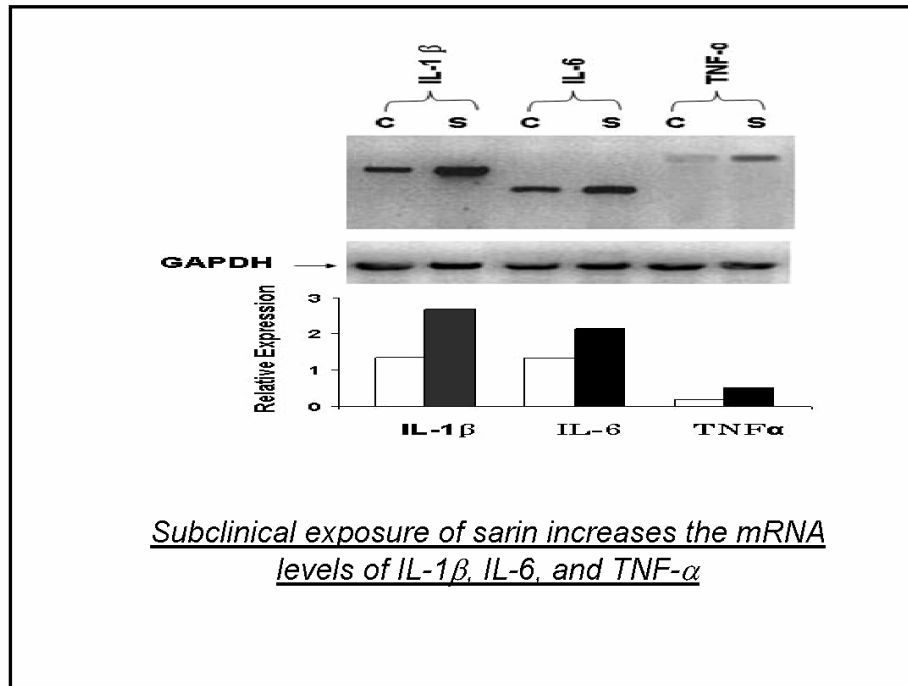


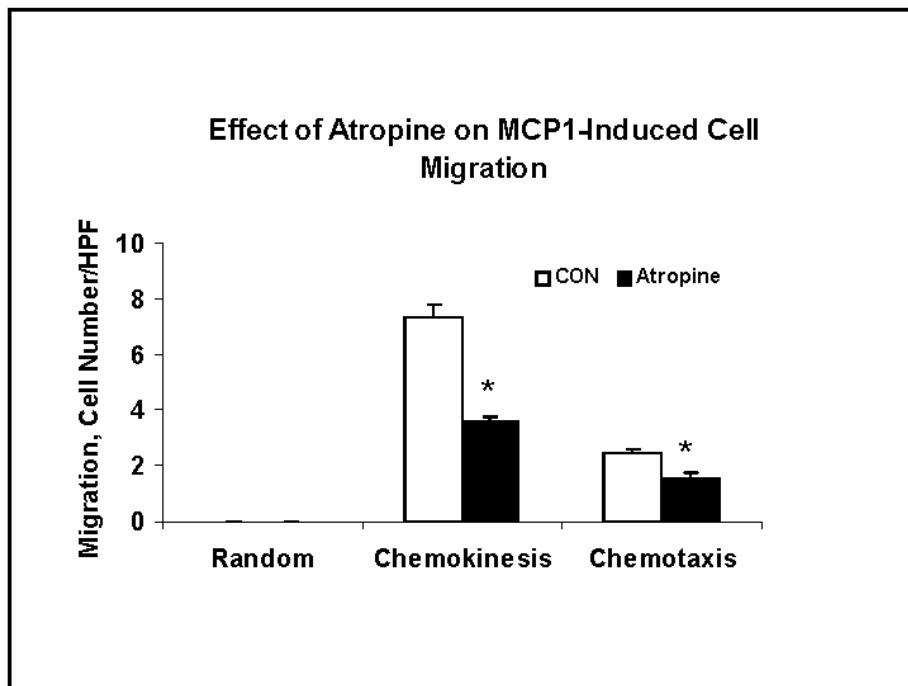
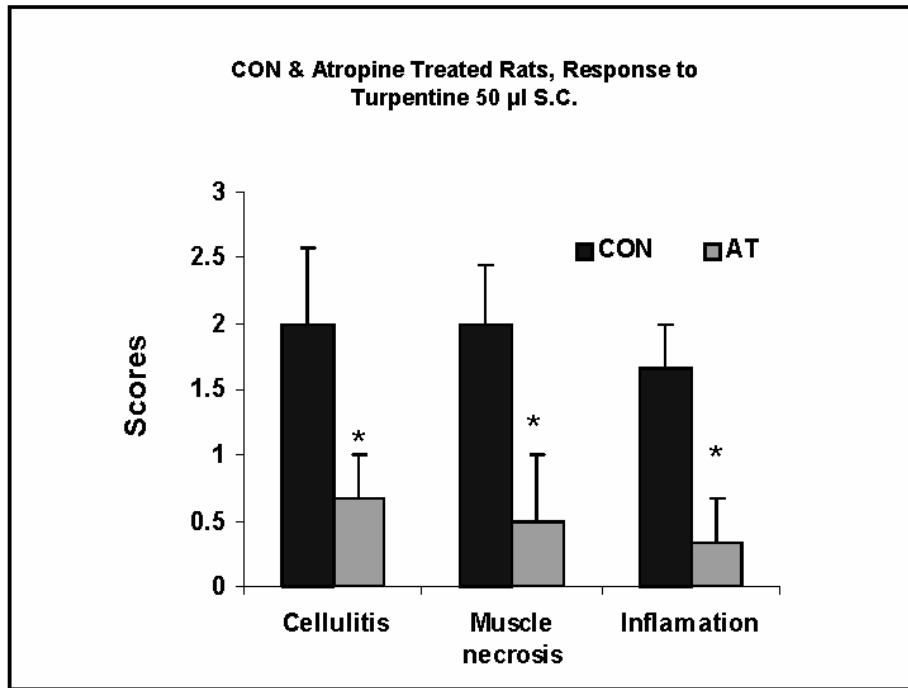
**Nicotine inhibits the migration of leukocytes to the site of inflammation**

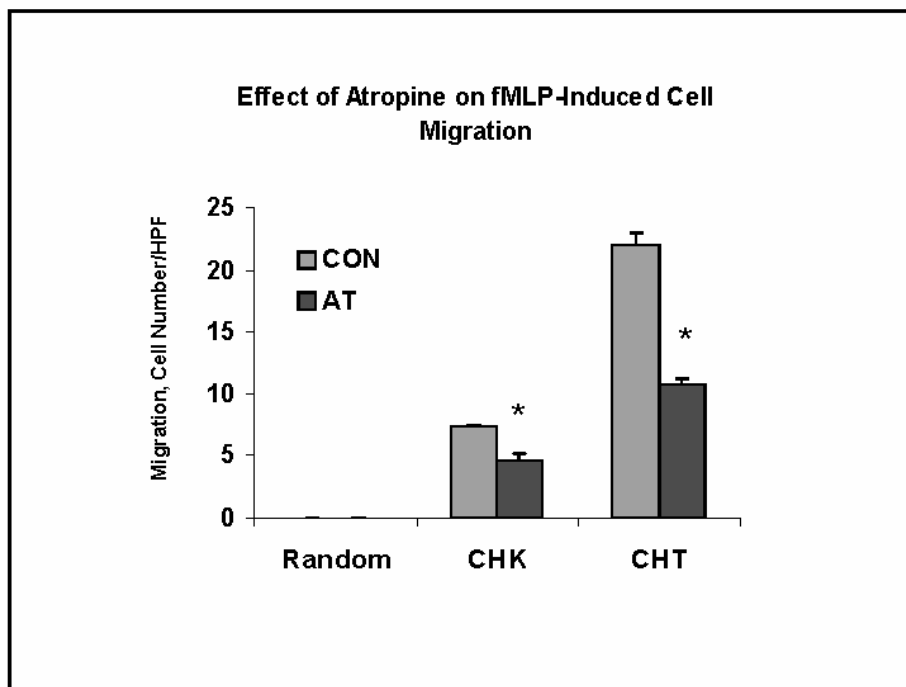












## CONCLUSIONS

1. Both sarin and nicotine inhibit T cell activation.
2. While nicotine has no significant effects on CORT levels, sarin and other cholinesterase inhibitors decrease serum CORT levels.
3. Nicotine is anti-inflammatory, while sarin is proinflammatory. Nicotine inhibits the expression of IL-1 $\beta$  in the brain, while sarin induces the expression of proinflammatory cytokines in the lung and the brain (activation of the NF $\kappa$ B/ERK pathway).
4. While activation of nAChRs suppresses, activation of muscarinic receptors stimulate the immune/inflammatory responses.

- Seddi Razani-Boroujerdi
- Roma Kalra
- Ray Langley
- Juan Carlos Philippides
- Shashi Singh
- Neerad Mishra
- Fletcher Hahn
- Julie Hutt
- RO1 DA017003
- R01 DA04208-15
- RO1DA04208-7S
- W81XWH-04-C-0071