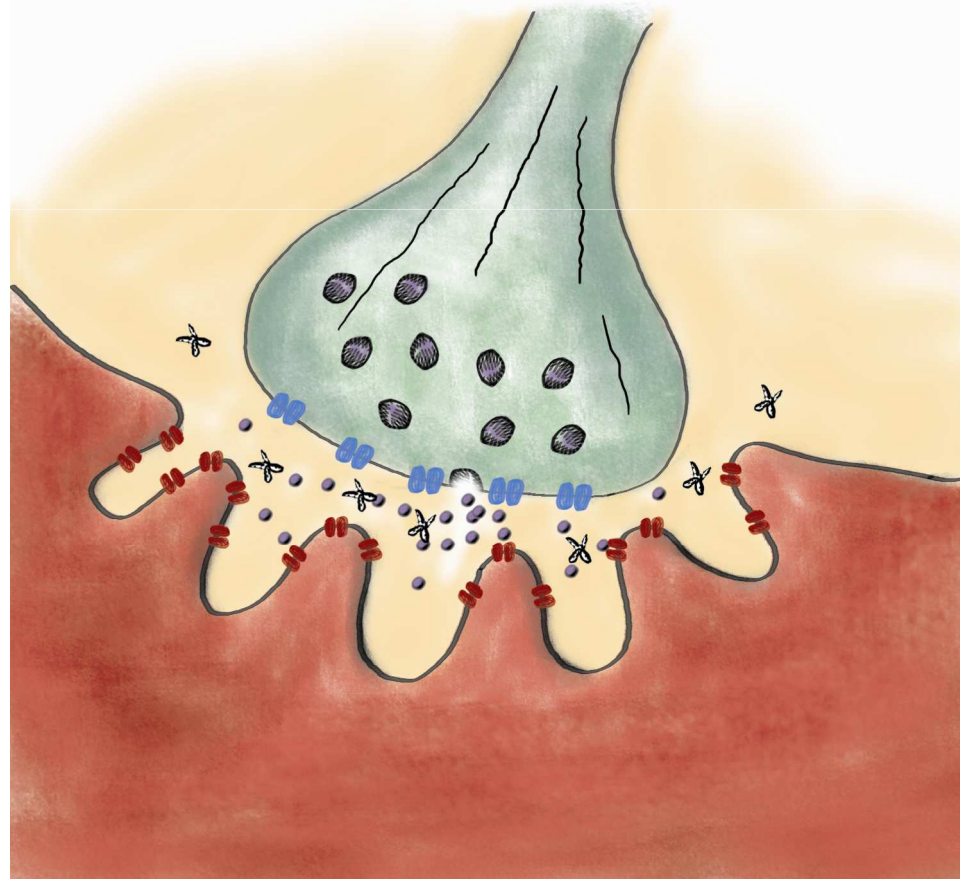


# Myasthenia Gravis: A Neurologist's Perspective

M. Nicolle MD FRCPC D. Phil.



# Introduction

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- This PowerPoint presentation is based on one given to the Myasthenia Gravis Ontario Chapter in Etobicoke Ontario, Canada.
- Many of the products discussed in this presentation are not ‘officially’ approved to treat Myasthenia Gravis. **However, most are widely used by neurologists who manage patients with MG.** In many cases investigations are underway.
- The material in this presentation is intended for patient educational purposes only. It should not be used in place of advice from your neurologist or family physician.
- *Acknowledgements:* I thank Talecris Biotherapeutics for making this educational CD possible through an unrestricted education grant.

M. Nicolle MD FRCPC D. Phil.



# Overview

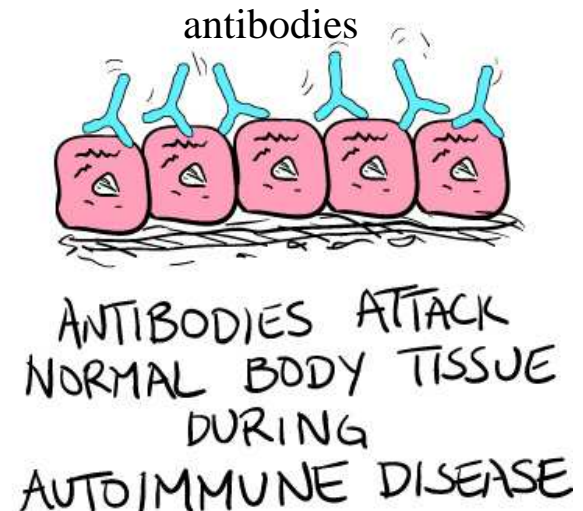
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- What is MG - an introduction
- Treatment of MG
- Management issues
- Future

# Myasthenia Gravis

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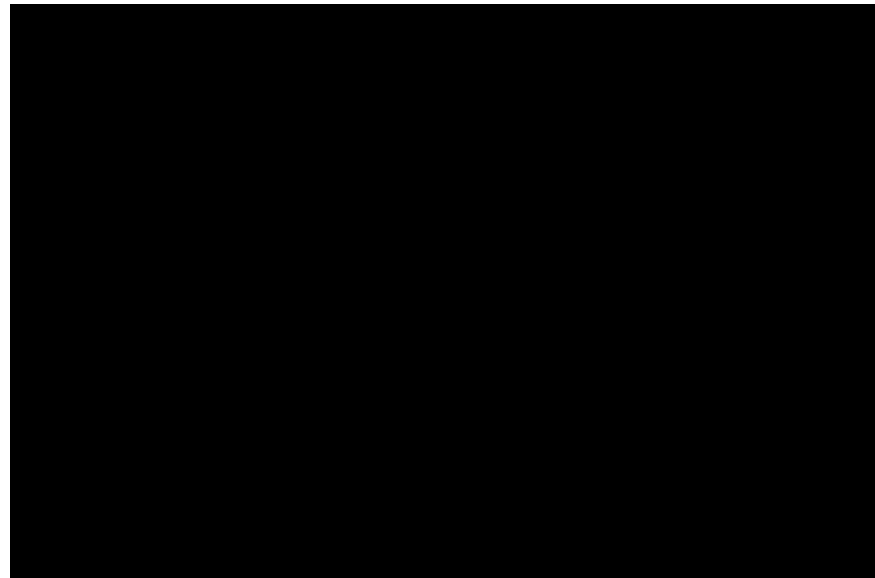
- An autoimmune disease in which the immune system attacks a protein on the surface of muscle
- Autoimmune disease = a disease in which parts of the immune system are overactive and start to damage the body tissues
- A normal immune system attacks 'foreign' organisms - for example infections
- In an autoimmune disease the immune system inappropriately damages normal body tissues



# Cause of Myasthenia Gravis

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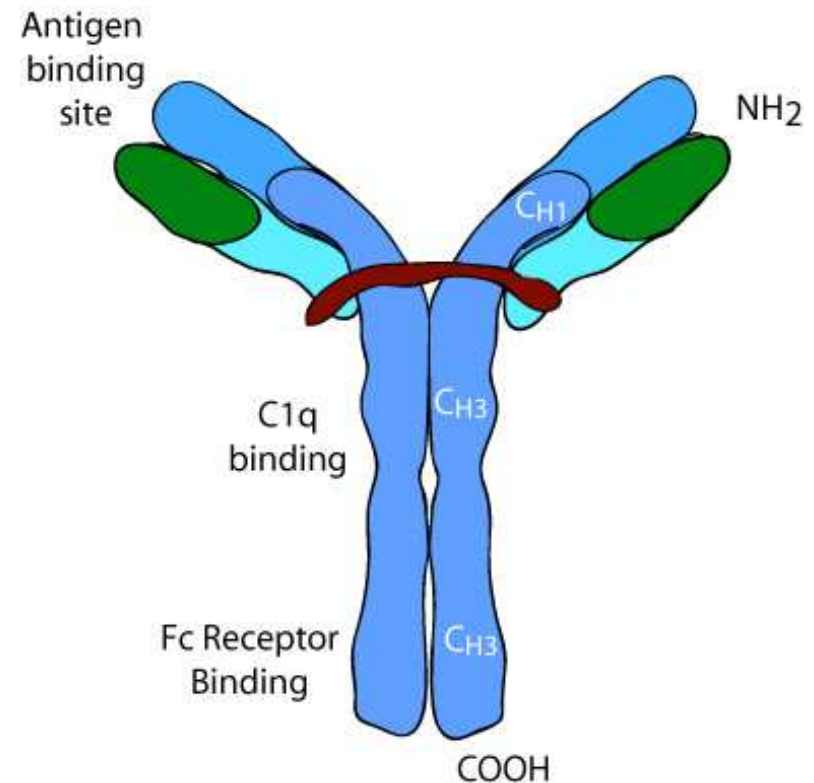
- Unknown
- One of many “autoimmune diseases”
- A basic problem with the immune system - parts of it are overactive
- Individuals with MG and their family members more likely to have one of these other autoimmune diseases



# What are Antibodies (Immunoglobulins)?

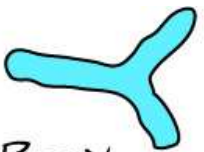
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- Antibodies are proteins that play an important role in the immune system.
- They are normally directed at foreign proteins called *antigens* that attack the body.
- Such foreign proteins include bacteria and viruses.
- Antibodies help the body to protect itself from these foreign proteins.




# Molecular Mimicry

## Infection

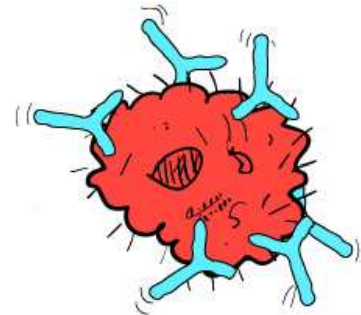


ANTIBODY  
FROM IMMUNE SYSTEM



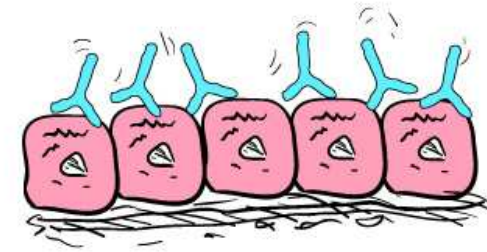
FOREIGN BODY  
(cell)

“Foreign protein” e.g.  
bacteria



ANTIBODIES ATTACK  
FOREIGN CELLS

## Autoimmune Antibody



ANTIBODIES ATTACK  
NORMAL BODY TISSUE  
DURING  
AUTOIMMUNE DISEASE

“Self protein”  
Acetylcholine receptor

# Myasthenia Gravis - the symptoms

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- Weakness
  - Fluctuates
  - Worse with use, at end of day
  - Periods of remission, periods of worsening
- Involving
  - Eyes - double vision and droopy eyes
    - Usually the first symptom
  - Face - facial weakness
  - Speech - slurred or hoarse
  - Swallowing problems
  - Breathing problems
  - Arm weakness - carrying, lifting
  - Leg weakness - stairs and chairs



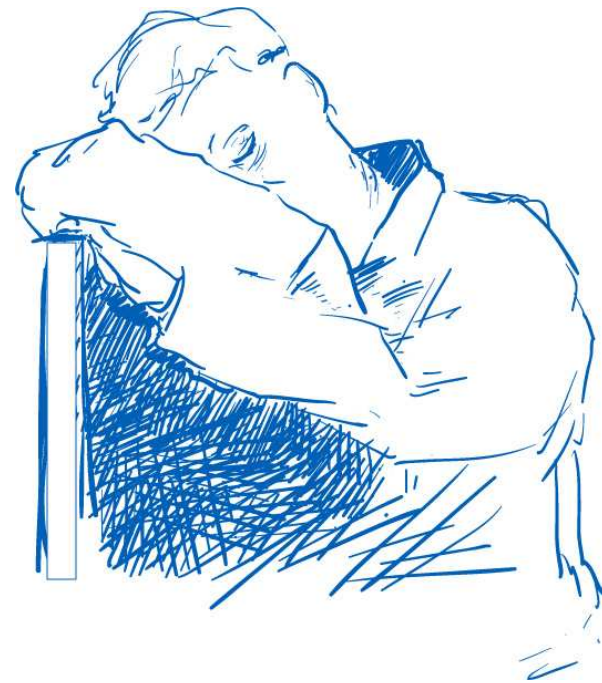
## But...

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- Many other diseases can cause weakness, tiredness and fatigue - even if you have myasthenia
- Not all symptoms in someone who has MG are directly related to MG
- Sometimes treatments for MG can worsen the symptoms of weakness if the weakness is caused by something other than MG.
- Important to know the cause of weakness

# These are not symptoms of Myasthenia Gravis:

- Pain
- Memory loss
- Numbness
- Sleepiness (at least directly)



# Other things that can bring out or worsen the symptoms of Myasthenia Gravis

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- Pregnancy
- Stress
- Operations
- Medications
  - Some
  - Many lists - none are absolutely contra-indicated



# Cause of Myasthenia Gravis

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- No evidence that MG is caused by:
  - Mercury fillings in teeth
  - Poor diet
  - Environmental exposure
  - Accidents or trauma
- Not contagious



# Cause of Myasthenia Gravis

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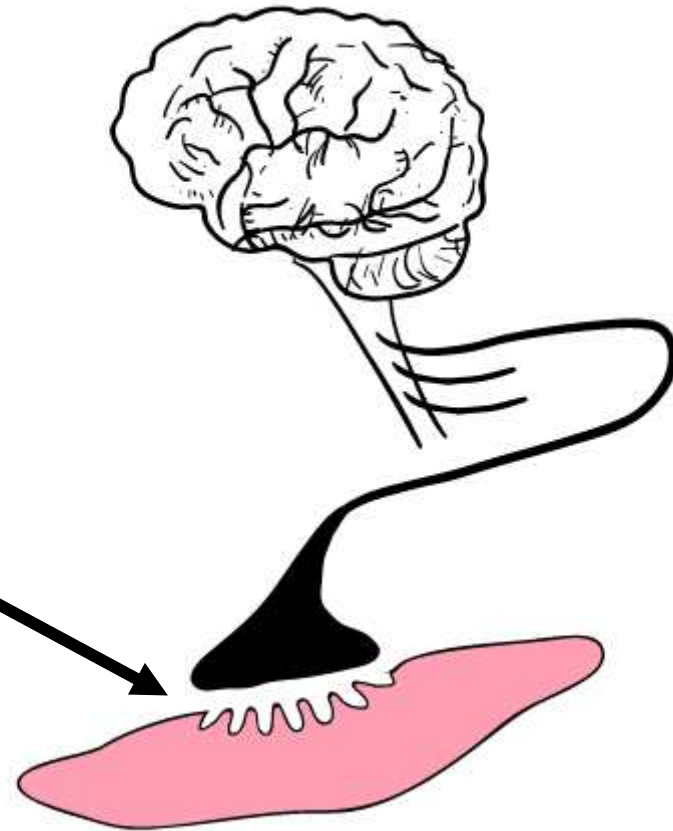
- There are non-immune hereditary forms of MG
  - Congenital myasthenic syndromes
  - Very rare - 1/1,000,000
  - Most start at birth - some later



# Neuromuscular junction

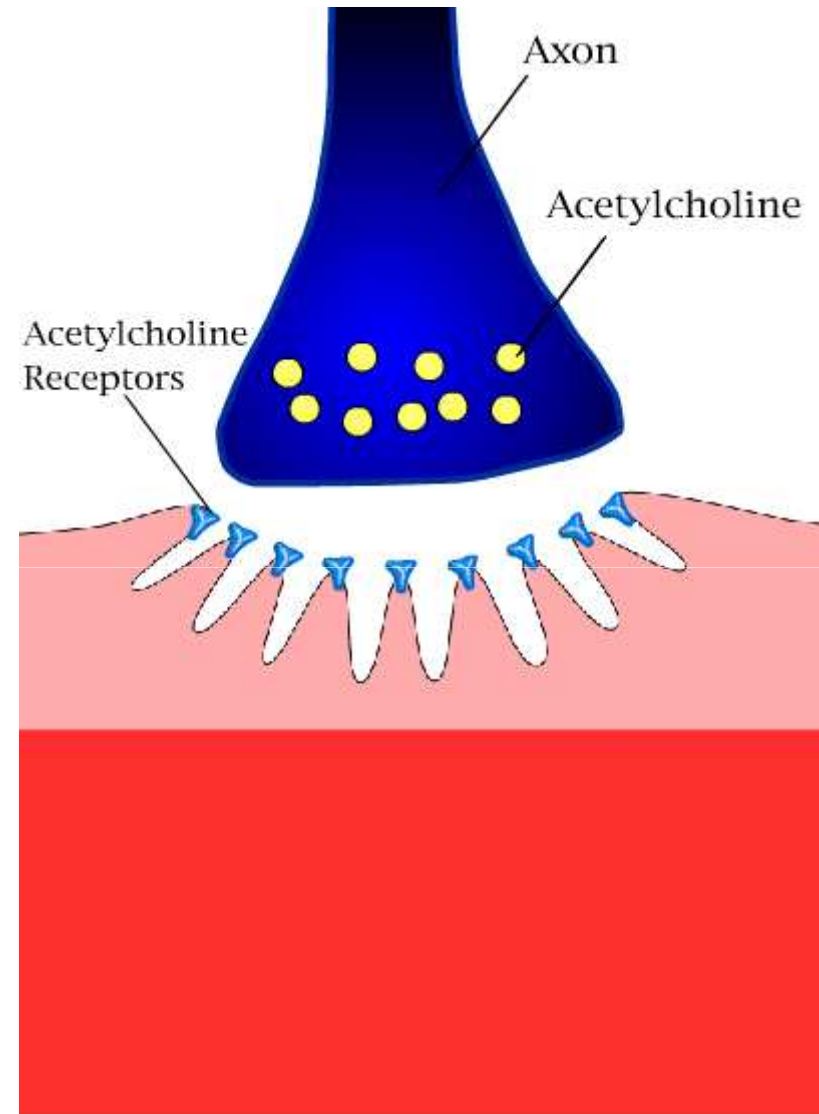
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- Normally, nerves 'talk' to muscles to make them move
- This occurs at the junction between nerves and muscles
  - The neuromuscular junction



# Normal Neuromuscular junction

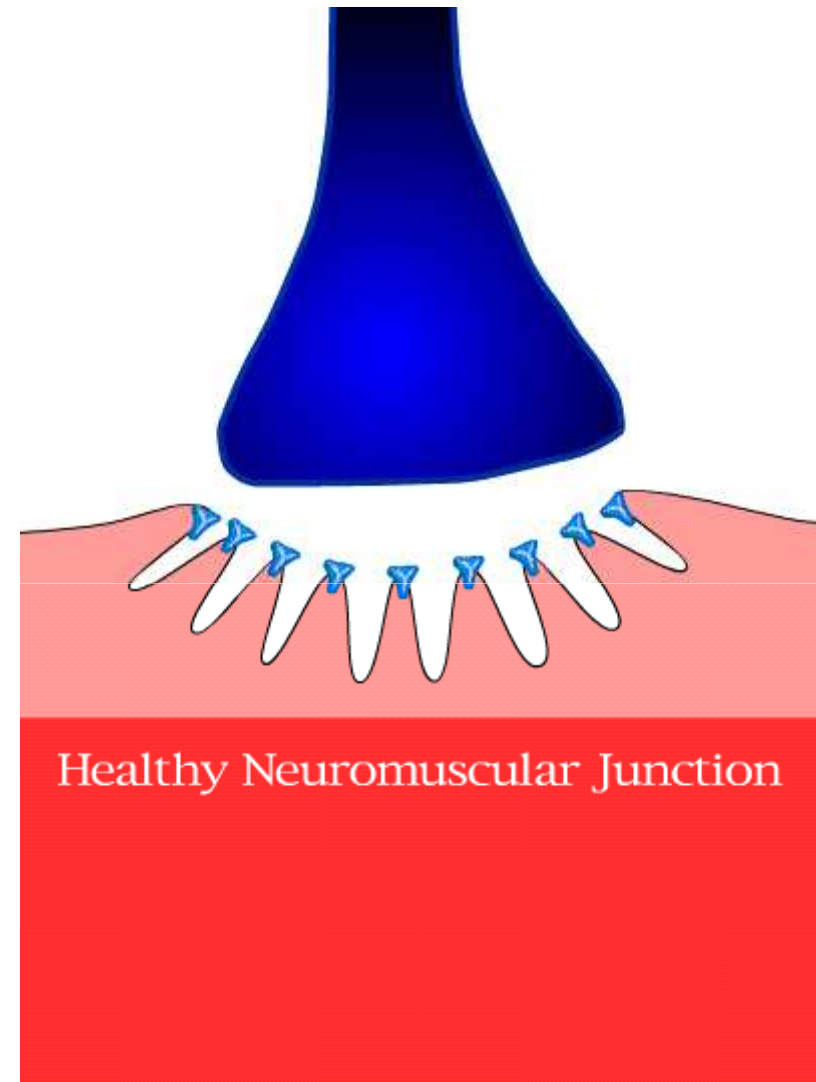
- Acetylcholine (ACh), a chemical messenger, is formed in the motor nerve terminal and stored in vesicles
- When an action potential (signal) travels down a motor nerve and reaches the nerve terminal, ACh is released and combines with ACh receptors on muscle fibers, triggering muscle contraction.
- The process is terminated by the breakdown of ACh by acetylcholinesterase.



# Myasthenia Gravis

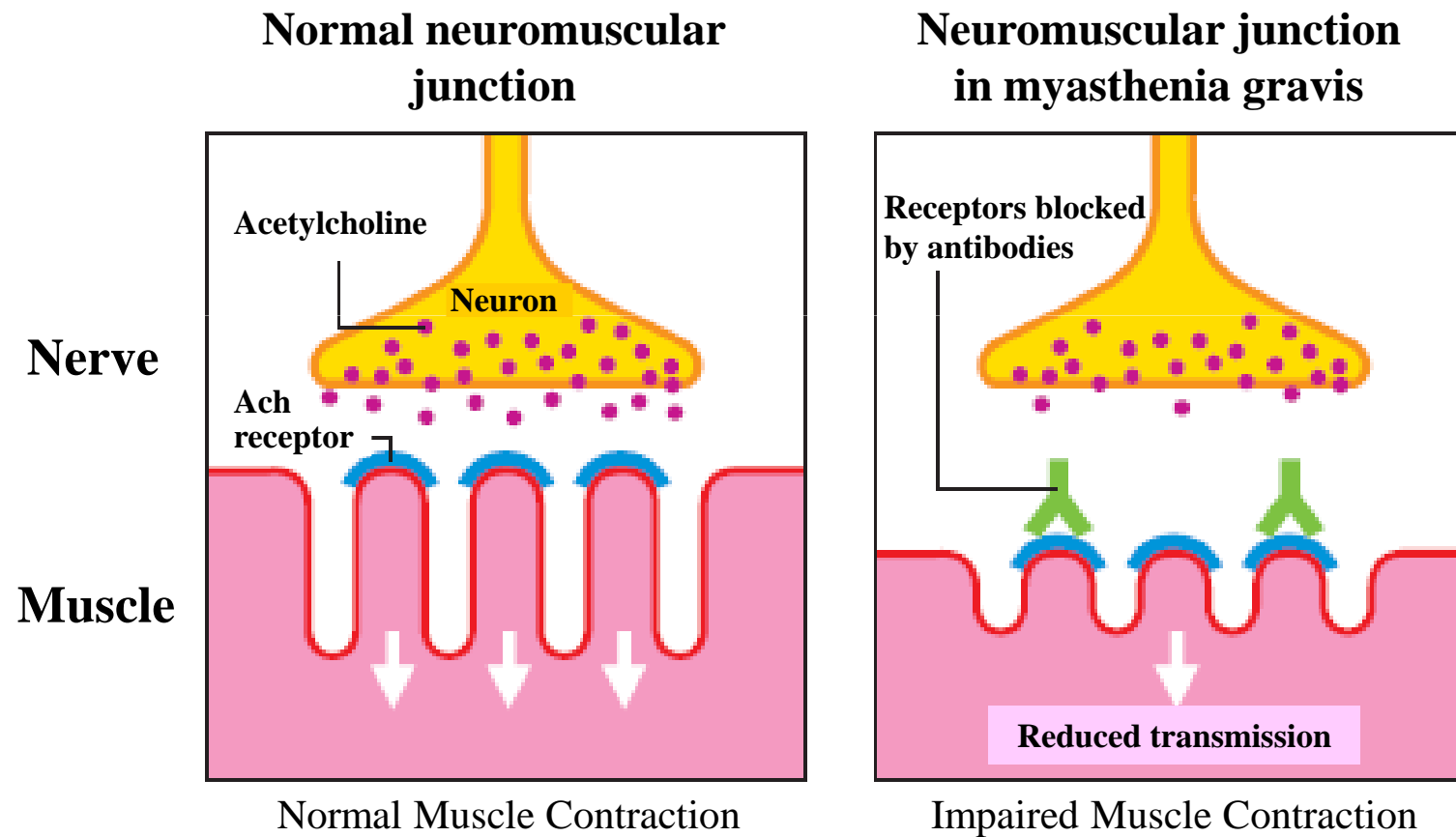
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- The most prevalent cause of myasthenia gravis is an autoimmune disorder in which the patient produces antibodies that attack the (acetylcholine) receptor at the neuromuscular junction.
- In MG, the key defect is a decrease in the number of available ACh receptors at the muscle membrane.
- This results in decreased efficiency of neuromuscular transmission, leading to weak muscle contractions.





# Myasthenia Gravis



# Diagnosis of Myasthenia Gravis

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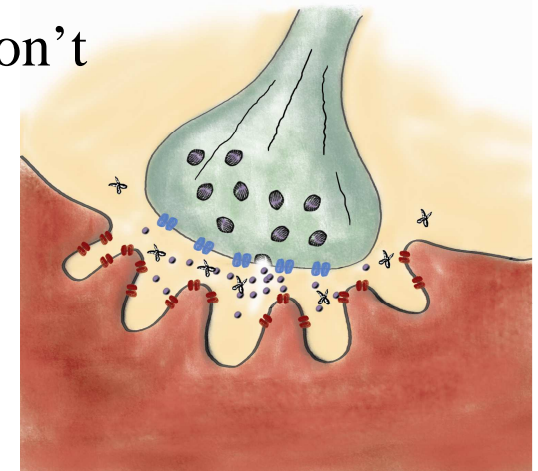
- Suspect it
- Tensilon test
- Electrical studies - repetitive nerve stimulation or single fiber EMG
- Anti-acetylcholine receptor antibodies or other antibodies



# Diagnosis of Myasthenia Gravis

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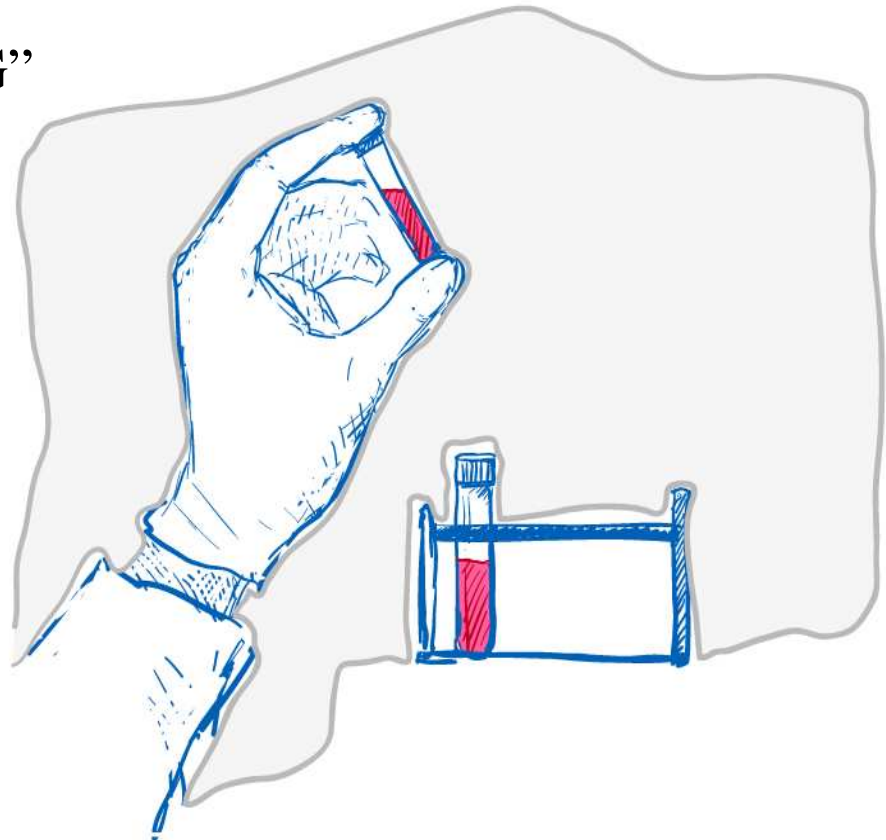
- Suspect it - often the biggest delay
  - Characteristic pattern of weakness
  - Everyone is different - some don't have characteristic pattern
  - Fluctuation in weakness
  - No other cause
- On average 1-2 years between first symptoms and diagnosis
  - Weakness fluctuates - now you see it now you don't
  - Uncommon disease



# Diagnosis of Myasthenia Gravis

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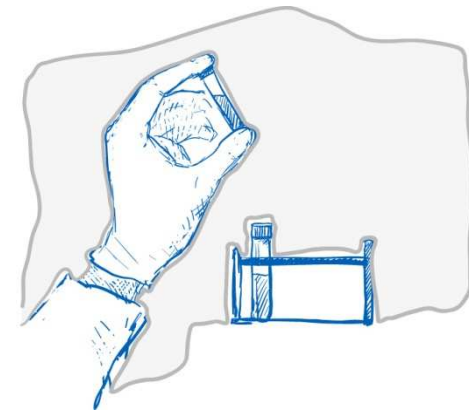
- Anti-acetylcholine receptor antibodies
  - Measured in the blood
  - Positive in 50% with “ocular MG” and 85% with “generalized MG”
  - Expensive (\$150)
  - 4-6 Weeks for results



# Seronegative Myasthenia Gravis

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- Some patients don't have antibodies against the acetylcholine receptor
  - 50% of those with only eye symptoms - "ocular MG"
  - 15% of those with generalized MG
- Seronegative MG"
  - Not MG
  - MG but non-immune
  - Congenital myasthenic syndromes
  - Immune MG but autoimmune attack is against something other than the acetylcholine receptor
    - MuSK
    - Others?



# Treatment of Myasthenia Gravis

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- Individualized
  - Don't compare your drugs/doses to the person beside you
  - The treatment changes over time
- Which drugs used, and doses of these drugs depends on your disease severity and other health problems
- In most people involves combinations of drugs



# Treatment of Myasthenia Gravis

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- The overall goal is to get you better and then start reducing the drugs to try and avoid side effects
- Attempts at reducing drugs while you still have MG symptoms are usually not successful
  - Although we try it sometimes if side effects are a problem
- For this to work your neurologist must know which symptoms are a result of MG and which are not



# Treatment of Myasthenia Gravis--Disclaimer

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- Many of the products discussed in this presentation are not 'officially' approved to treat Myasthenia Gravis. However, most are widely used by neurologists who manage patients with MG. In many cases investigations are underway.





# Treatment of Myasthenia Gravis

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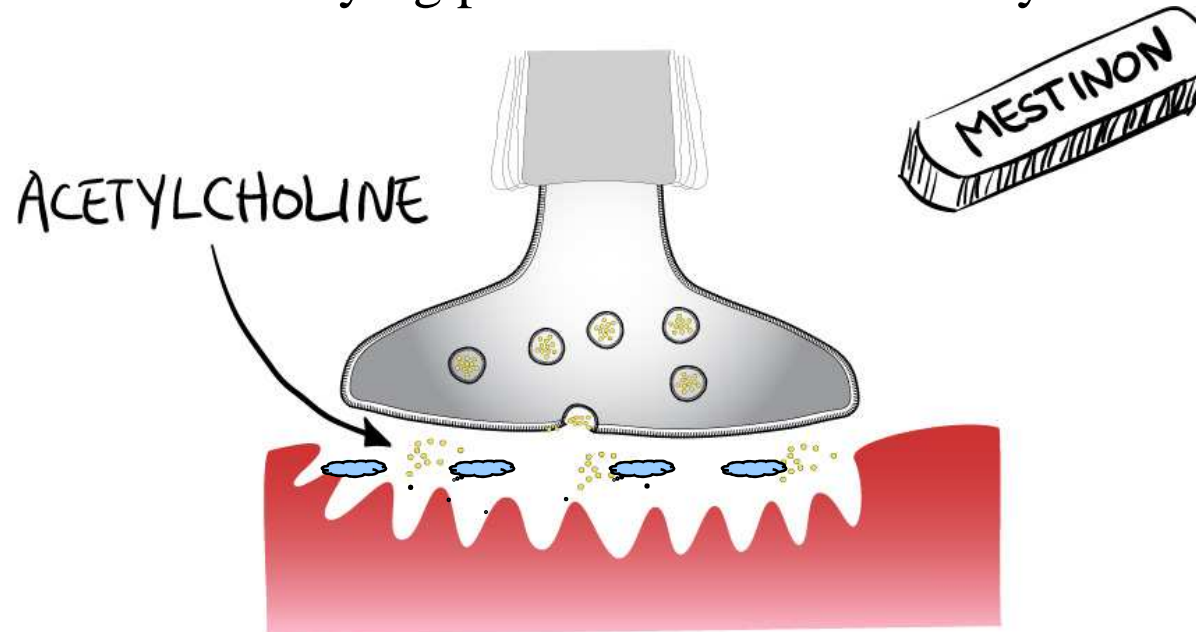
- Treat the symptoms
  - Mestinon (pyridostigmine)
- Treat the immune problem - immunosuppression
  - Prednisone
  - Imuran (azathioprine)
  - Mycophenolate mofetil (Cellcept)
  - Cyclosporine (Neoral)
  - others
- Short term fixes
- Long term fixes?



# Treating the symptoms - Mestinon

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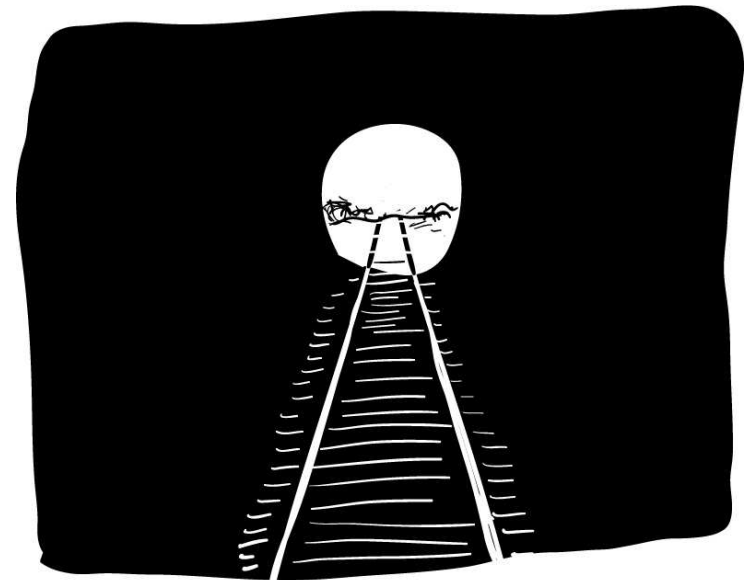
- Increases the amount of acetylcholine available to make the muscles move
- If it works, improvement within hours
- Inexpensive
- Few serious side effects
- Doesn't treat underlying problem with immune system



# Immunosuppression - Prednisone

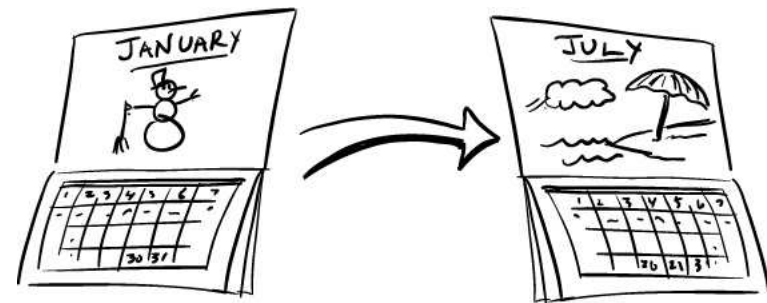
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- Suppresses immune system
- Works in most people
- Takes months
  - 1 month minimum
  - 3-6 months optimum
  - Sometimes 12 months
- Many side effects - some serious
  - Smallest dose for shortest time possible
  - When going through this -remember the light at the end of the tunnel



# Immunosuppression - Imuran (Azathioprine)

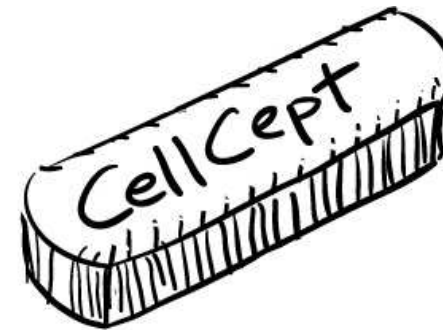
- Works well in MG
- Allows the use of lower doses of prednisone
- However, takes 12 months or longer
- Fewer side effects but needs monitoring with blood tests
  - Flu-like
  - Liver
  - Blood counts
  - ? Cancer of lymph glands (probably not in MG)



# Immunosuppression - Mycophenolate mofetil (Cellcept)

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- First used to suppress immune system after transplants
- Expensive
  - \$15-20/day
- No proof that it is any better than prednisone
- May have fewer side effects compared to either prednisone or Imuran
- Onset of benefits fairly rapid - 2-4 months



# Immunosuppression - Other drugs

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- Any medication which suppresses the immune system
  - Cyclosporine (Neoral)
  - Methotrexate
  - Cyclophosphamide ....others



# Short term fixes - What if I really get in trouble and the medications aren't working?

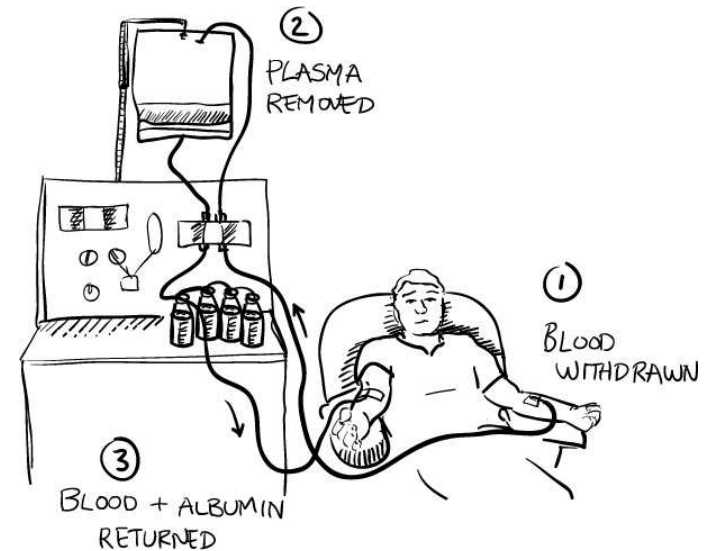
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# Temporary treatments in Myasthenia Gravis

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- Plasma exchange (PLEx)
  - Removes the antibodies which cause weakness
  - Benefits in 70% of patients within two weeks
  - Few serious side effects
  - More difficult to arrange short notice



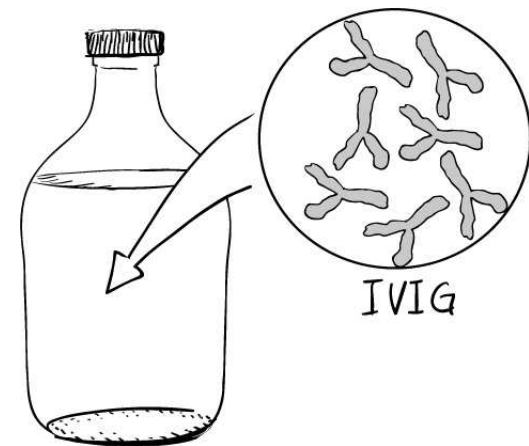
Plasma exchange (PLEx)



# Temporary treatments in Myasthenia Gravis

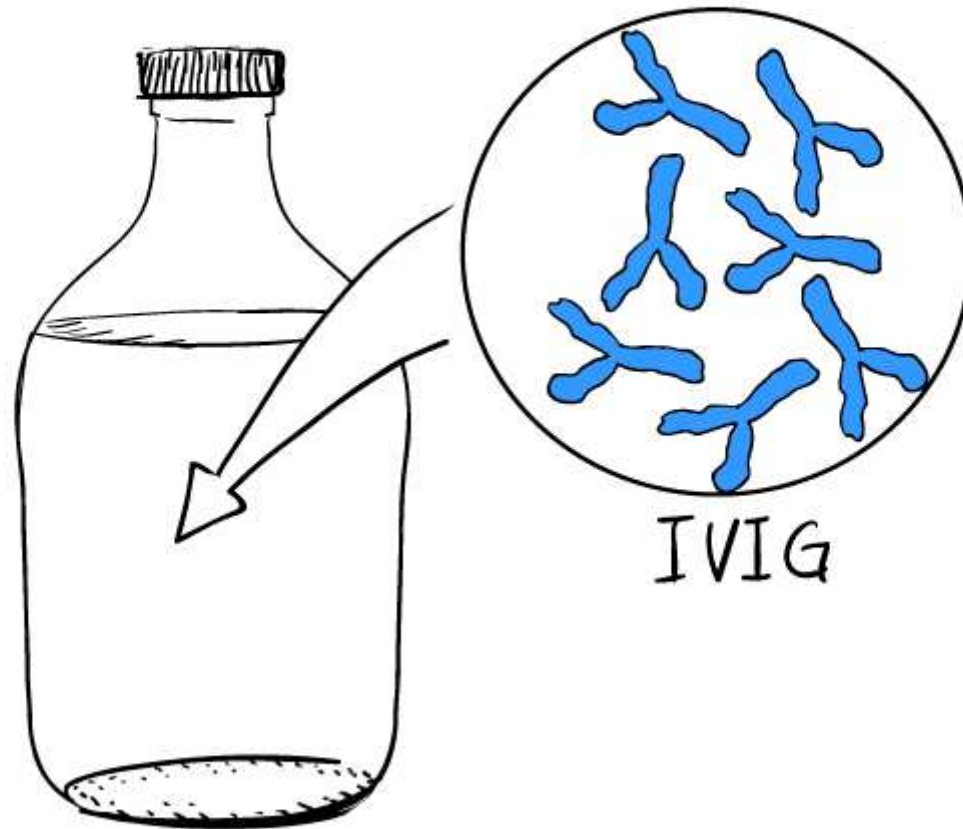
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- Intravenous immunoglobulin (IVIg)
  - A blood product – safe
  - IVIGs are a concentrated preparation of human antibodies, produced from plasma pooled from thousands of blood donors
  - Modulates the immune system - ? How
  - Benefit in 70% of patients within two weeks
  - Common side effects are mild
    - IVIg = PLEx in terms of benefit in MG
    - Neither are recommended for long term treatment of MG
    - Both are expensive : \$8-10,000 per round of treatment



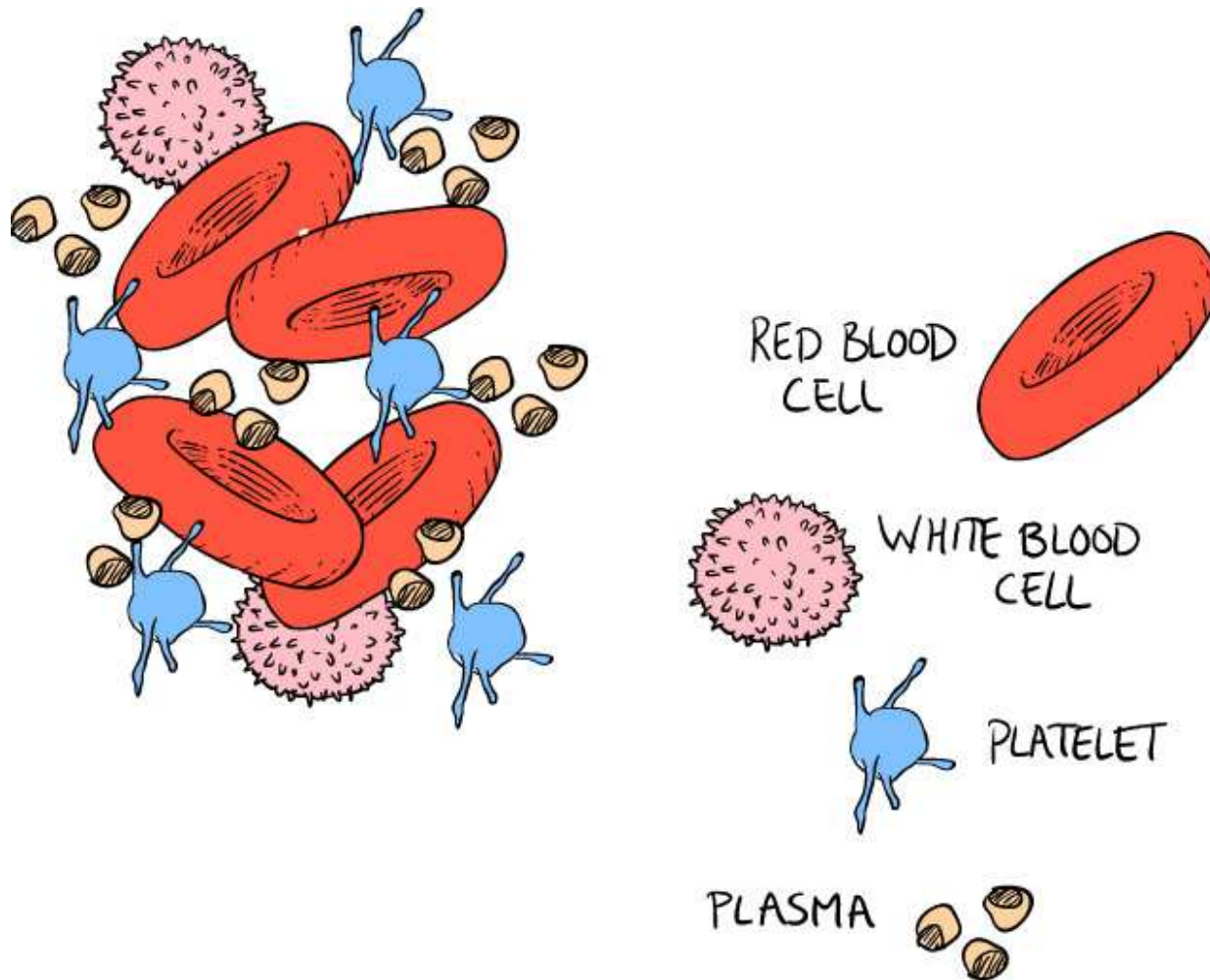
# What is IVIG?

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# Blood Components

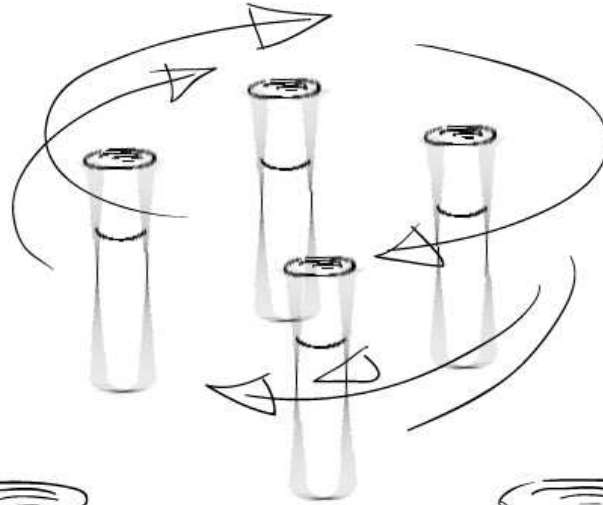
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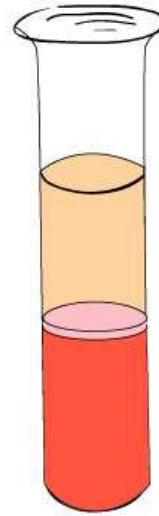
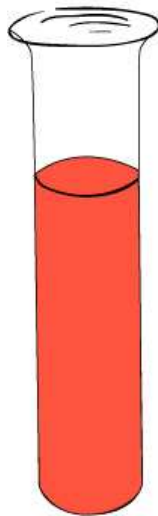
Blood contains: Red Blood Cells, White Blood Cells, Platelets, and Plasma

# Separation of Blood Components

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Centrifugation: a way to separate out particles

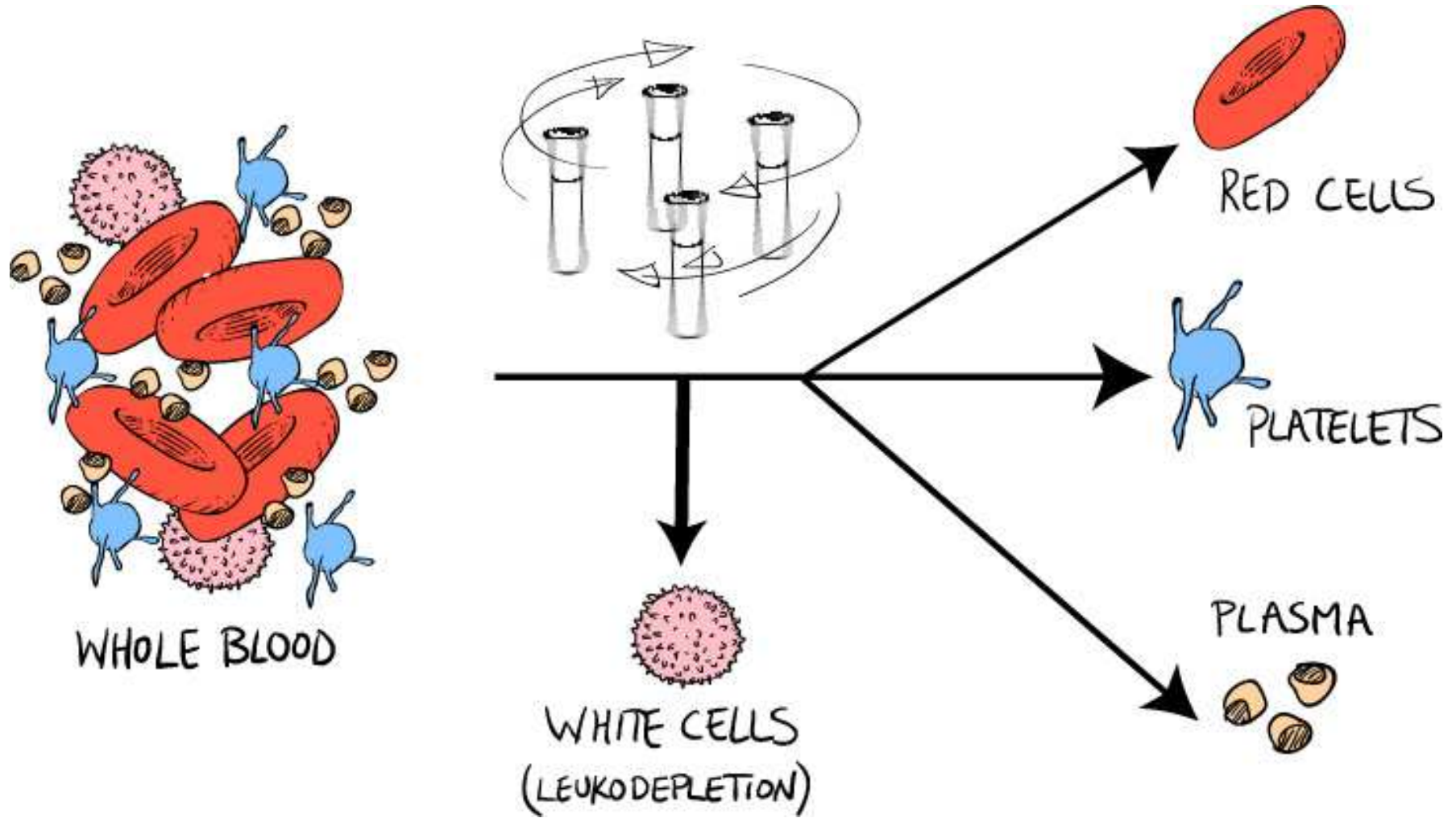


PLASMA

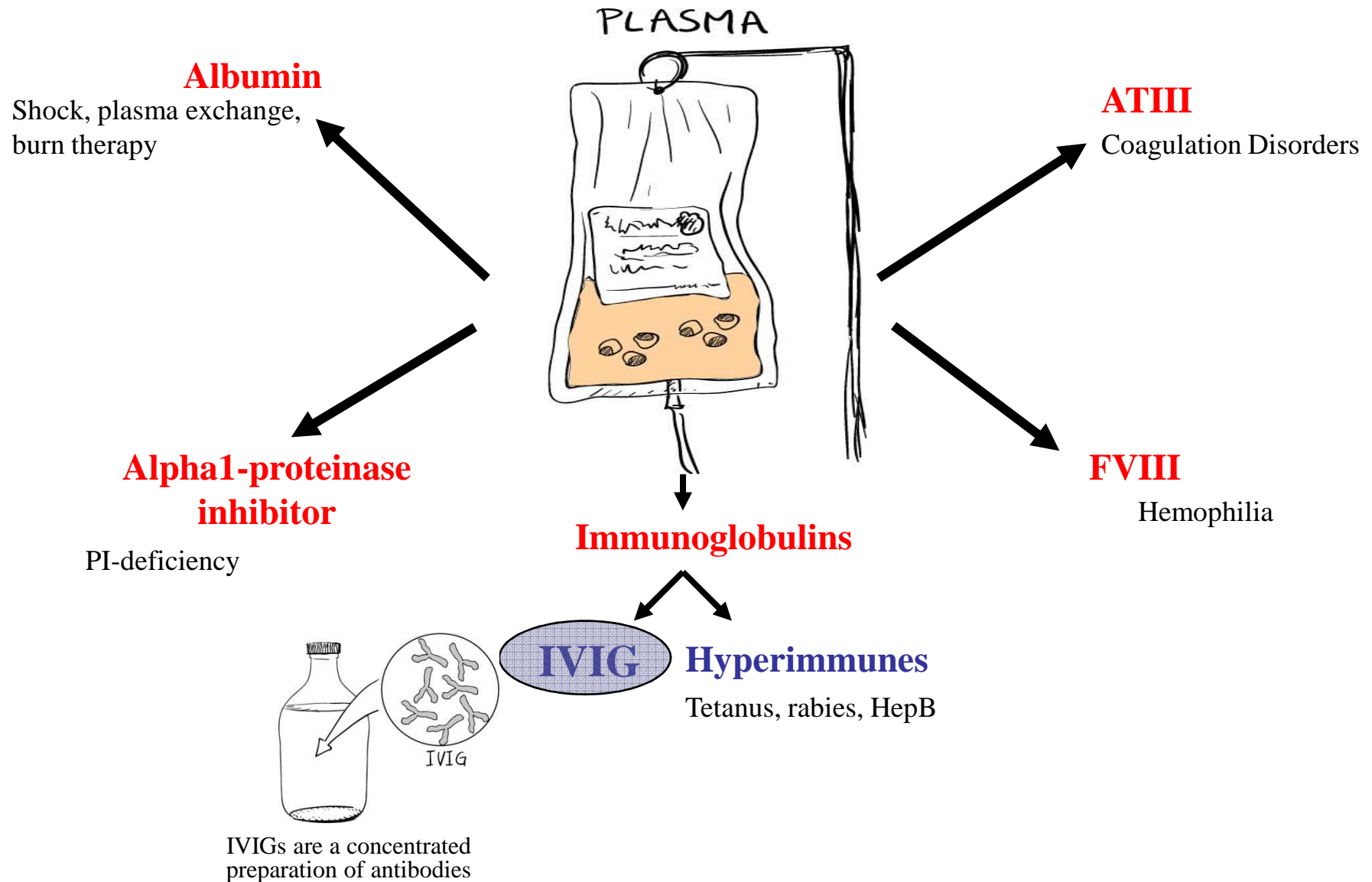
WHITE BLOOD CELLS

RED BLOOD CELLS

# Useful Blood Components



# Useful Blood Products



# How does IVIg work in MG?

## Possible mechanisms

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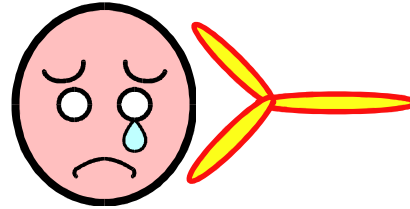
- The infused antibodies will, for a time, dilute the abnormal host antibodies that are causing the diseases
- The presence of large amounts of IgG will also suppress the production of host IgG and increases its breakdown
- The donated antibodies will also bind to the other components of the immune system, thereby using up resources, resulting in fewer immune resources to do damage
- The infused antibodies may bind to host antibodies, including those causing disease, and take them out of action

# How does IVIg work in MG?

One possible mechanism

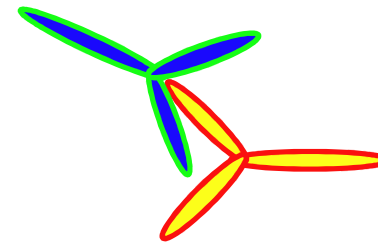
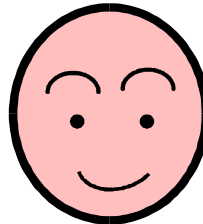
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Acetylcholine receptor



'Bad' antibody against AChR

IVIg infusion

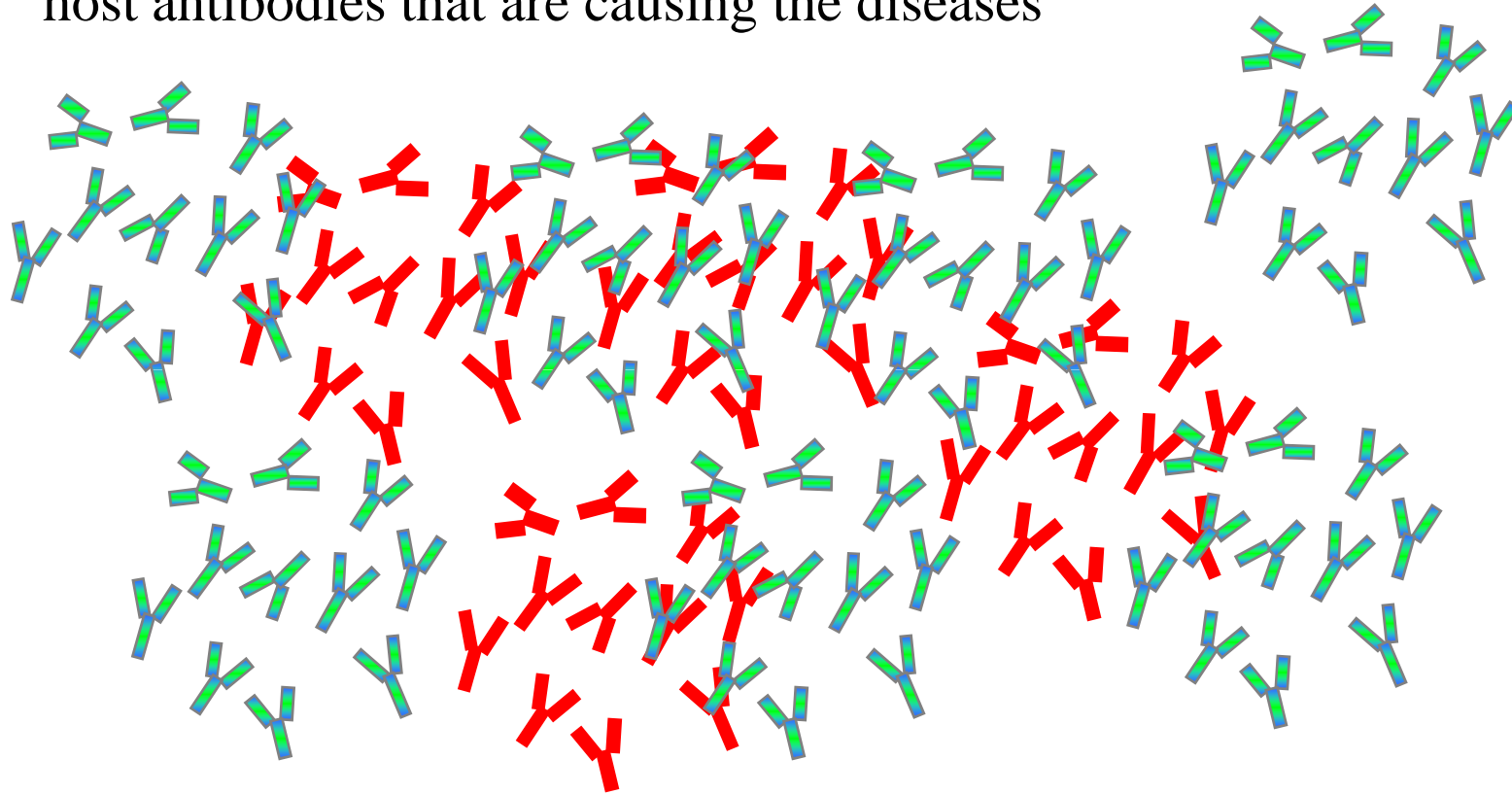


'Good' antibodies against  
bad antibodies




# Mechanism of Immune Suppression with IVIg

- The infused antibodies will, for a time, dilute the abnormal host antibodies that are causing the diseases



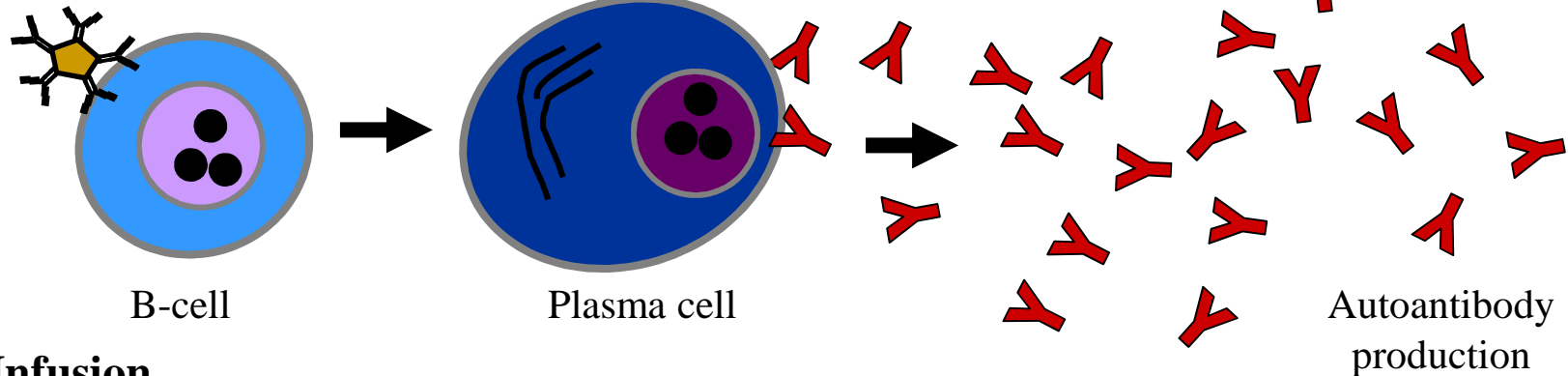
- IVIg also increases the breakdown of host immunoglobulin

 “good” antibodies in IVIG

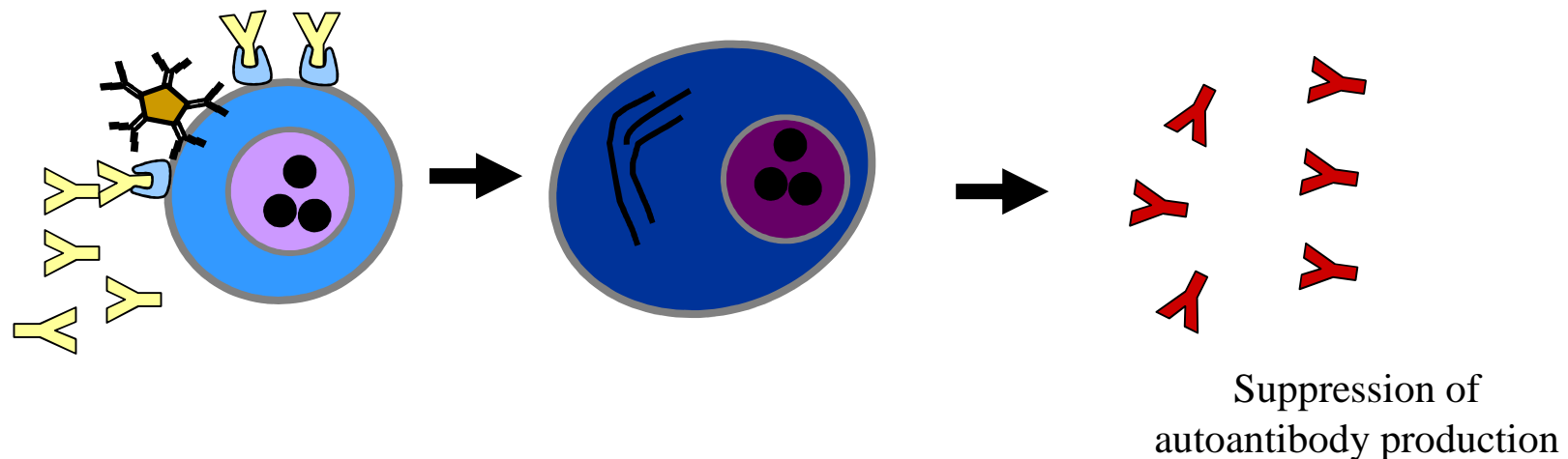
 “bad” auto- antibodies in MG

# The presence of large amounts of IgG will also suppress the production of host IgG

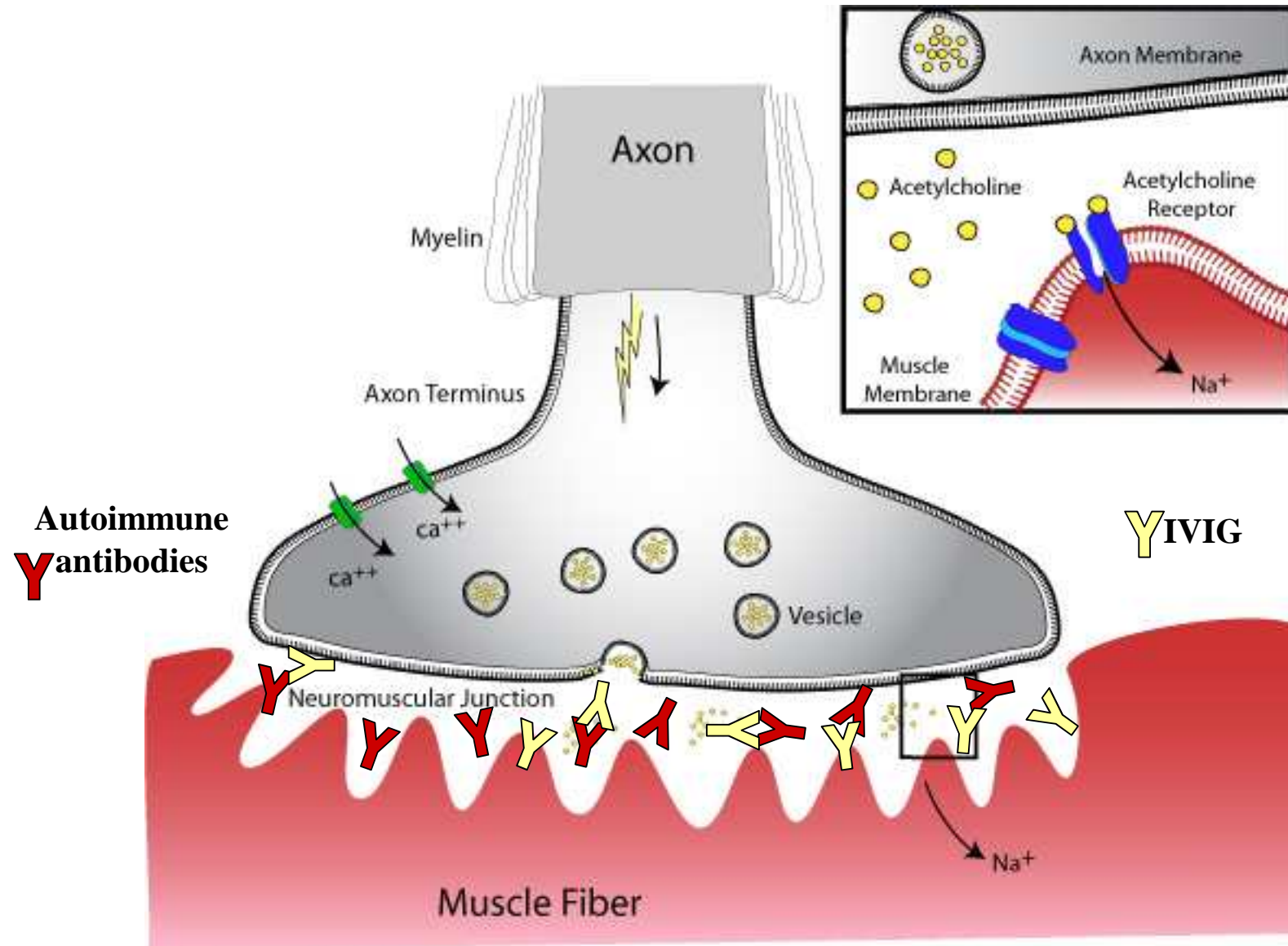
## Auto-Antibody Production in Myasthenia Gravis



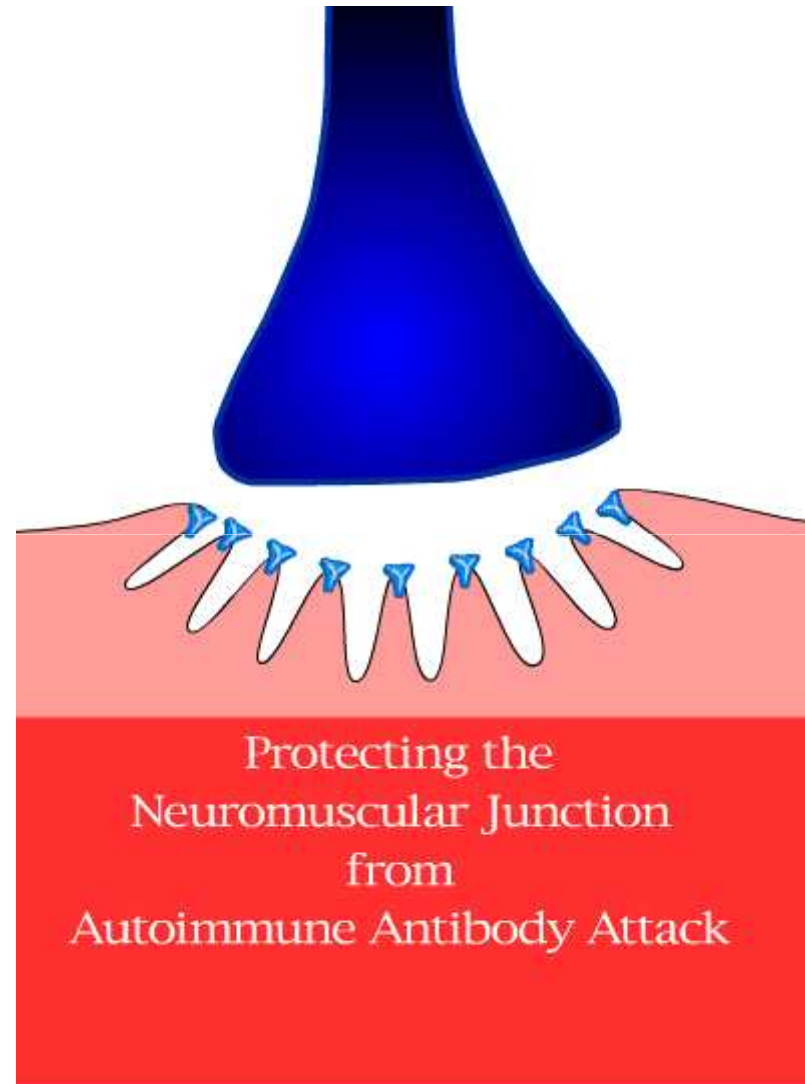
## IVIg Infusion



The infused antibodies may bind to host antibodies, including those causing disease, and take them out of action



The infused (IVIG) antibodies may bind to host autoantibodies, including those causing disease, and take them out of action



## Long-term - Is there a cure?

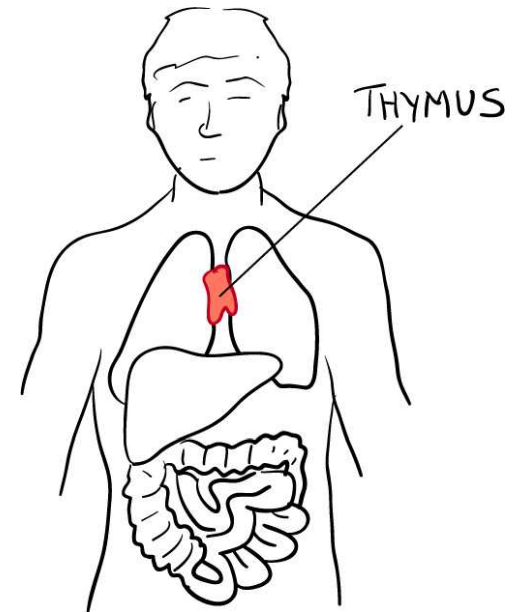
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- Although MG is highly treatable - there is no cure (yet)
- Most patients end up on medications for years or forever, but do very well
  - With medical (pills) treatment over 90% of individuals will get better
  - Expense, life-long treatment, side effects

# Long term - Is there a cure?

---

- Thymectomy may offer chance for drug-free remission in some patients
  - Early onset (< 50 years)
  - Generalized (not just ocular)
  - Within 2-3 years of disease onset
  - Seropositive (AChR antibodies)
  - Trans-sternal thymectomy
    - ? Cervical ? Video-assisted



- What we think (not what we know)
  - Without treatment 20% of MG patients will have a sustained (years) remission
  - After thymectomy in young MG patients it doubles to about 40%
  - Another 30-40% are better, but not off medications and therefore not “cured”
- .....Current international research trial may answer this

# Management issues

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- You're not getting better
- Where do you get information?
- What about other drugs - what is safe to take?



# You're not getting better - why?

---

- You don't have MG
  - Not all weakness = MG
  - If you're going to take drugs which can cause side effects, make sure you have MG first
    - I see 1-2 patients a year who have been diagnosed with, and treated for MG which I don't think they ever had.
- Many GPs will never see a case
  - MG is a rare disease - affects roughly 1 in 10,000 individuals
  - 4-5 GPs X 2-3,000 patients in each practice = one case of MG
- Even some neurologists may only see 1-2 cases in a year



# You're not getting better - why?

---

- You do have MG
  - You aren't on the right drugs or on the right doses
  - You're not taking your medications
  - You haven't been on them long enough
  - Although you have MG, it isn't the cause of your symptoms
    - 'Weakness' ≠ weakness
    - Other diseases
    - Side effects of medications
    - Depression
- You have severe MG

# You're not getting better

---

- You do have MG
  - Although you have MG, it isn't the cause of your symptoms
    - 'Weakness' ≠ weakness

## **Sleep apnea in patients with myasthenia gravis**

**Abstract**—To assess the prevalence of obstructive sleep apnea (OSA) in myasthenia gravis, the authors identified patients at risk of OSA using the multivariable apnea prediction index. OSA was diagnosed with polysomnography. The prevalence of OSA was 36% compared to an expected prevalence of 15 to 20% in the general population. When including the presence of daytime sleepiness (OSA syndrome), the prevalence was 11% compared to 3% in the general population.

NEUROLOGY 2006;67:140–142

M.W. Nicolle, MD, FRCPC, DPhil; S. Rask, BSc; W.J. Koopman, RN, MScN;  
C.F.P. George, MD, FRCPC, DABSM; J. Adams, MD, FRCPC, MSc; and S. Wiebe, MD, FRCPC, MSc

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# Where do you get information?

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- Your neurologist
- Internet
  - Not all information is accurate - some is downright dangerous
- Myasthenia gravis Ontario Chapter and its resources
  - Tel: 905-827-1957
  - [mgontariochapter@rogers.com](mailto:mgontariochapter@rogers.com)
- MG Coalition of Canada
  - Tel: 866-999-6422
  - [info@mgcc-ccmg.org](mailto:info@mgcc-ccmg.org)
  - [www.mgcc-ccmg.org](http://www.mgcc-ccmg.org)
- Myasthenia Gravis Foundation of America (MGFA)
- Other patients



# Other drugs and MG

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- There are some drugs which MAY worsen the weakness in a patient with MG
- There are many different lists of these drugs.
- Some of the drugs on some of these lists should not be there
  - Little evidence that they worsen weakness
- Use common sense
  - If you don't really need a drug - you shouldn't be taking it anyway
  - If you do really need a drug - try to use one that is not on the list
  - If it's on the list - it's probably safe anyway but discuss it with your neurologist
    - Less than 1 in 4 patients with MG will get worse with one of the 'bad' drugs
- Real risk is with drugs used for surgery when they may have very different effects in someone with MG
  - Medical Alert bracelet - in case you can't tell the doctor you have MG
  - Make sure surgeon/other doctors know you have MG and that it can cause weakness which may be worsened by some drugs.

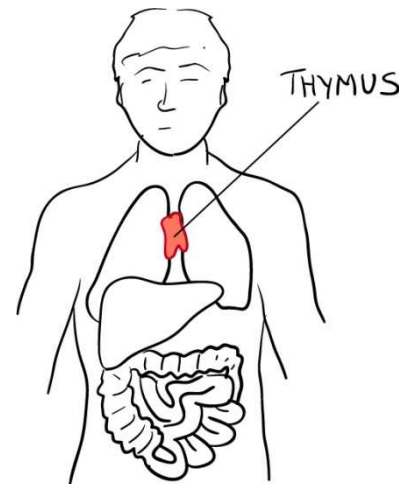
# Future

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- Drugs
  - New drugs to suppress immune system
    - More effective?
    - As effective but fewer side effects
    - Less expensive
    - Have to take less often



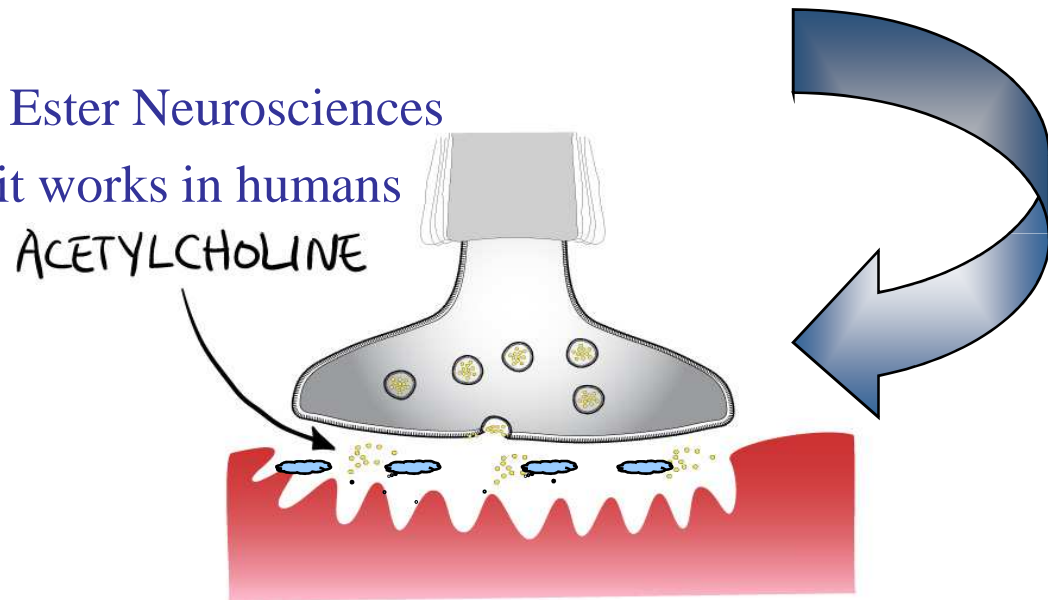
- Surgery – thymectomy
  - Does it work?
  - On who?
  - How should it be done?



# Future

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- Other types of treatments
  - Anti-sense nucleotides - ‘Monarsen’
    - Long-acting inhibitor of acetylcholinesterase - same enzyme which Mestinon inhibits
    - Israeli Company - Ester Neurosciences
    - No Evidence that it works in humans
    - ? real benefit

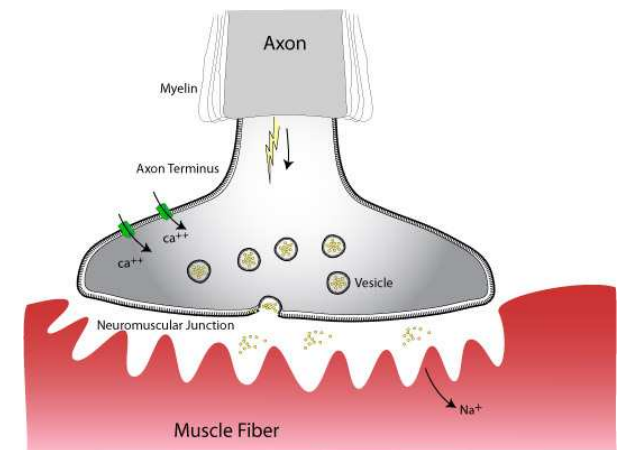


- Vaccine
  - Vaccinating against peptides (proteins) derived from acetylcholine receptor or T cell receptor could turn off or blunt immune response to this
  - So far, no evidence that these approaches work in humans

# Future

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- Discovering different types of MG
  - MG with antibodies against AChR vs MG with antibodies against MuSK
    - Different characteristics
    - Different treatment
- Other targets in other types of MG
  - Other proteins (different from AChR and MuSK) at neuromuscular junction
- New mutations discovered in congenital myasthenic syndrome
  - Not all MG immune mediated
  - Different treatments - drugs which act on channels (pores)



# The End

