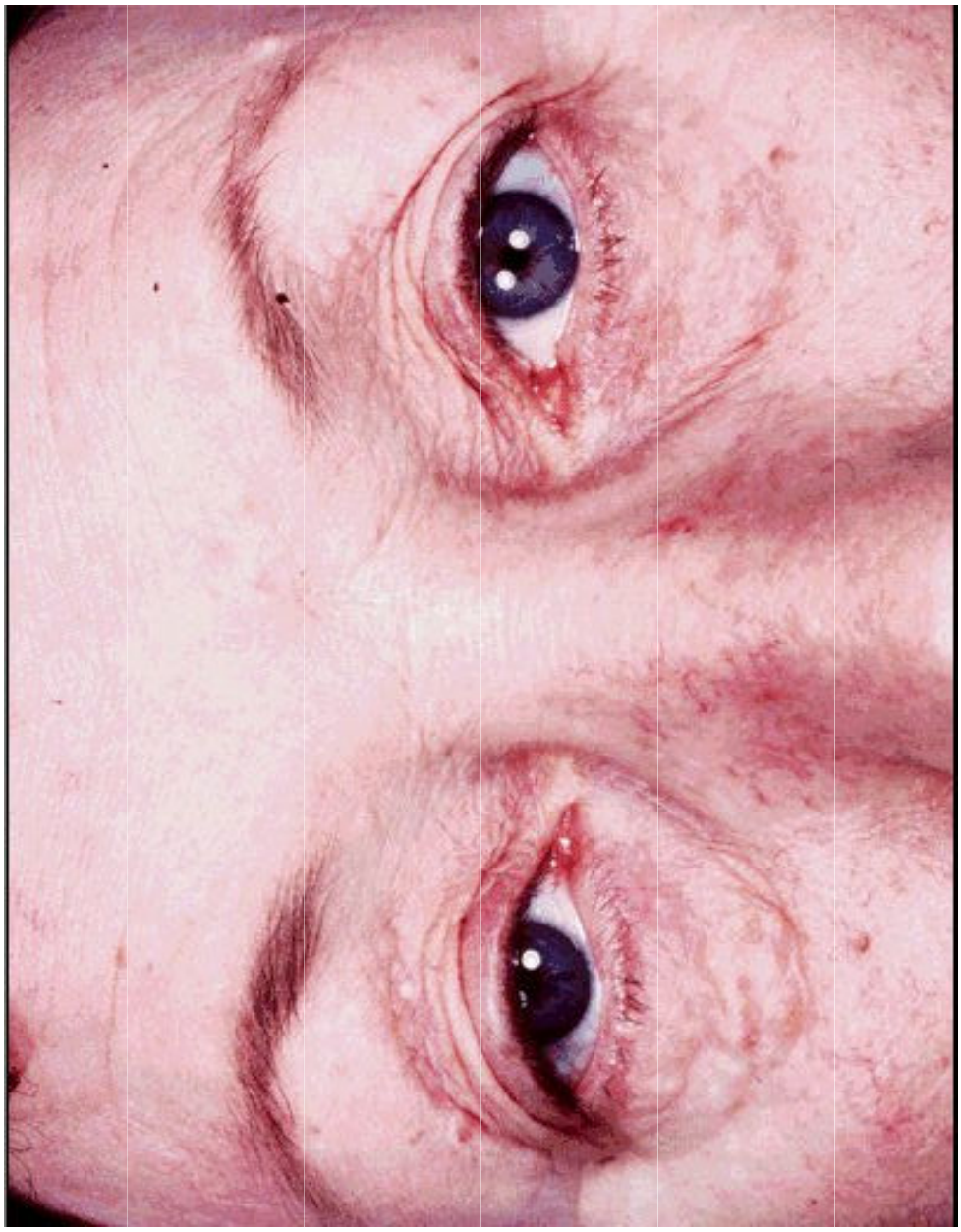
Miastenia Gravis:
Inquadramento clinico

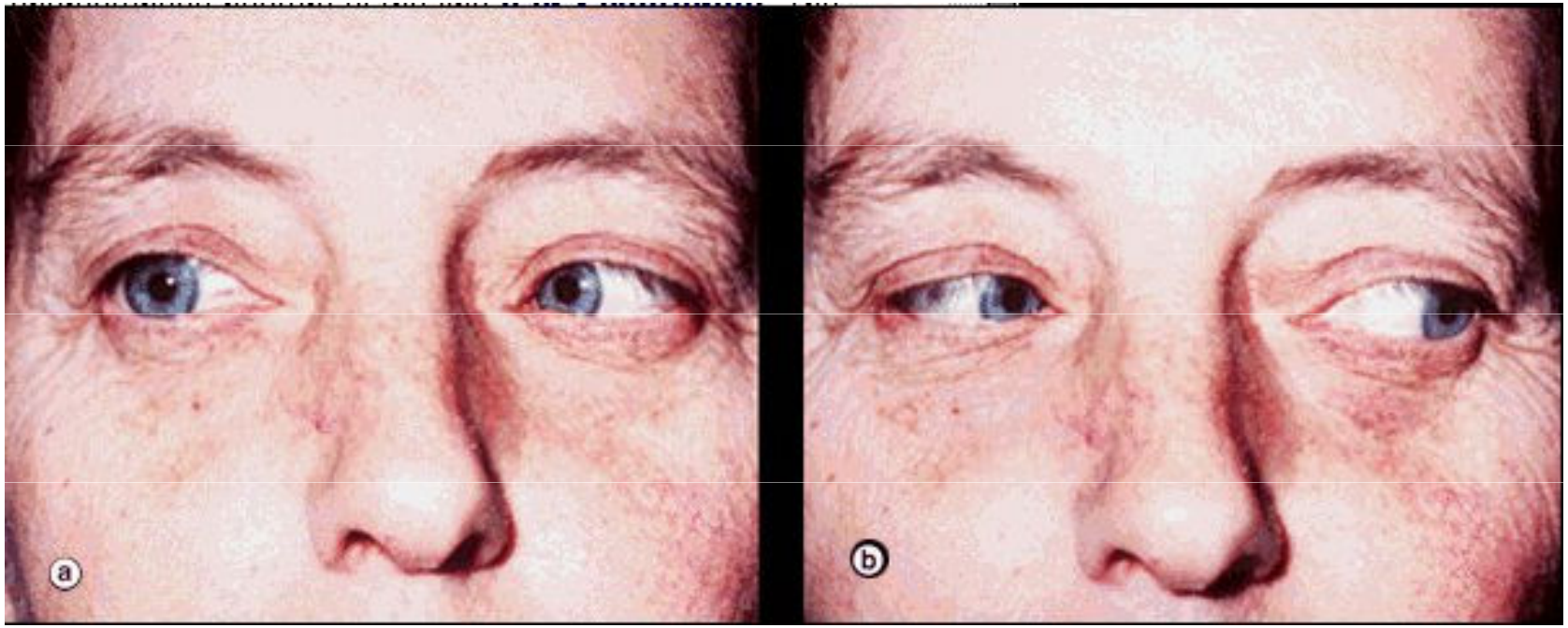
DIPARTIMENTO
DI SCIENZE NEUROLOGICHE

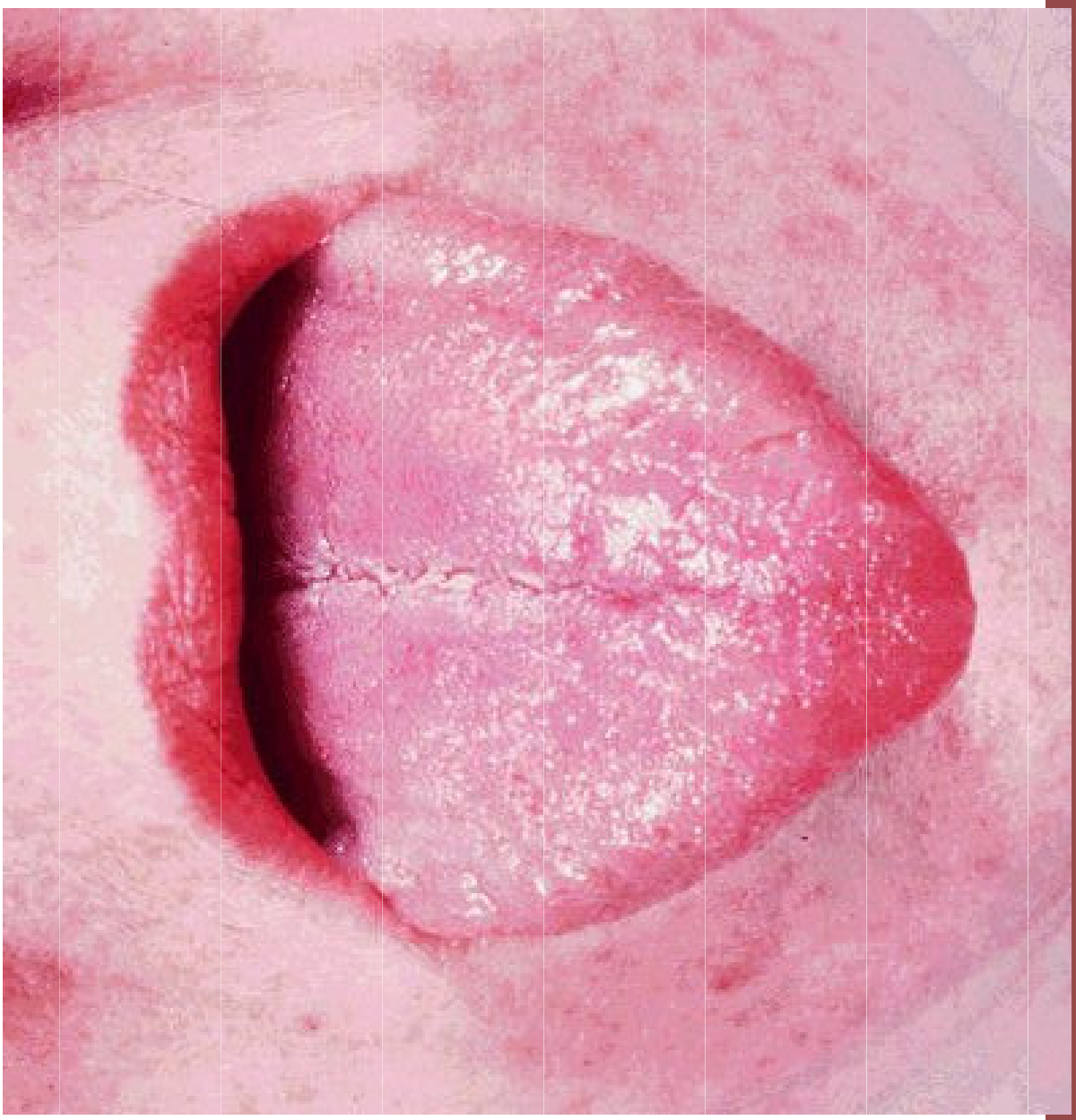
SAPIENZA
UNIVERSITÀ DI ROMA

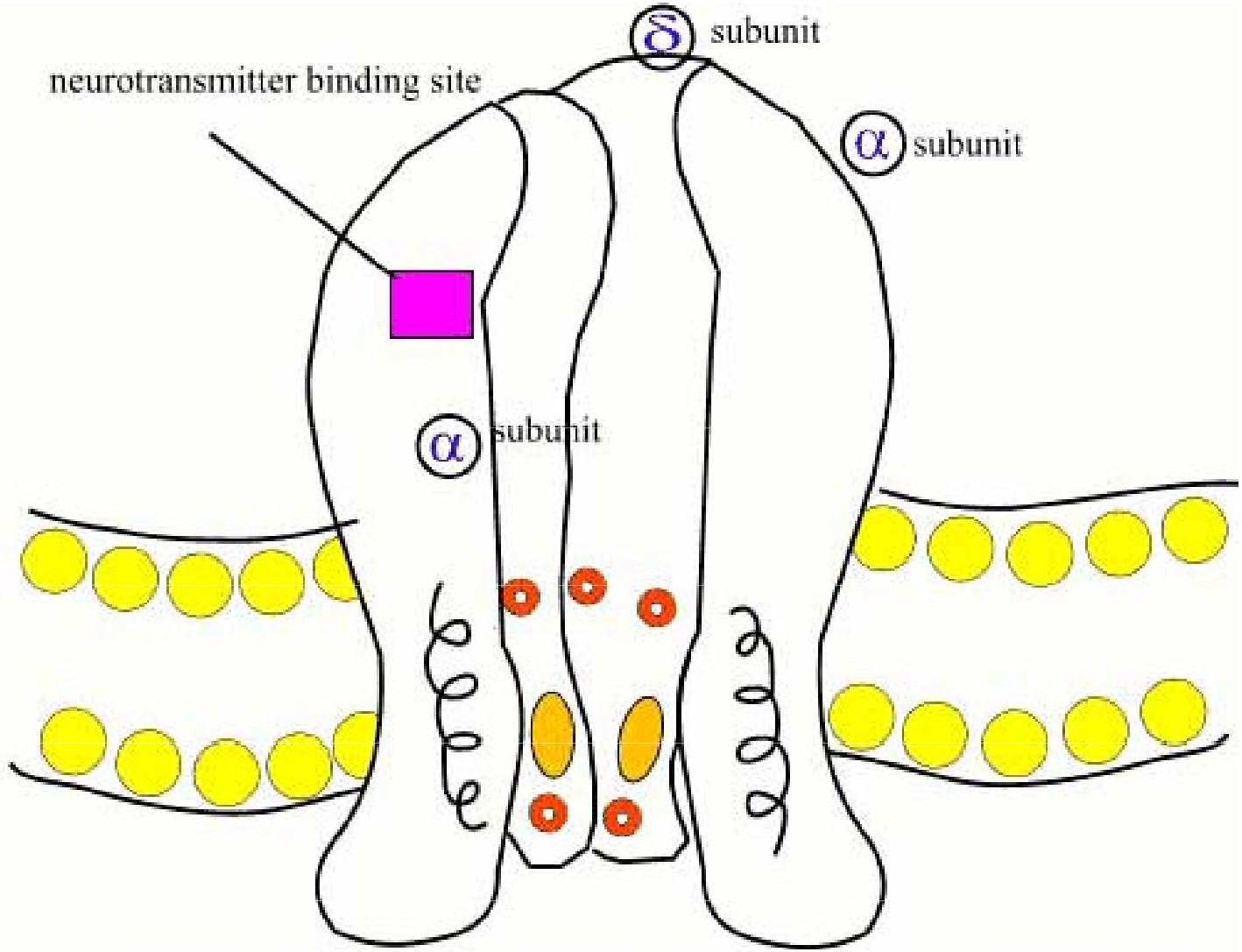
Maurizio Inghilleri

Autore	paese	abitanti	prevalenza (casi/100000)
Garland Leeds	(UK)	500000	2,60
Alter	Charleston (US)	188000	3,20
Okinaka	Fukoaka (Jp)	608000	1,20
Okinaka	Niigata (Jp)	230000	2,60
Gudmundsson	Islandia	187200	6,40
Hokkanen	Helsinki (Fin)	945000	4,20
Kuroiwa	Hirosaki (Jp)	159000	5,10
Kuroiwa	Aomori (Jp)	244000	3,70
Philips	Virginia (US)	357,159	10,90
Cisneros (5)	Cuba	5782302	4,52
presente	La Palma (Esp)	81507	8,58

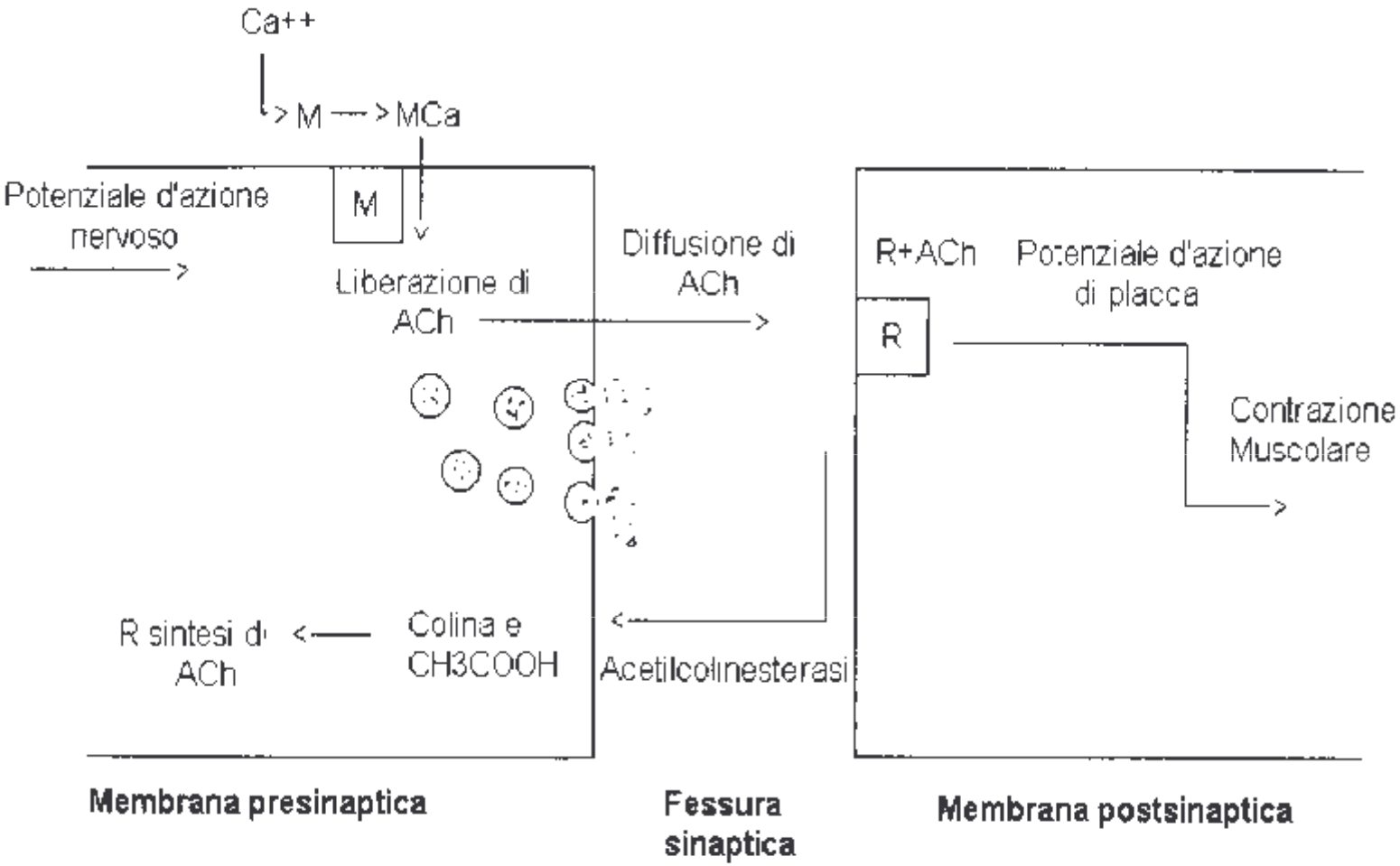


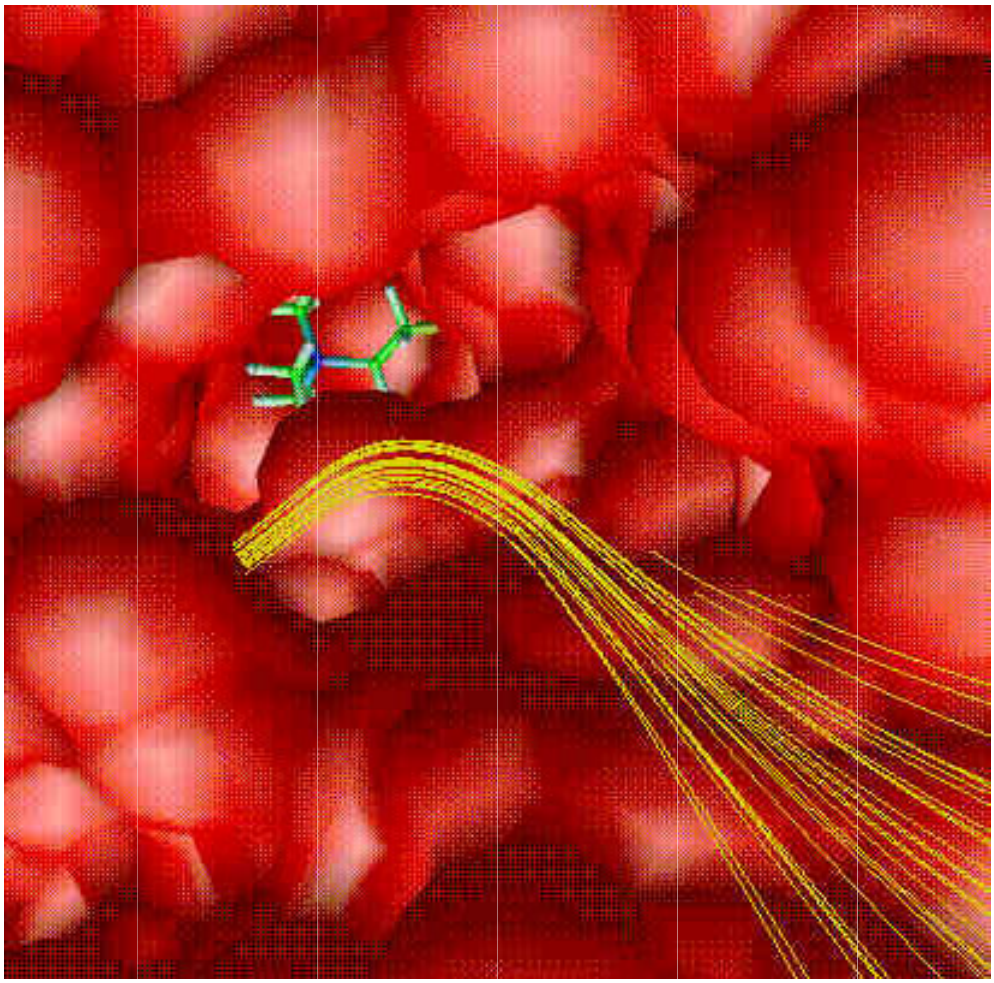

a
b





NICOTINIC ACH RECEPTOR AND SUBUNITS

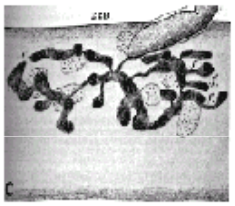

Ca++
> M —— > MCa
Potenziale d'azione nervoso
M
Liberazione di ACh
Diffusione di ACh
R+ACh
Potenziale d'azione di placca
R
Contrazione Muscolare
R sintesi di ACh
Colina e CH3COOH
Acetilcolinesterasi
Membrana presinaptica
Fessura sinaptica
Membrana postsinaptica



MYASTHENIC & NEUROMUSCULAR JUNCTION (NMJ) DISORDERS

BASIC CONCEPTS
- Acetylcholine receptors (AChRs)
- AChR structure
- AChR subunit mutations: α; β; ε; δ
- Neuromuscular junction (NMJ)
  - Presynaptic
  - Postsynaptic

ACQUIRED NMJ DISORDERS
- Botulism
- Myasthenia gravis
  - Autoimmune myasthenia gravis
  - Childhood MG
  - Drug-induced MG
  - Neonatal: Transient MG
  - Ocular
  - Sero-Negative
  - Domestic animals
- Myasthenic syndrome (Lambert-Eaton)
- Snake venom toxins



CONGENITAL & FAMILIAL NMJ DISORDERS[2]

General features

AChRs: Kinetic abnormalities

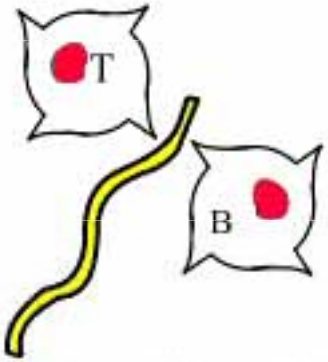
Presynaptic defects
- Congenital MG + Episodic apnea (Familial infantile): ChAT; 10q11
- Paucity of synaptic vesicles & Reduced quantal release
- Congenital Lambert-Eaton-like
- Episodic ataxia 2: CACNA1A; 19p13

Synaptic defects
- Acetylcholinesterase (AChE) deficiency at NMJs: ColQ; 3p25

Postsynaptic defects: AChR disorders
- Kinetic abnormalities in AChR function
  - ↓ Numbers of AChRs at NMJs
    - ↑ Response to ACh: Slow AChR channel syndromes
      - Delayed channel closure*
      - Repeated channel reopenings*
    - ↓ Response to ACh
      - Fast-channel syndrome: Mode-switching kinetics Δ; ε subunit
      - Fast channel syndrome: Gating abnormality; α or ε subunit
      - Fast channel syndrome: Arthrogryposis; δ subunit
    - Also see: ε subunit disorders
  - Normal numbers of AChRs at NMJs: ↓ Response to ACh
    - Fast-channel syndrome: Low ACh-affinity of AChR; ε subunit
    - Fast-channel syndrome: ↓ Probability of channel opening; α subunit
    - High conductance & Fast closure of AChRs
  - ↑ Numbers of AChRs at NMJs
    - Slow AChR channel syndrome: βL262M*
- No kinetic abnormalities in AChR function
  - ↓ Numbers of AChRs at NMJs*
    - AChR mutations
      - Usually ε subunit
      - Rare α, β, δ subunit

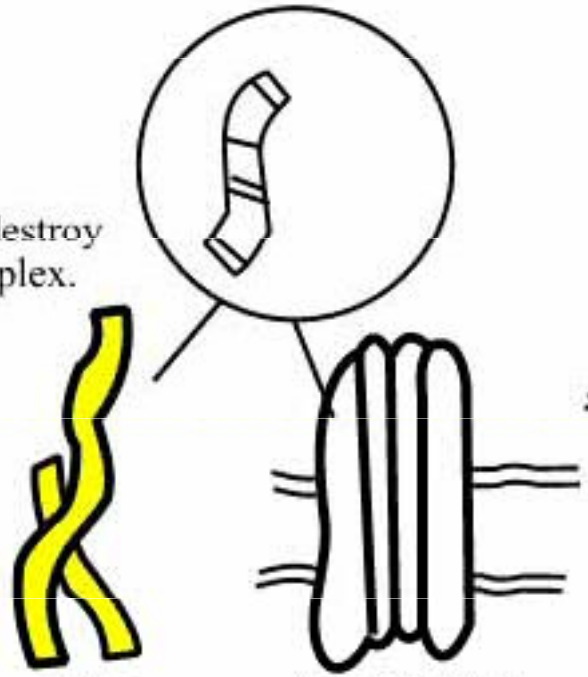
Other hereditary MG syndromes
- Benign congenital MG & Facial malformations
- Congenital MG: Other
- Familial immune
- Limb-girdle MG: Familial
- Plectin deficiency: Plectin; 8q24

Origin of Viral Onset Autoimmune Response



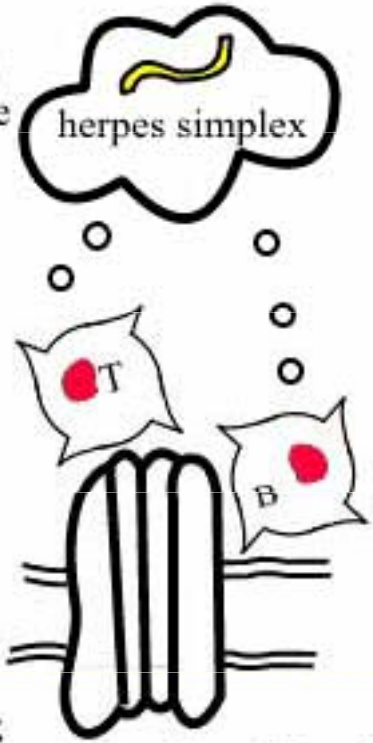
T-cells and B-cells attack and destroy a virus, In this case, herpes simplex.

Unfortunately, the herpes simplex virus has the same peptide sequence in one area as the Ach receptor.



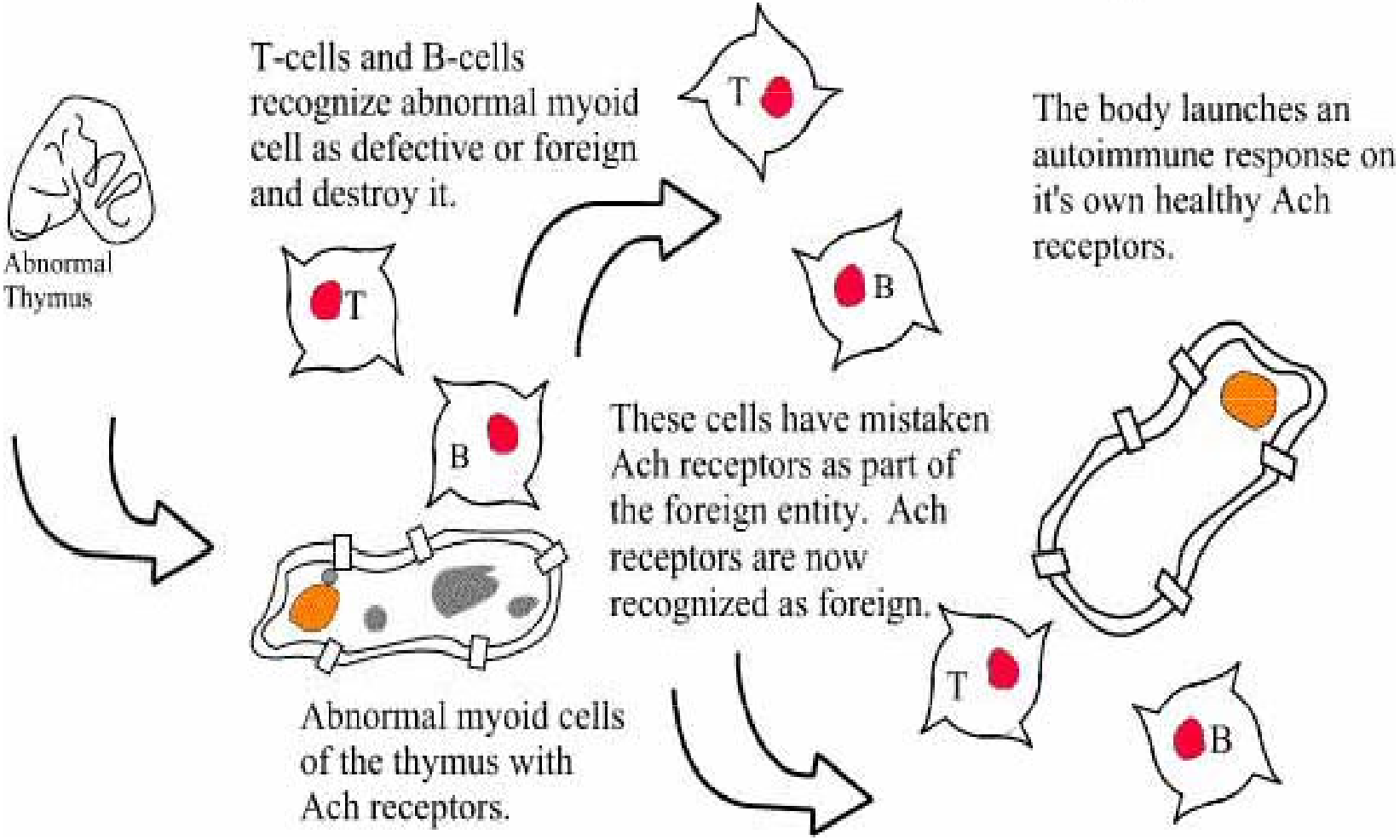
virus

Ach Receptor

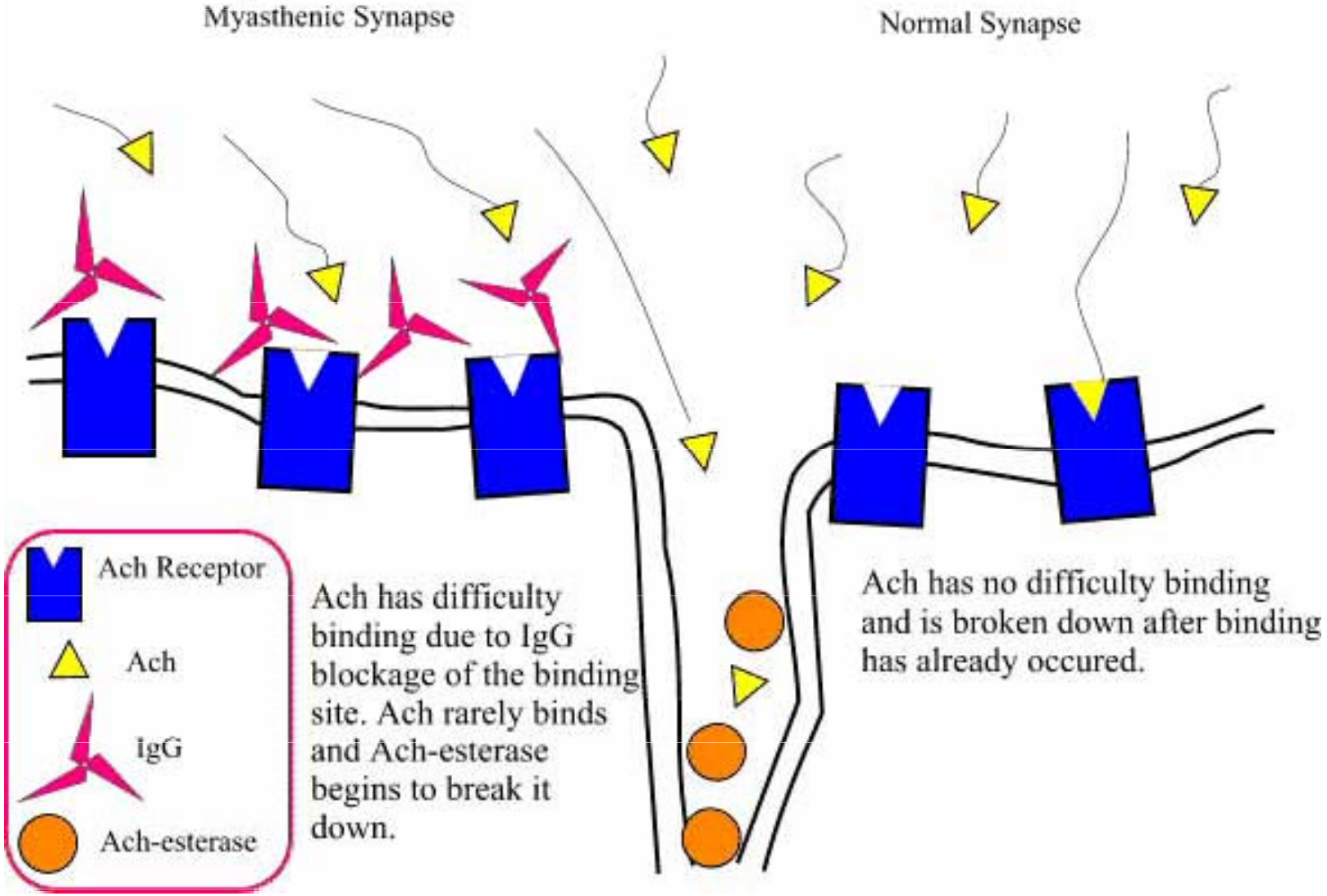


T-cells and B-cells now mistake the Ach receptor as the herpes simplex virus. The body then begins an autoimmune attack on it's own Ach receptors.

Adult-Onset Autoimmune Response

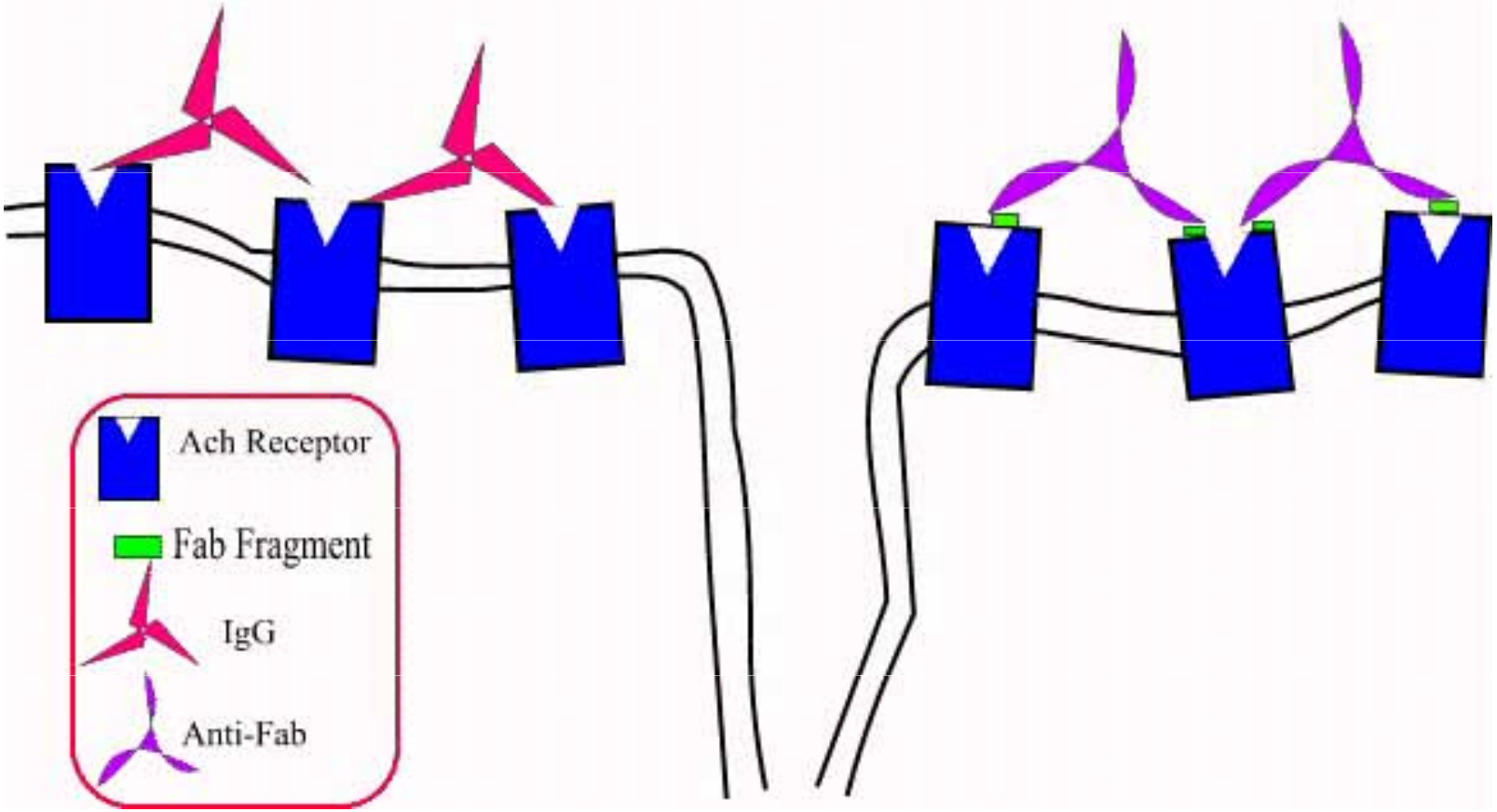


Antibody Mediated Mechanism: Blockade of Ach

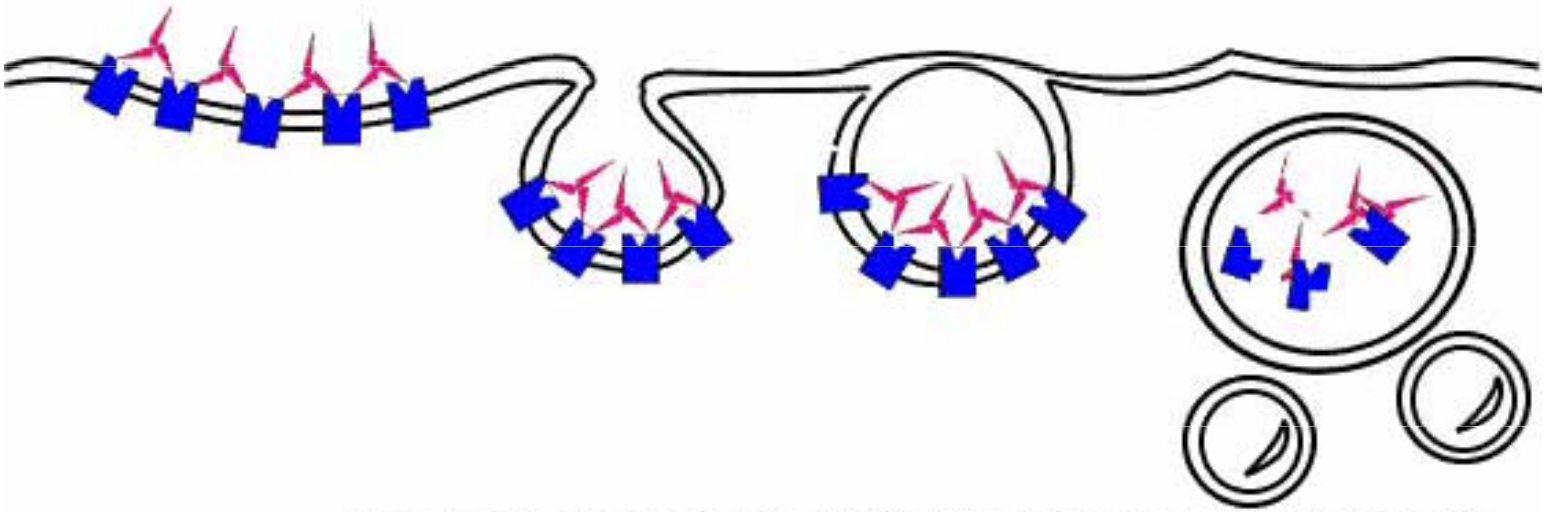


Antibody Mediated Mechanism: Crosslinking

Crosslinking by IgG or Fab/ Anti- Fab mechanisms begins accelerated degradation of the post-synaptic terminal.

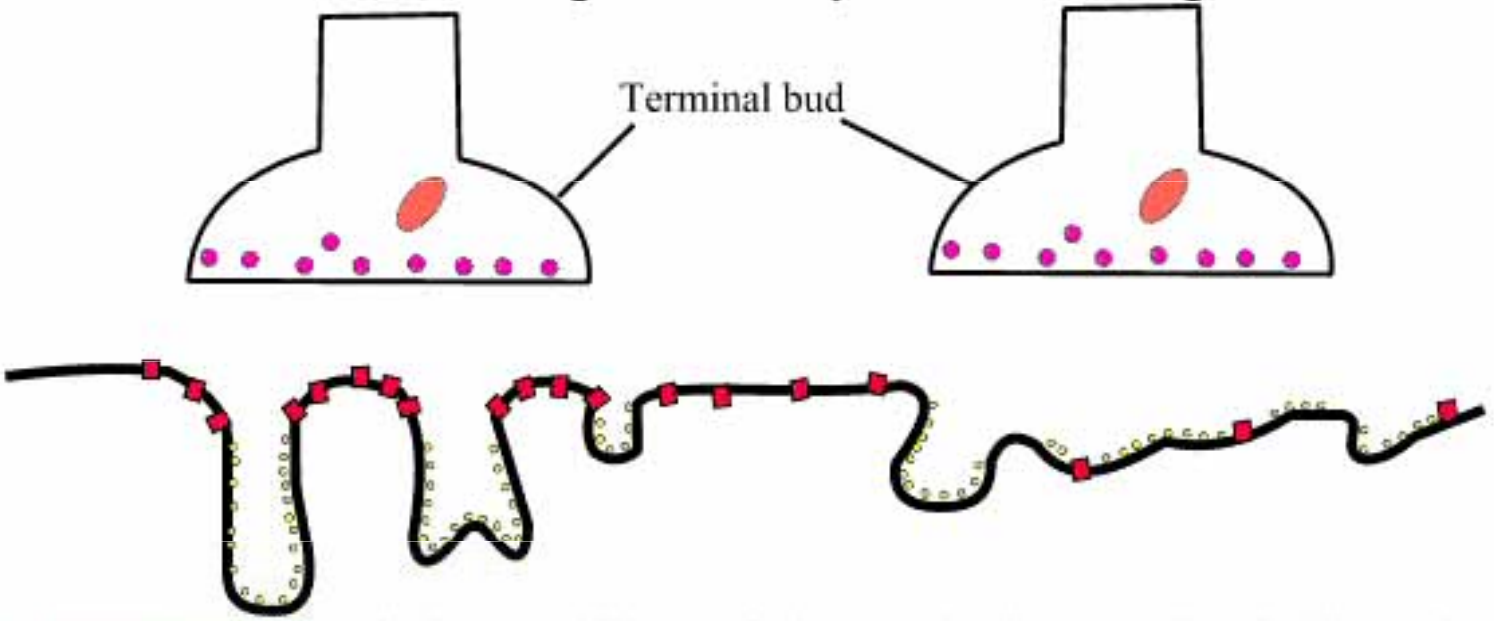


After cells become crosslinked, signals are sent to speed up decomposition by phagocytosis.

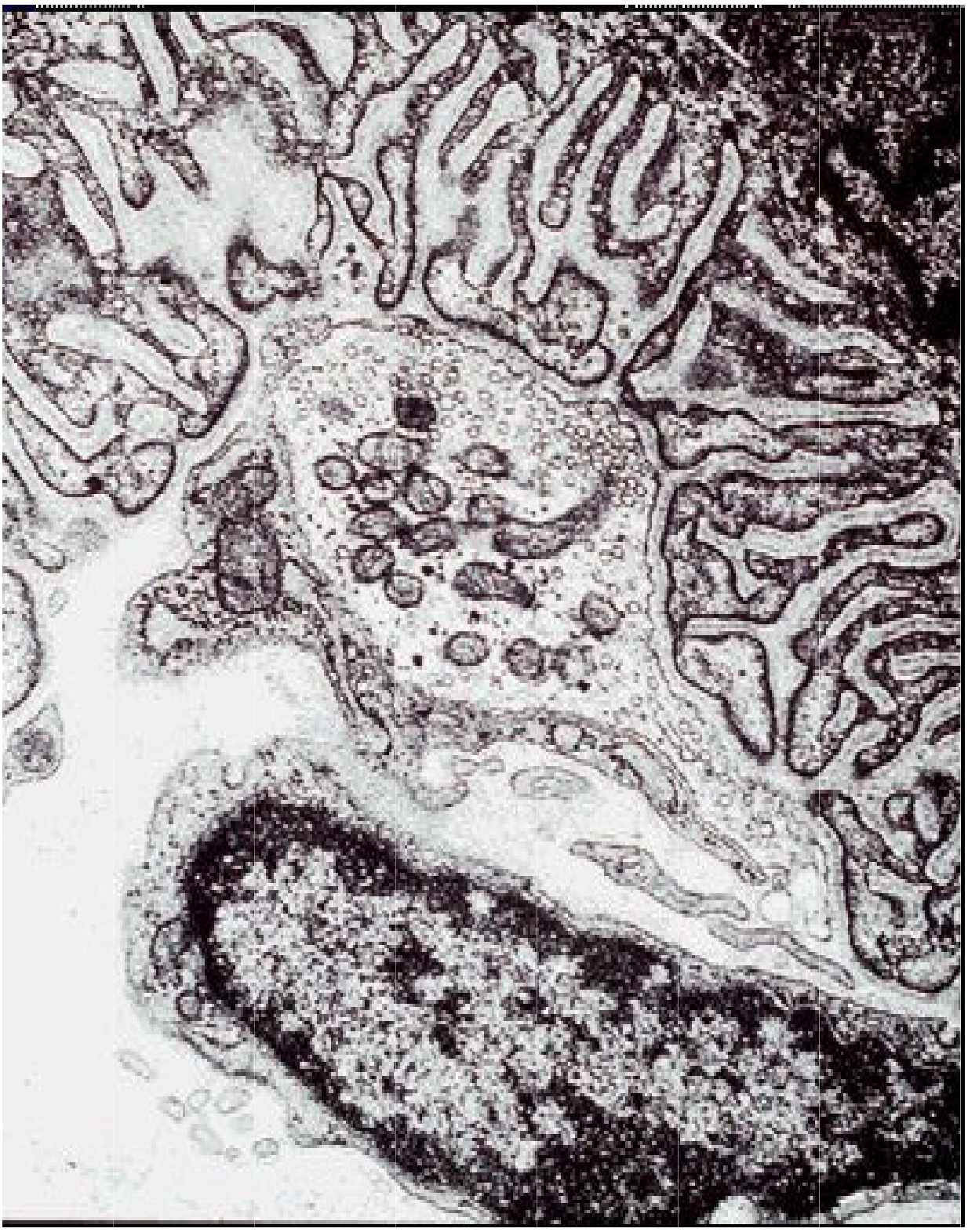


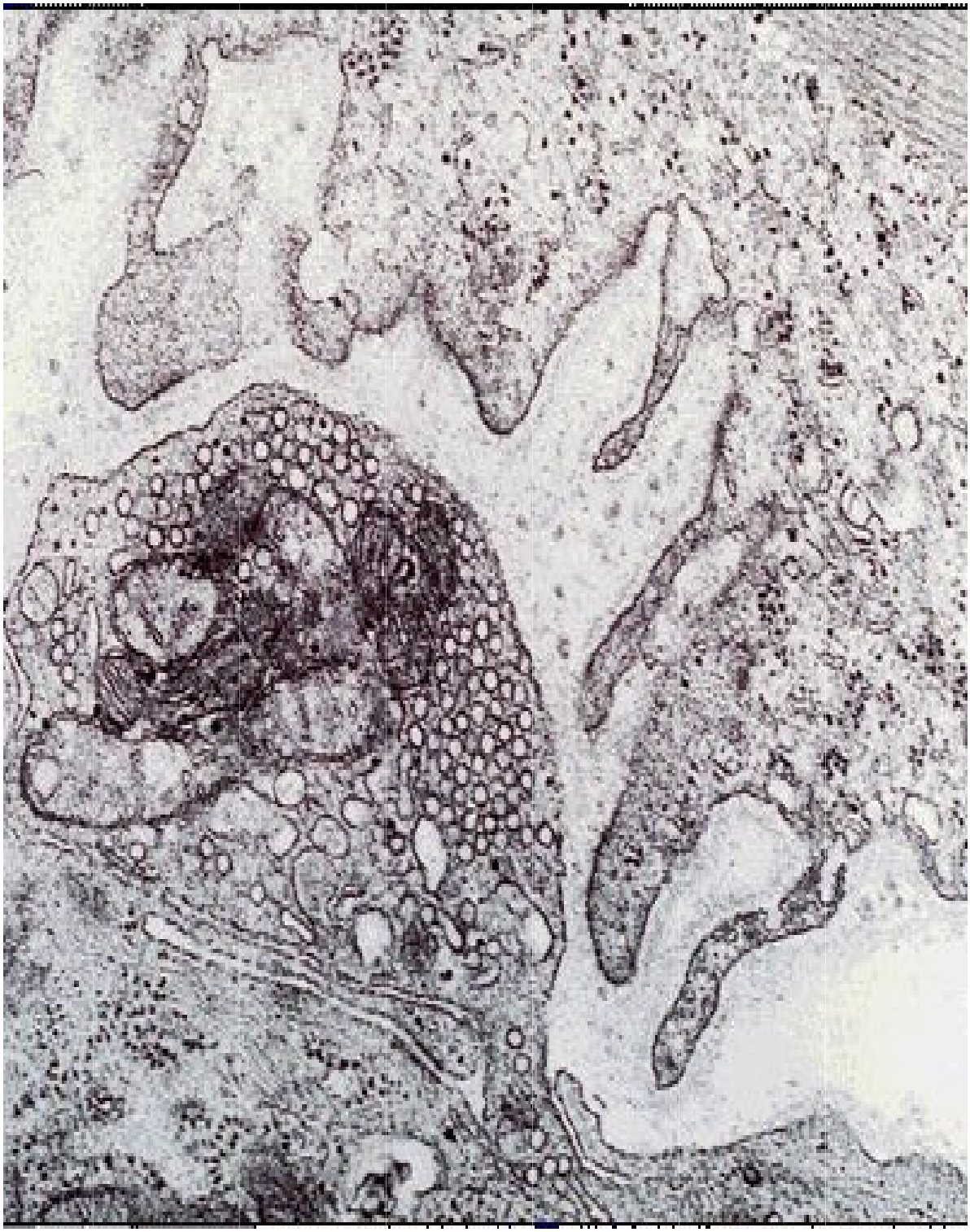
Lysosomes come to help with the decomposition. This continuous process results in the smoothing and simplifying of the post- synaptic terminal.

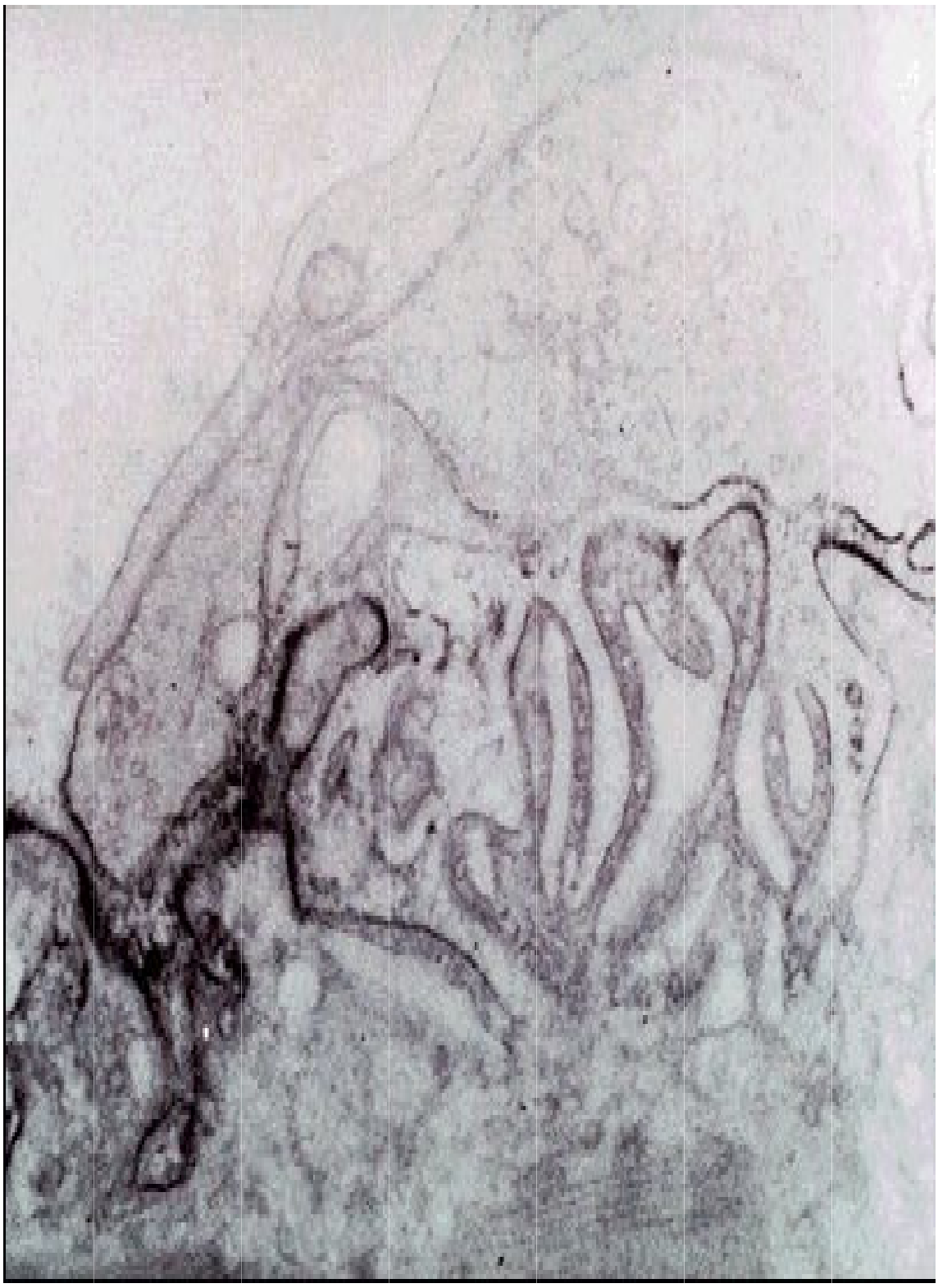
Normal Receptor Vs. Myasthenic Receptor



The increased distance in the myasthenic receptor drastically cuts down on the chances of Ach finding one of the already scarce receptors. The Ach-esterase then " recycles " the Ach by breaking it into it' s component parts, acetate and choline.

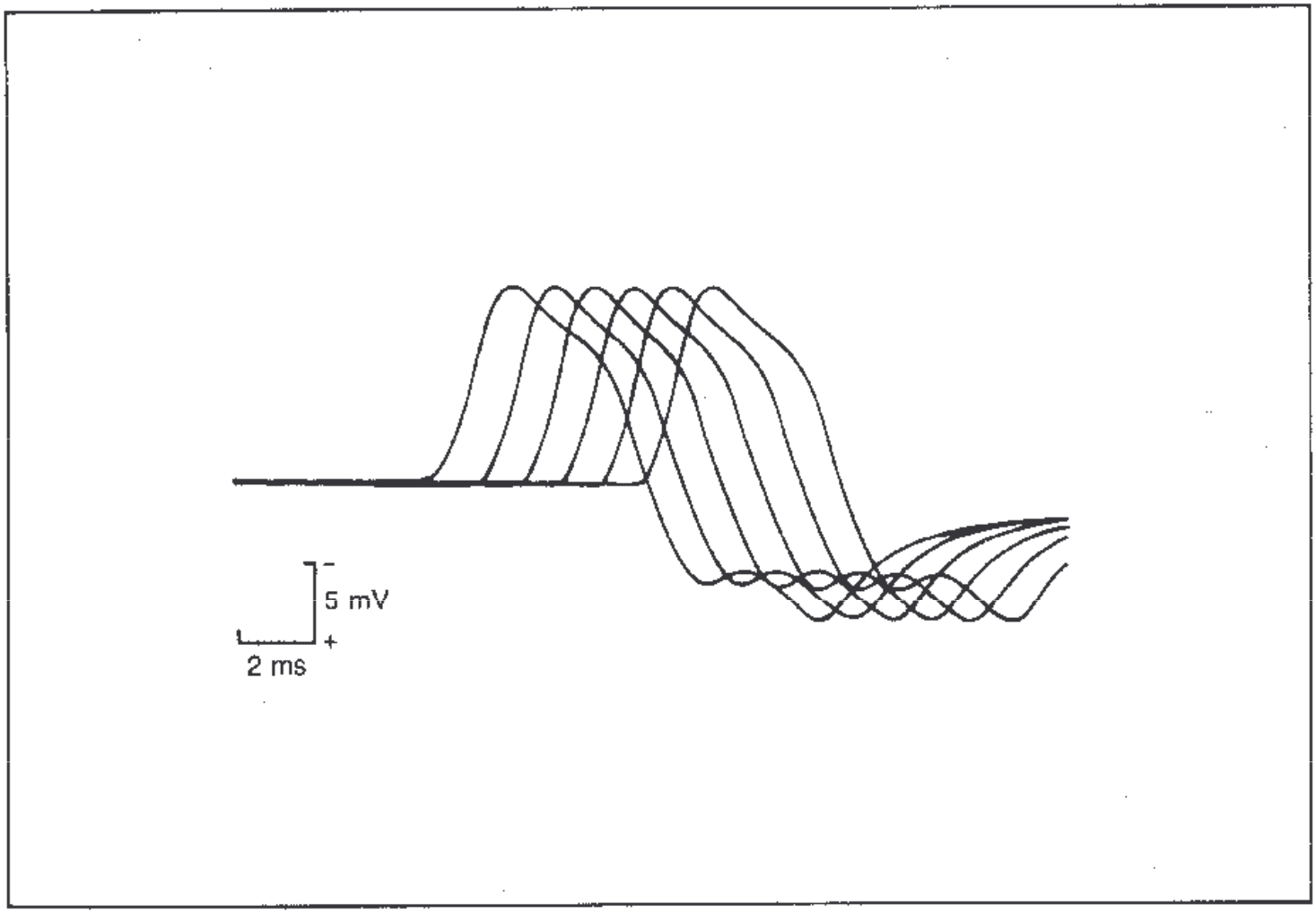






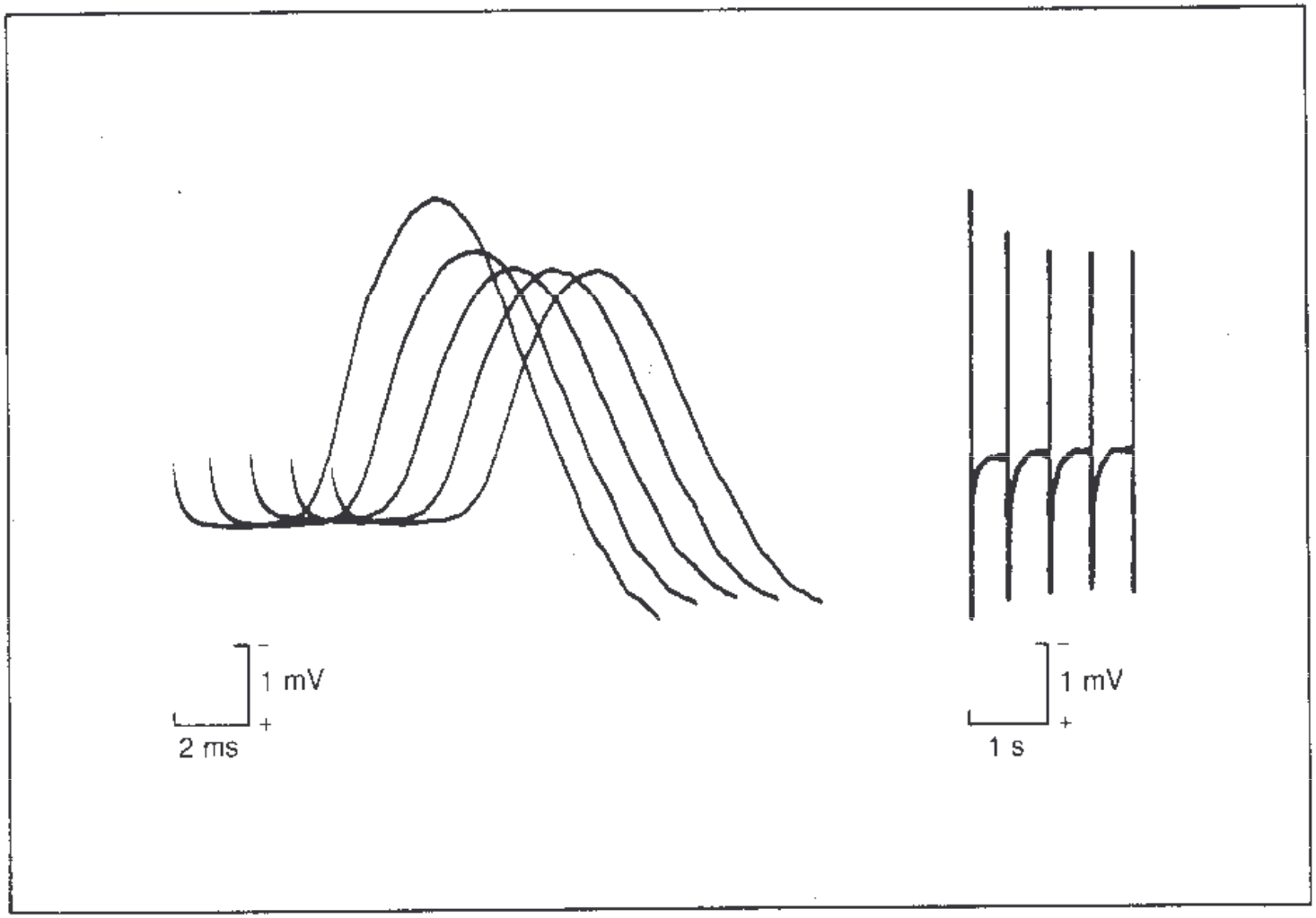
REPETITIVE NERVE STIMULATION

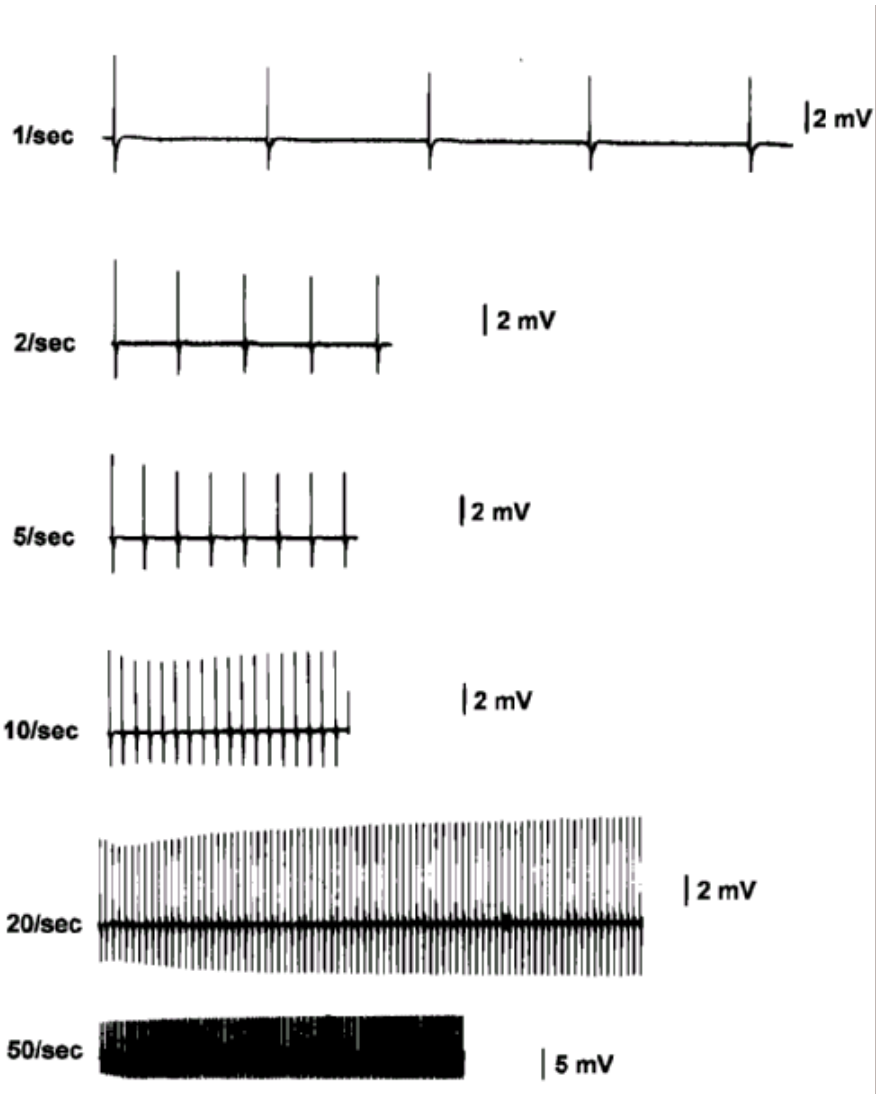
NORMAL RESPONSE

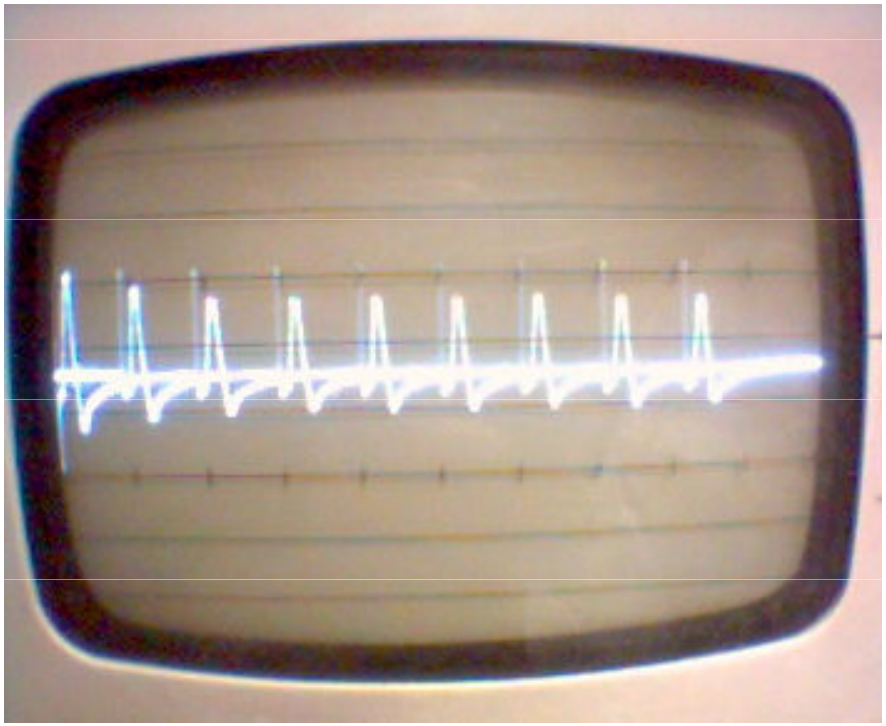


REPETITIVE NERVE STIMULATION

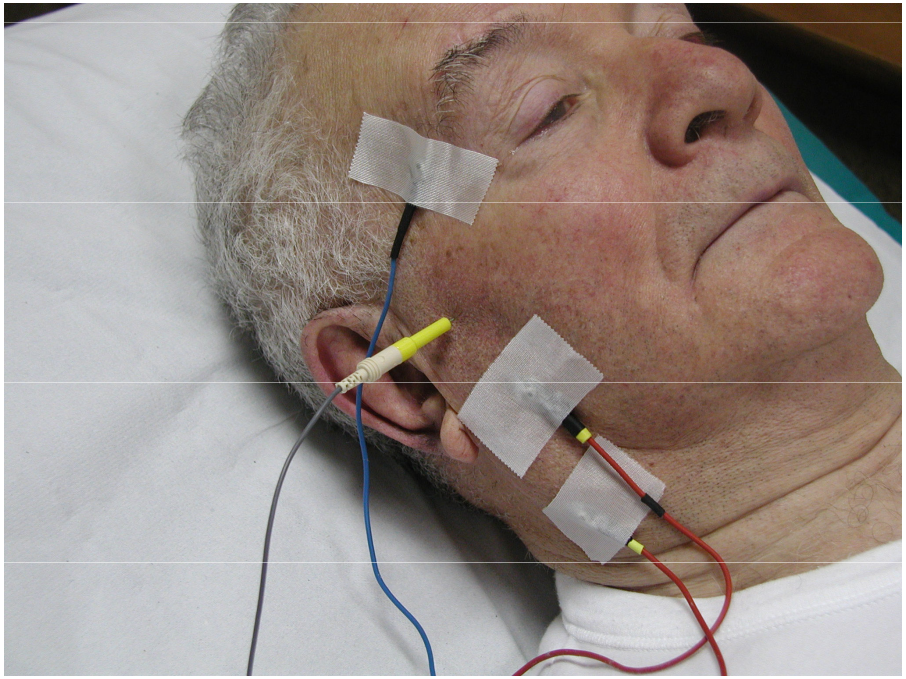
DECREMENTING RESPONSE



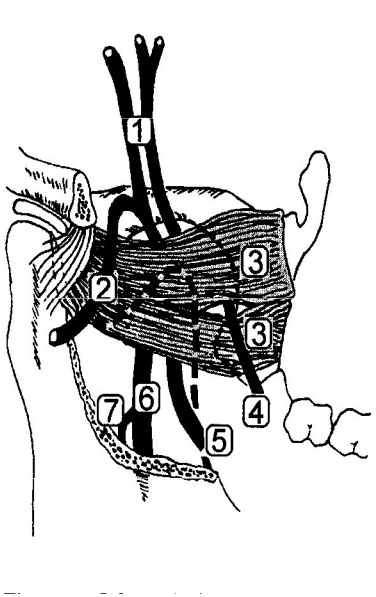

1/sec
2 mV
2/sec
2 mV
5/sec
2 mV
10/sec
2 mV
20/sec
2 mV
50/sec
5 mV

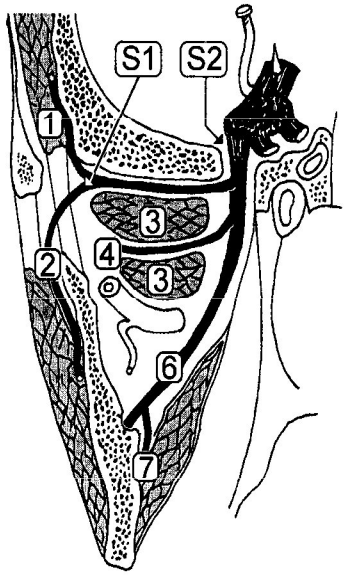


m. Massetere



n. Trigemino

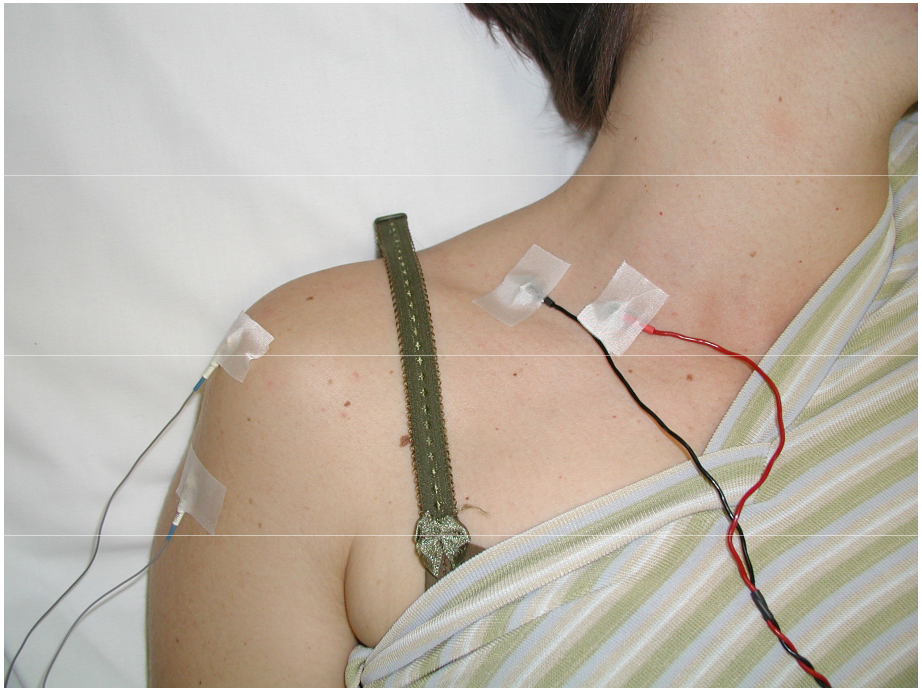


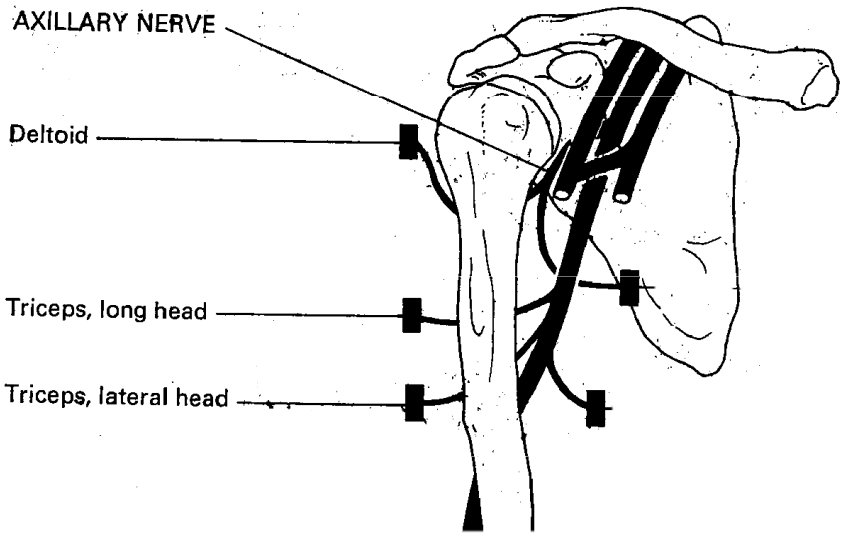


Decremento positivo nel 78 - 100% (88%)

m. Deltoide

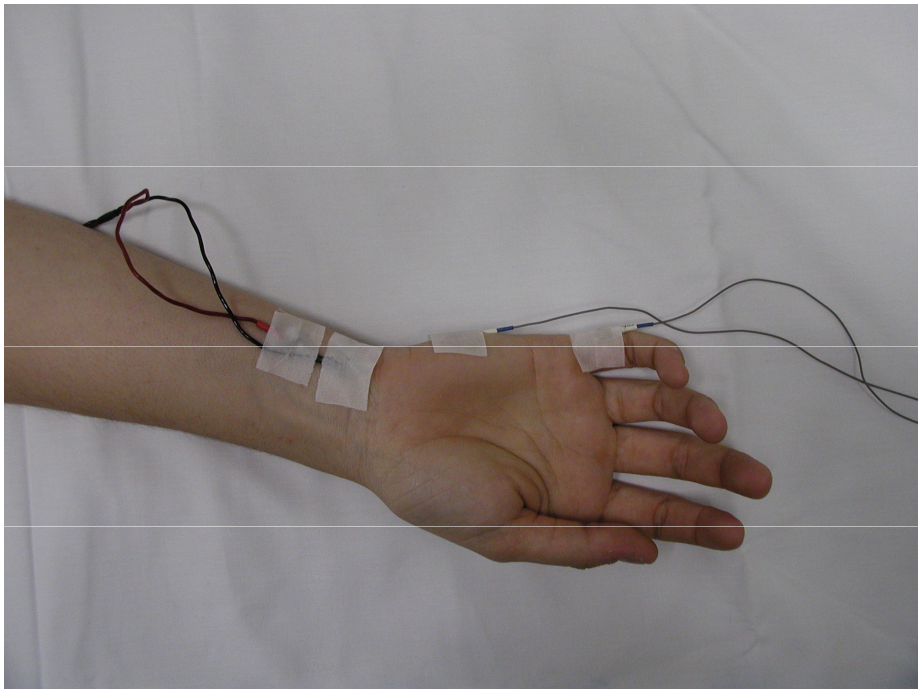
n. Circonflesso



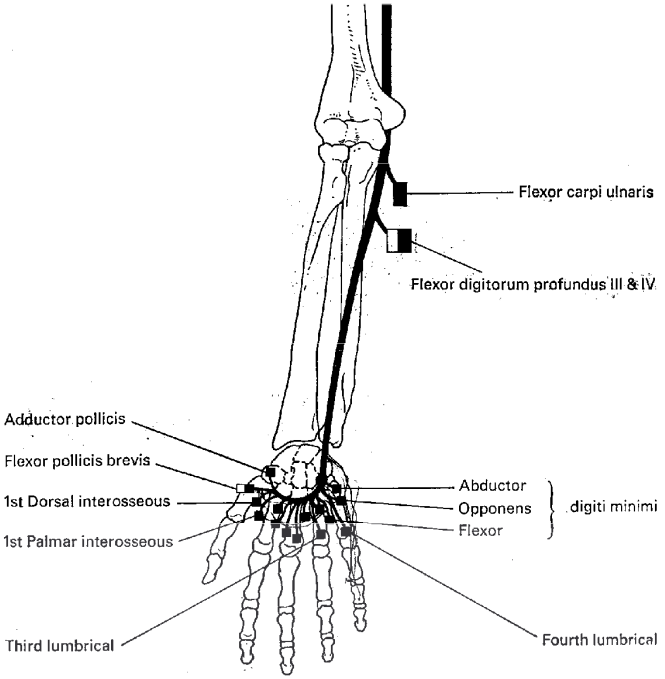


Decremento positivo nel 40 - 100% (65%)

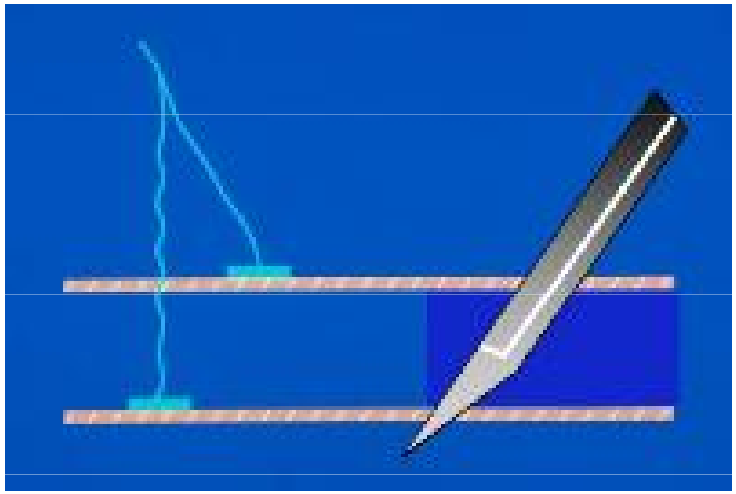
m. Abduttore del V dito

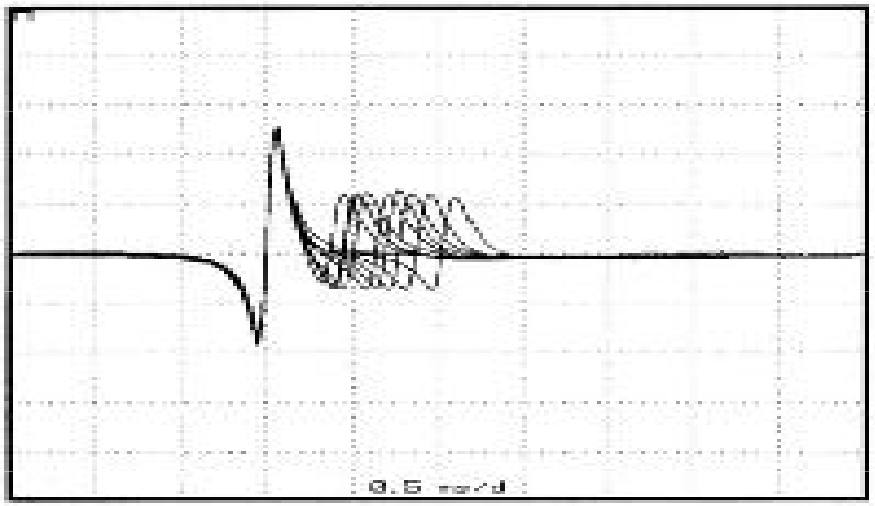


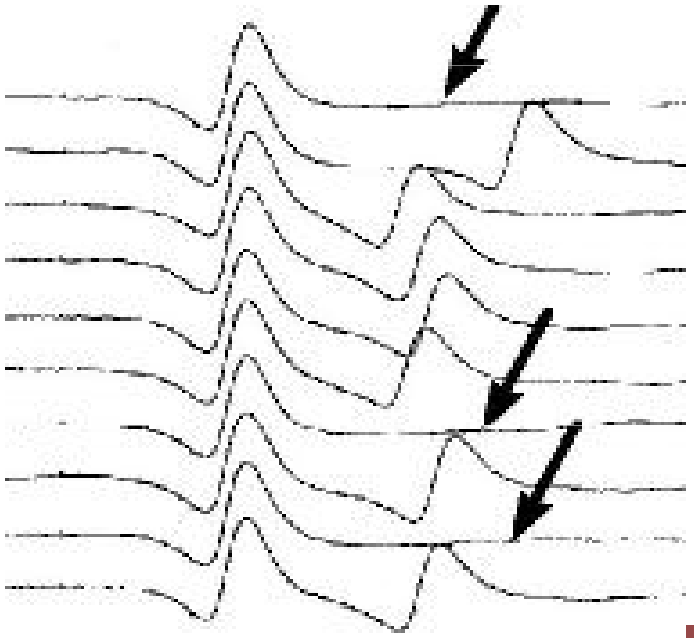
n. Ulnare

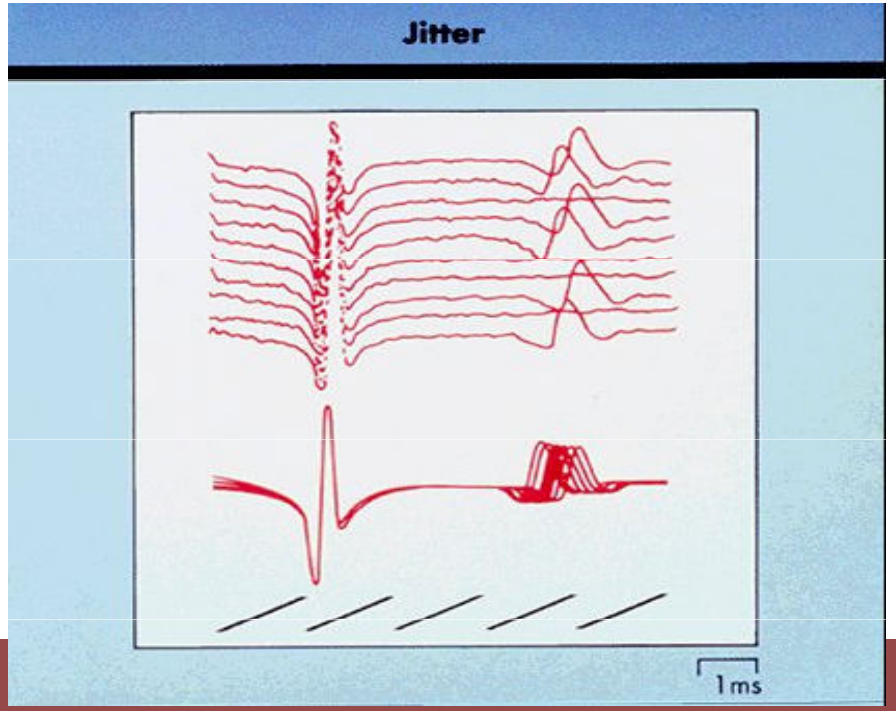


Decremento positivo nel 0 - 37% (18%)





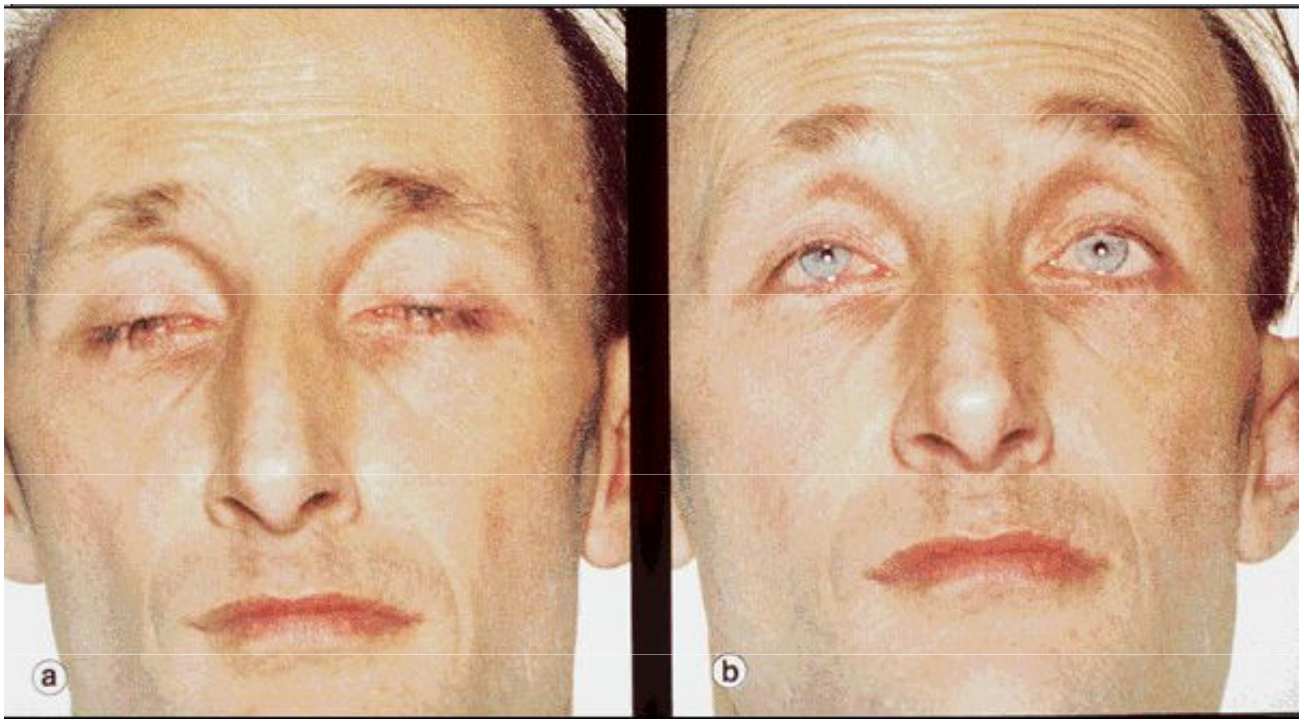


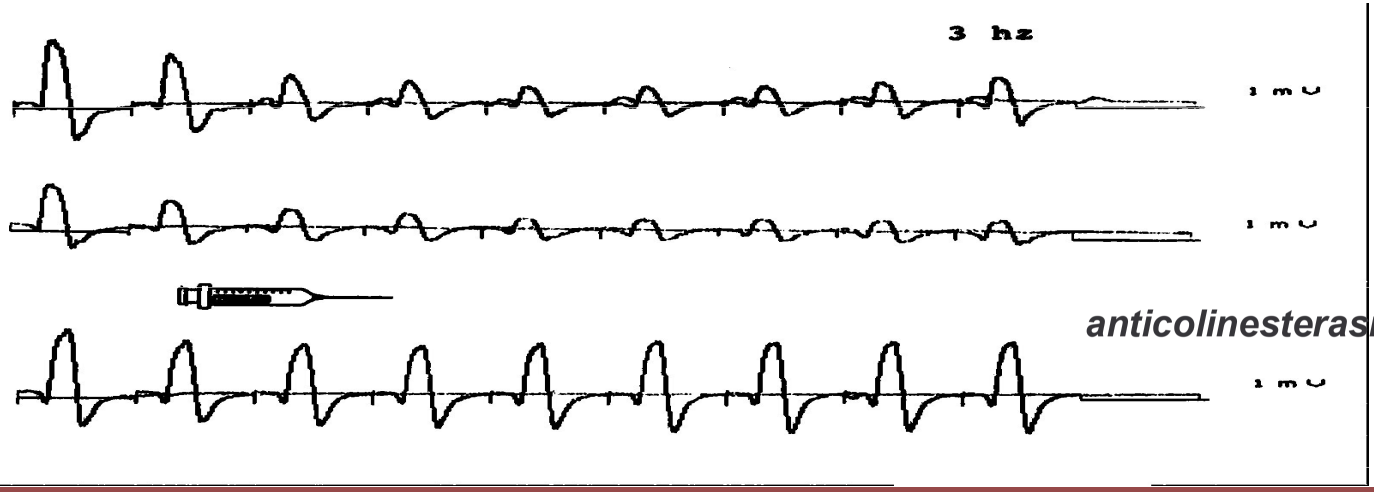

Jitter
1ms

MYASTHENIC MUSCULAR SCORE

Mantenere gli arti superiori distesi orizzontalmente **1 punto ogni 10 sec**	**Max 15** **Min 0**
Mantenere gli arti inferiori al di sopra del piano del letto in posizione supina **1 punto ogni 5 sec**	**Max 15** **Min 0**
Mantenere il capo sopra il piano del letto	
Contro resistenza	**10**
Senza resistenza	**5**
Impossibile	**0**
Alzarsi dalla posizione supina	
Senza l'aiuto delle mani	**10**
Impossibile	**0**
Muscolatura estrinseca degli occhi	
Normale	**10**
Ptosi	**5**
Diplopia	**0**
Chiusura delle palpebre	
Completa	**10**
Debole	**5**
Impossibile	**0**
Masticazione	
Normale	**10**
Debole	**5**
Impossibile	**0**
Deglutizione	
Normale	**10**
Difficoltosa, senza aspirazione	**5**
Difficoltosa, con aspirazione	**0**
Fonazione	
Normale	**10**
Nasale	**5**
Difficoltosa	**0**

TOTALE ...../ 100





anticolinesterasici

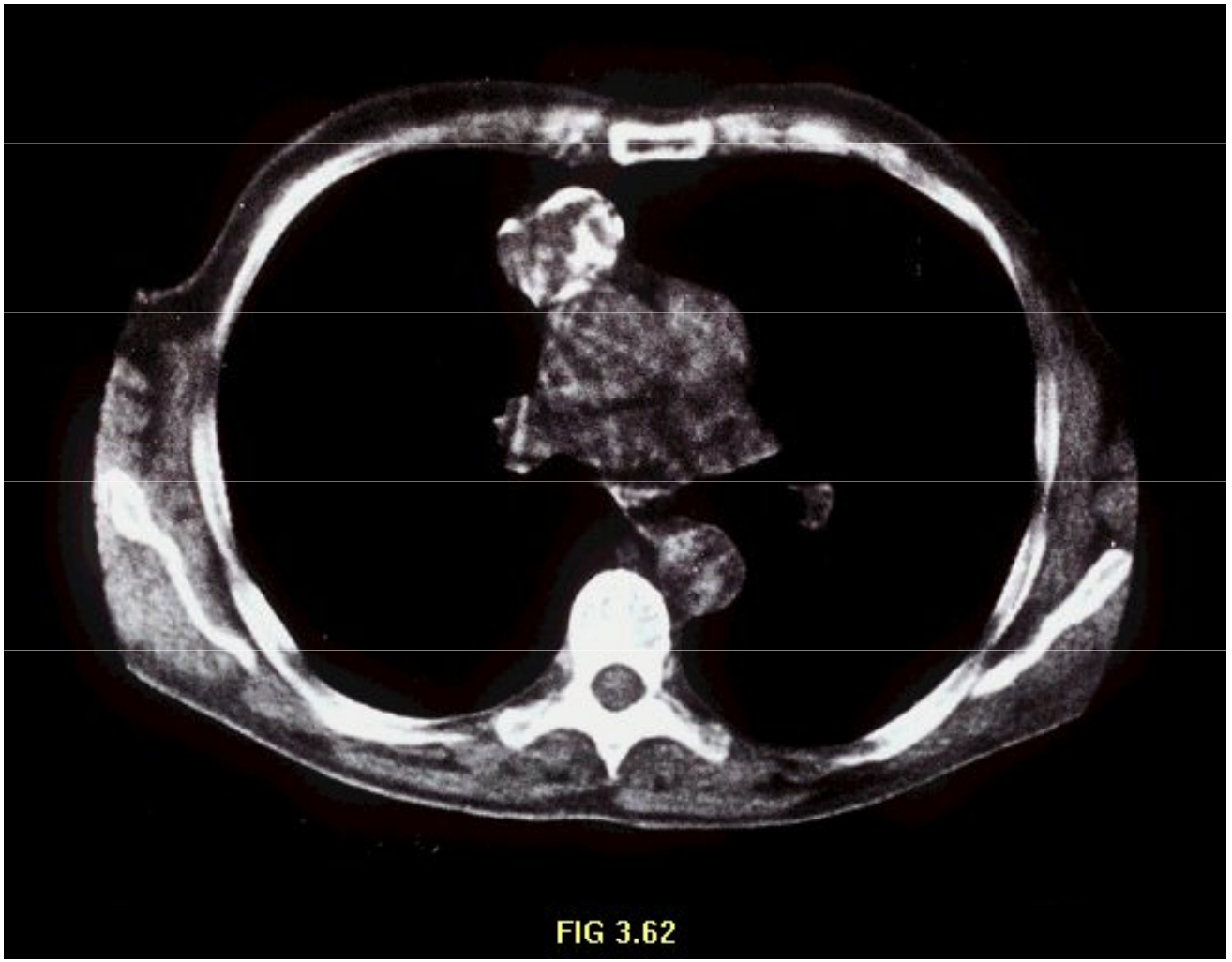
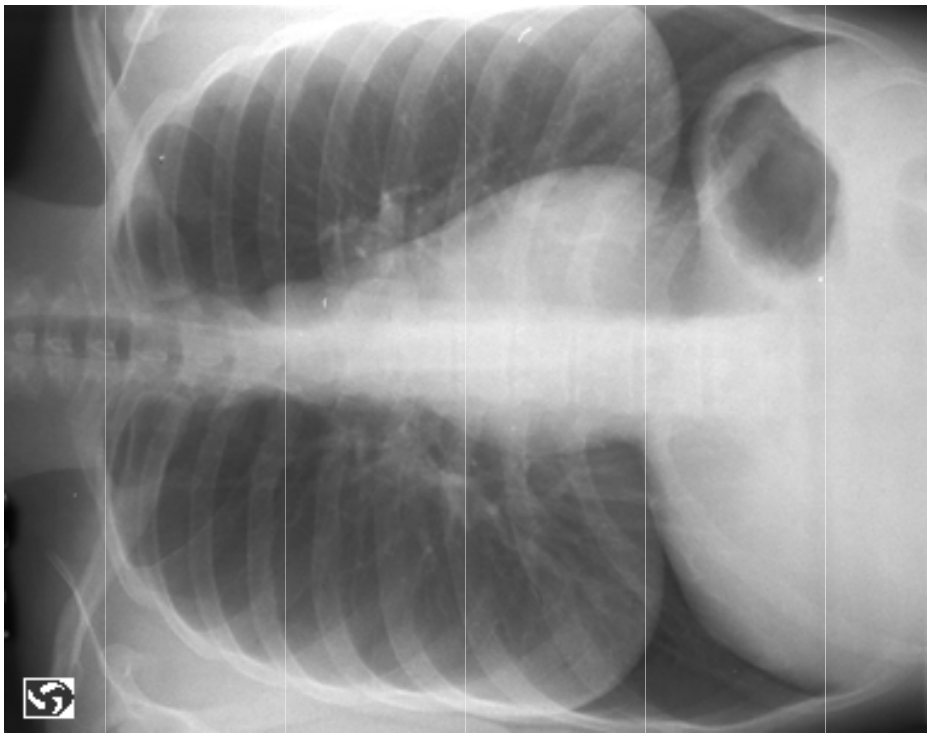


FIG 3.62



GRAZIE PER L'ATTENZIONE