APPROACHES TO THE MANAGEMENT OF SPASTICITY: ORAL MEDICATIONS, INTRATHECAL BACLOFEN AND BOTULINUM TOXIN

Spasticity:
Traditional Treatment Options

- **Pharmacological**
  - **Oral**
  - **Nerve Blocks**
- **Rehabilitation**
- **Surgical**

Oral medications have traditionally included:

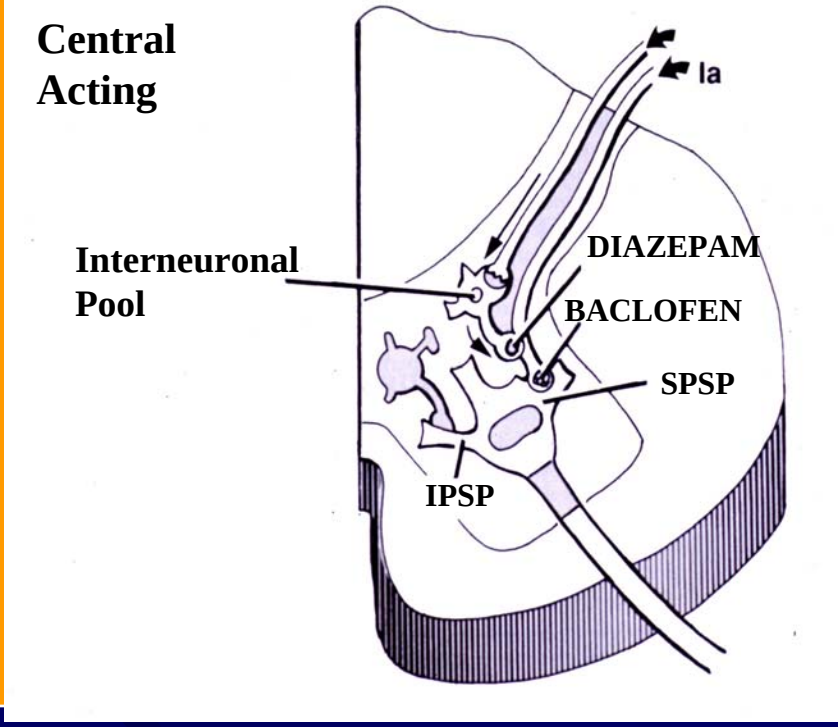
- benzodiazepines (diazepam/Valium®, clonazepam/Klonopin®)
- baclofen (Lioresal®)
- dantrolene sodium (Dantrium®)

Other oral medications include:

- clonadine (Catapres®)
- cyproheptadine (Periactin®)

Benzodiazepines

- Long-acting and short-acting formulations
- Mechanism of Action (CNS):
  - binds in brain stem and spinal cord
  - post-synaptic site of action
  - potentiates presynaptic effect of GABA



Benzodiazepines

- Clinical Indications: SCI, MS
- Possible Applications: TBI, CP, CVA
- Clinical Effects:
  - decreased resistance to passive ROM
  - decrease in hyperreflexia
  - reduction in painful spasms
  - sedation and reduced anxiety

Diazepam

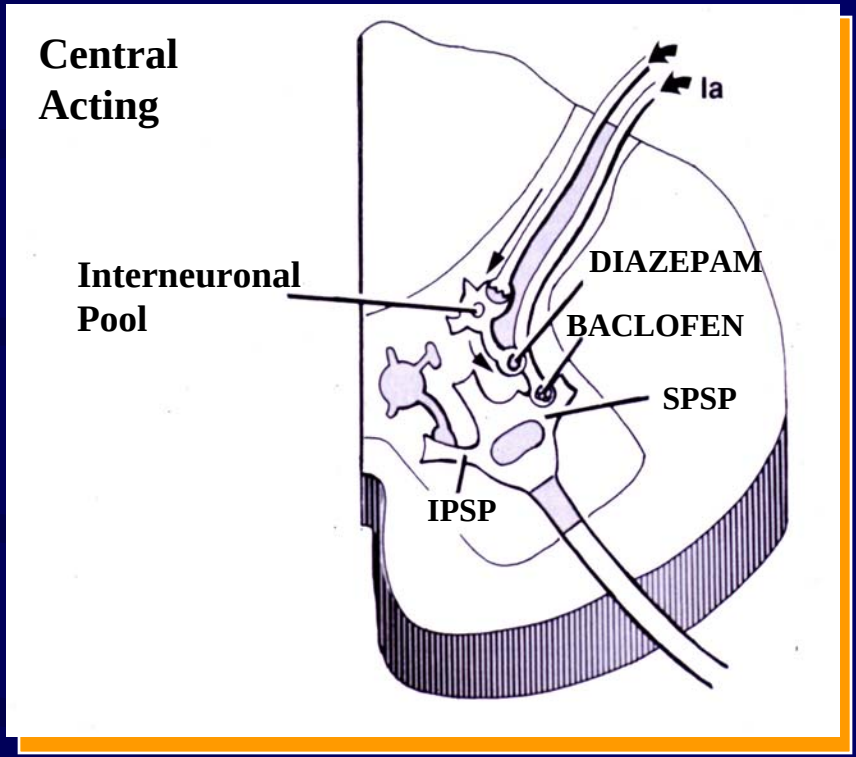
- **Recommended Dose:**
  - **initial = 2 mg. bid**

  (consider starting with single dose at night if nocturnal spasticity is the presenting problem)
  - **maximum = 60 mg. daily (20 mg. tid)**

NB: long half-life; active metabolite

- **Side Effects: weakness, sedation, hypotension, GI symptoms, memory impairment, uncoordination, confusion, depression, ataxia**
- **Controlled substance with potential for dependency**

Oral Baclofen



- **Mechanism of Action (CNS):**
  - **$GABA_b$ selective agonist**
  - **pre- and post-synaptic actions**
  - **acts on mono and polysynaptic pathways**

Oral Baclofen

- **Clinical Indications: spasticity of spinal origin**

  NB: Intrathecal Baclofen approved for cerebral and spinal spasticity

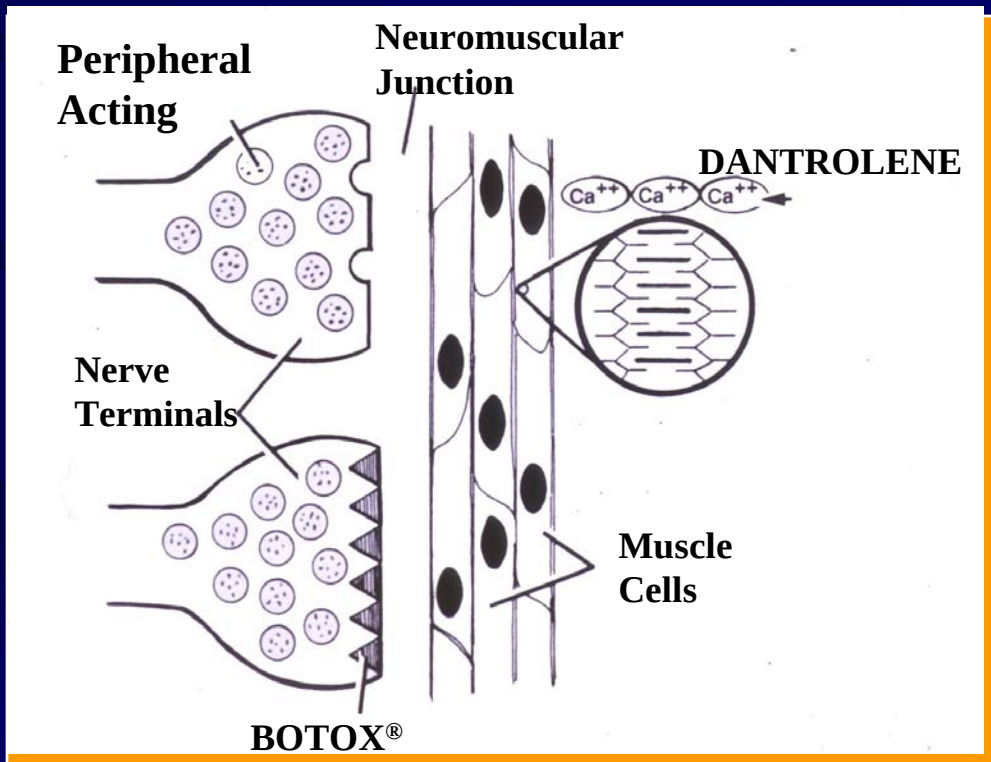
- **Clinical Effects:**
  - **decreased hyperreflexia and resistance to passive ROM**
  - **reduction in painful spasms and clonus**

Oral Baclofen

- **Recommended Dose:**
  - **initial = 5 mg. tid**
  - **maximum = 80 mg. Daily (20 mg. qid)**
- **Side Effects: weakness, sedation, hypotonia, ataxia, confusion, fatigue, nausea, dizziness, lower seizure threshold**
- **Sudden withdrawal may cause seizures, hallucinations, and rebound spasticity**
- **May potentiate effects of antihypertensive agents**

Dantrolene Sodium

- Mechanism of Action = peripheral
  - interferes with calcium release
  - uncouples muscle contraction from excitation
  - effects both intrafusal and extrafusal fibers



Dantrolene Sodium

- Clinical Indications: CVA, CP
- Possible Applications: TBI, SCI, MS
- Clinical Effects:
  - decreased resistance to ROM
  - decrease in hyperreflexia and tone
  - reduction in painful spasms and clonus
  - problems with weakness

New for Spasticity: Tizanidine (Zanaflex®)

- **Tizanidine effectively decreases tone and spasm frequency *preferentially* in spastic muscles.**
- **It has been reported to eliminate the unwanted side effect of muscle weakness**

Tizanidine

- Appropriate as first line oral monotherapy; may have utility in polypharmacy program
- No evidence of dependency, withdrawal, or tolerance effects

Tizanidine:
P*harmacology and Mechanism of Action*

- **Mechanism of Action (spinal and supraspinal):**
  - **decreases facilitory inputs by acting primarily on spinal polysynaptic pathways**
- **Alpha-2, noradrenergic receptor agonist**
- **Peak effect occurs 1-2 hours following administration**

Tizanidine: *Clinical Effects*

- Reduces muscle tone
- Reduces spasm frequency
- Reduces hyperreflexia
- Does not decrease muscle strength

Tizanidine: *Dosage*

- **Starting dose: 4 mg. At HS**
- **Optimum dose:**
  12-36 mg./day in 3 or 4 divided doses
- **Daily maximum dose = 36 mg.**
- **Requires gradual titration to optimal dose in 2-4 mg. steps**
- **Check liver function tests at baseline and during treatment**

Tizanidine: *Side Effects*

- **Most frequent side effects include: drowsiness, dry mouth, tiredness, dizziness (as with other anti-spasticity agents, side effects are dose related and may be mitigated by dosage titration)**
- **Literature suggests that tizanidine may be better tolerated than other anti-spasticity agents, as measured by "global tolerance rating scale"***

***** ***Lataste et al., 1994***

Regional Treatments

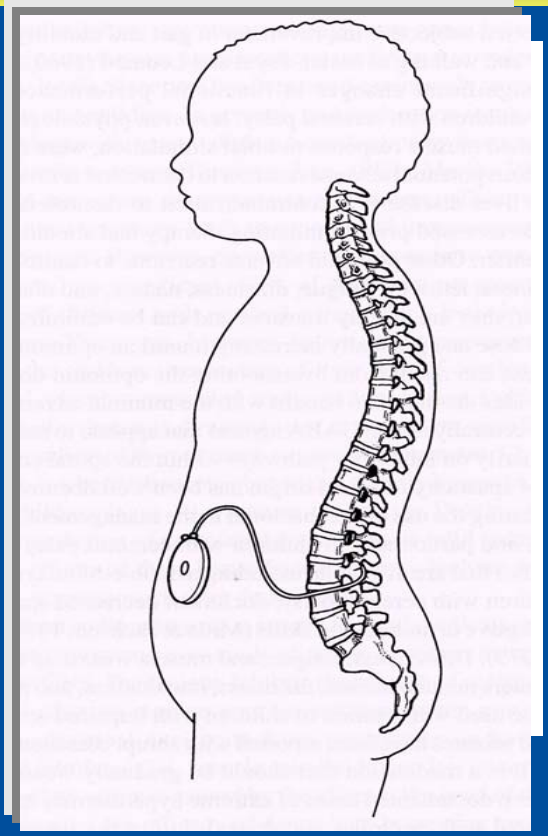
Intrathecal Baclofen Infusion System

- Implanted in subcutaneous fat (RLQ)
- Drug reservoir (10 mL or 18 mL) and pump connected to catheter
- Battery
- External radio-telemetry wand to control pump

Penn RD et al. *N Engl J Med.* 1989;320:1517-1522.
Albright AL. *JAMA.* 1993;270:2475-2479.
Albright AL. *J Child Neurol.* 1996;11(suppl 1):S29-S35.

Intrathecal Baclofen: Implantation

- Tip placed intrathecally between T10 and L1
- Pump is implanted into a subcutaneous pocket in the abdomen



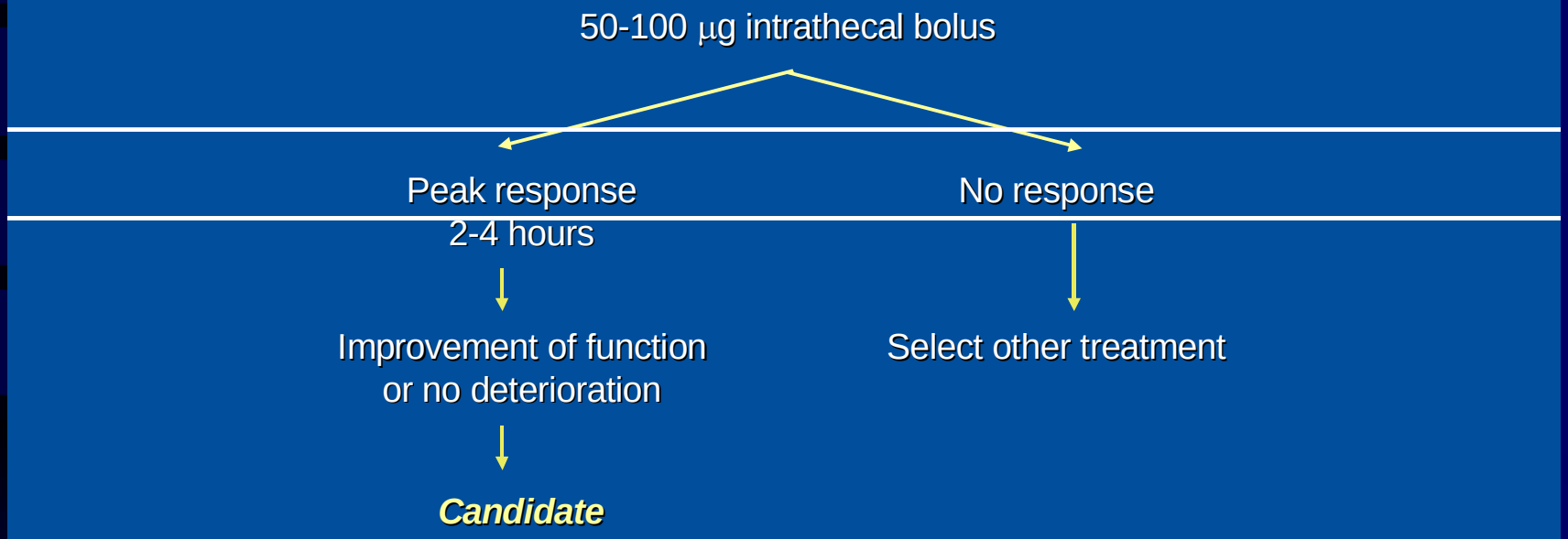
Kamensek J. *Axone*. 1999;20:67-72.

Intrathecal Baclofen: Selection Criteria

- Severe multifocal and regional muscle overactivity
- Failed adequate trial of oral agents
- Minimum age 4 years (body-size dependent) and clinically stable
- Patient/caregiver goals for treatment are realistic
- Family committed to intrathecal baclofen as a treatment option
- Exclusion criteria
  - Infection, history of allergy, or hypersensitivity to baclofen
  - Potential for pregnancy or active breast-feeding

Penn RD et al. *N Engl J Med.* 1989;320:1517-1521.

Intrathecal Baclofen: Screening



Coffey RJ et al. *J Neurosurg.* 1993;78:226-232.
Albright AL. *J Child Neurol.* 1996;11(suppl 1):S29-S35.
Ordia JI et al. *J Neurosurg.* 1996;85:452-457.
Becker R et al. *J Neurol*. 1997;240:160-166.

Intrathecal Baclofen: Follow-up

- Postimplantation
  - Titrate dose to ensure balance, stability, and postural control
  - Instruct patient and caregiver about refill schedule, management of complications, and potential adverse effects
  - Refills, assessments, and possible dose adjustments are at ITB therapy center at 4- to 12-week intervals
  - Replace pump after 5–7 years

Albright AL. *J Child Neurol.* 1996;11(suppl 1):S29-S35.

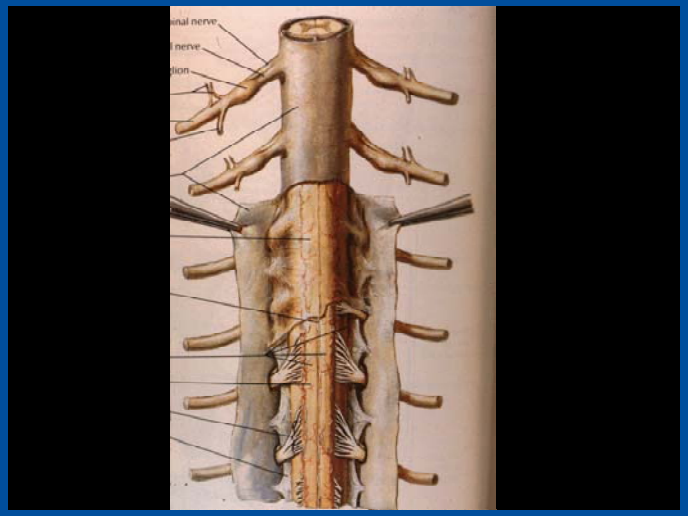
Intrathecal Baclofen: Complications

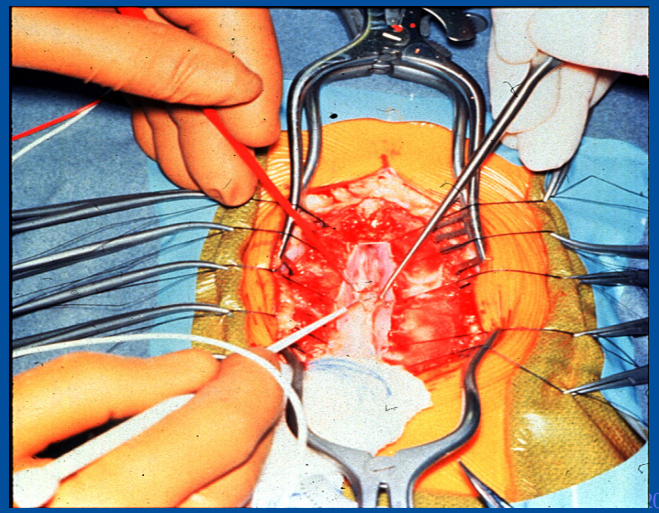
- Local
  - Seroma
  - Hematoma
  - Erosion
  - Infection
- Systemic
  - Withdrawal
  - Drug toxicity
- Catheter
  - Migration
  - Breakage
  - Puncture/rupture
  - Dislodgment
  - Disconnection
  - CSF leaks

Kamensek J. *Axone*. 1999;20:67-72.

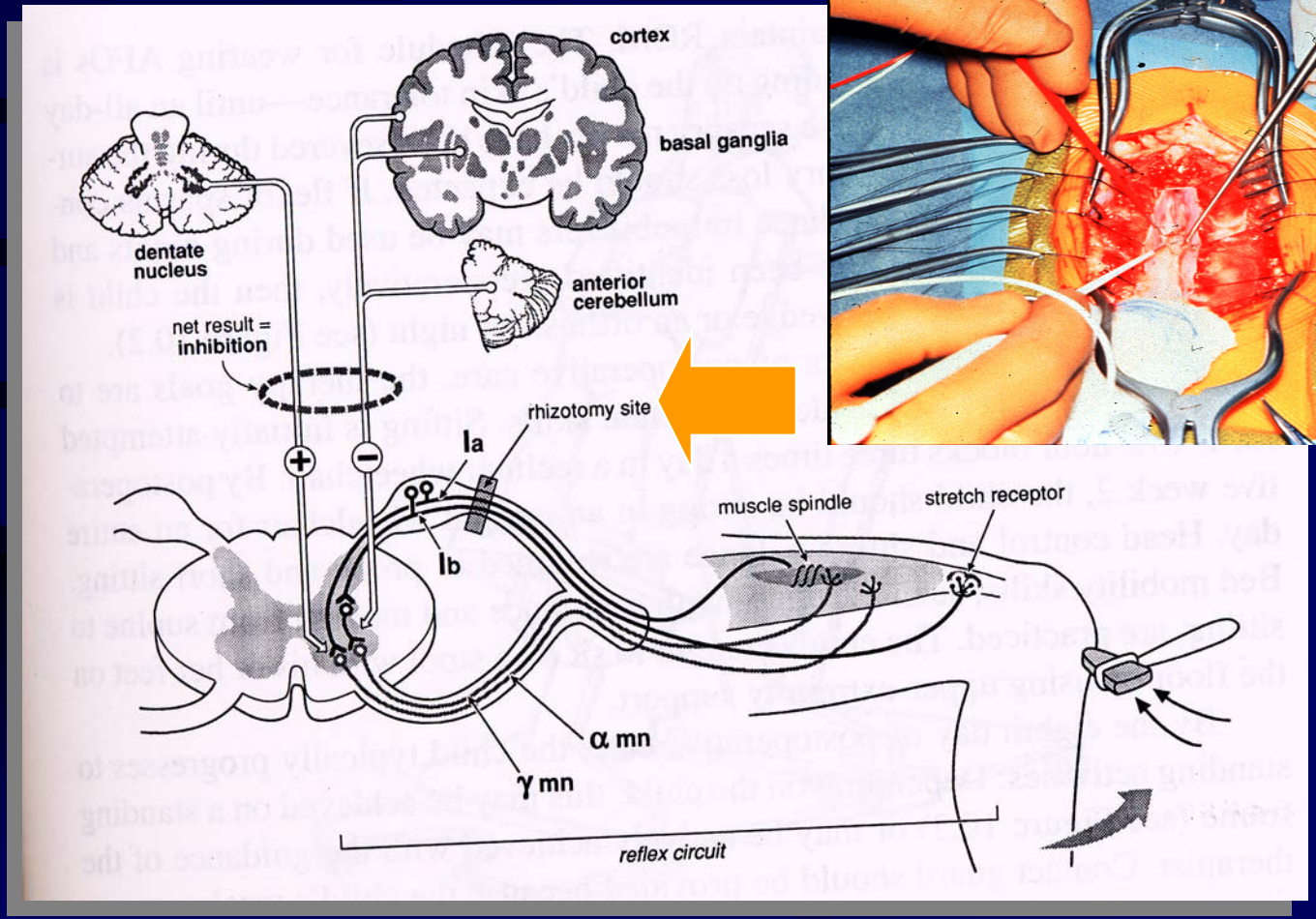
Current Treatment Options: Neurosurgical Interventions

- Selective dorsal rhizotomy
- Peripheral neurectomy
- Myelotomy
- Dorsal column electrical stimulation





Selective Dorsal Rhizotomy



Spasticity: *Injection*

- **Regional and local**
  - **Motor point and nerve blocks; phenol, alcohol**

NB: Limitations - painful; time-consuming; dysesthesia; variable duration of effect

Alcohol

- Indications
- Cost
- Outcome

Phenol

- Indications
- Cost
- Outcome

Botulinum Toxin and Spasticity

- Local injections of botulinum toxin are well accepted as treatment for:
  - focal dystonias
  - spasticity
  - other neurological disorders characterized by inappropriate muscle spasms
  - Not approved for use in CP by the FDA

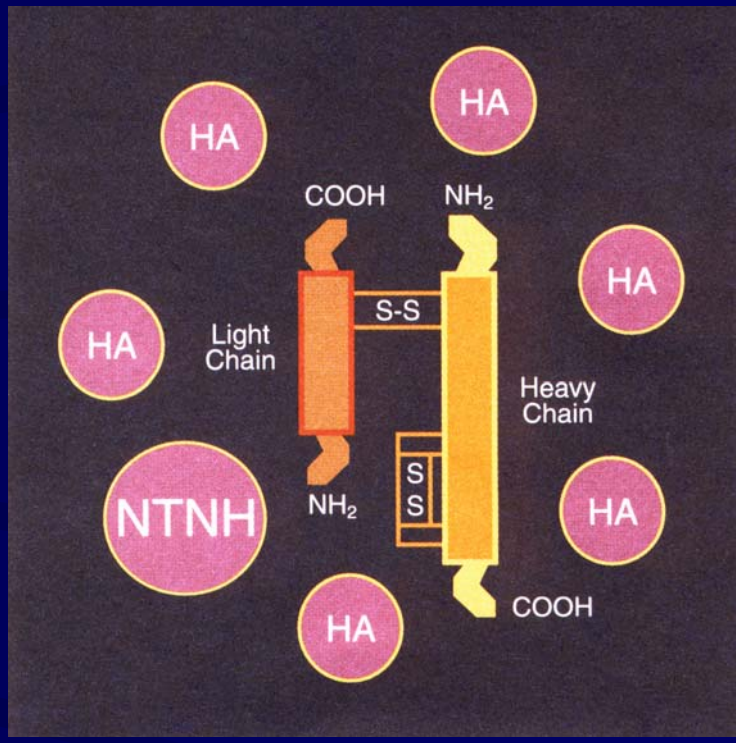
Botulinum Toxin A

- **Botulinum toxin produced by the bacteria:*Clostridium botulinum***
- **Seven serotypes of toxin (A-G)**
  - **Trade names of botulinum toxin type A are: BOTOX® (Allergan, Inc.)**
  - **DYSPORT® (Speywood Pharmaceuticals Ltd.)**

Botulinum Toxin Type B

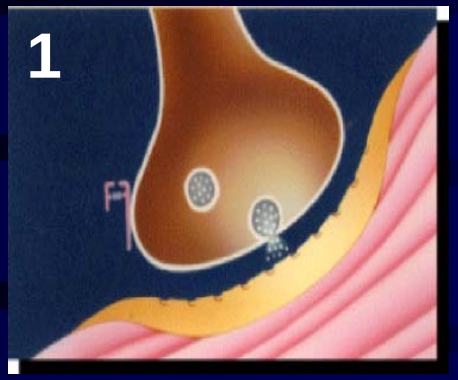
- Approved for use for cervical dystonia
- Manufactured as Myobloc (Elan Pharmaceuticals)
- Studies on the use of Myobloc in children with spasticity have not been published

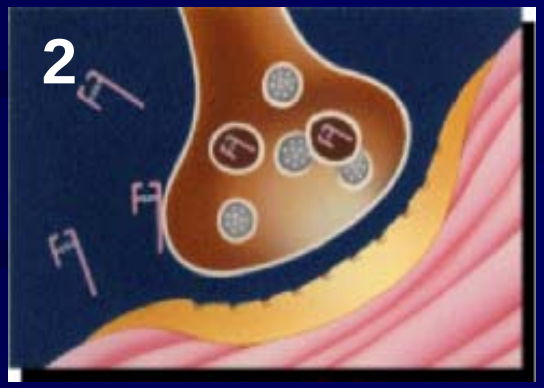
Botulinum Toxin A:
Mechanism of Action

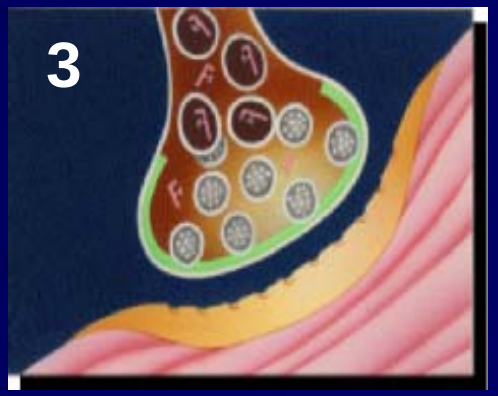


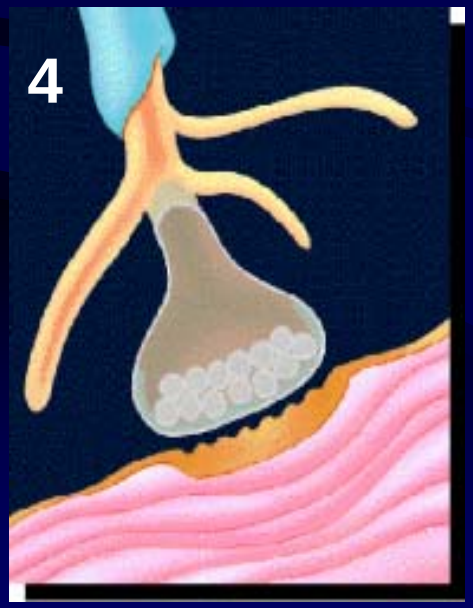
- Botulinum toxin molecule = light and heavy chain linked by a disulfide bond
- Inhibits release of acetylcholine
  - toxin binds to presynaptic axon terminal
  - internalization of toxin (endocytosis)
  - inhibition of neurotransmitter release
- Storage and synthesis of acetylcholine is normal
- Toxin is a zinc-dependent enzyme, substrates identified

Botulinum Toxin Type A Mechanism
Current Hypothesis







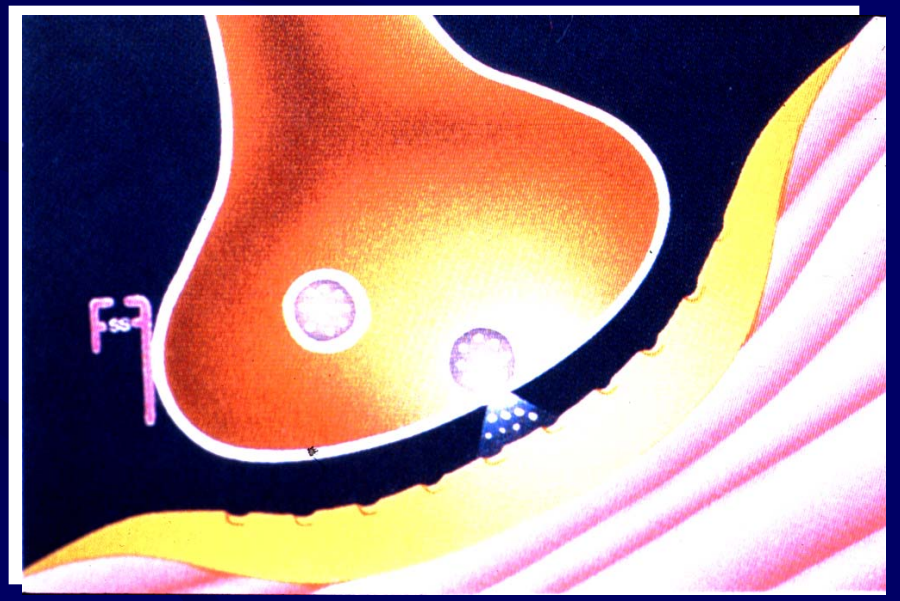


Data published: dePaiva et al. PNAS 1999, 96:3200

Botulinum Toxin Type A: *Mechanism of Action*

- **Binding:**

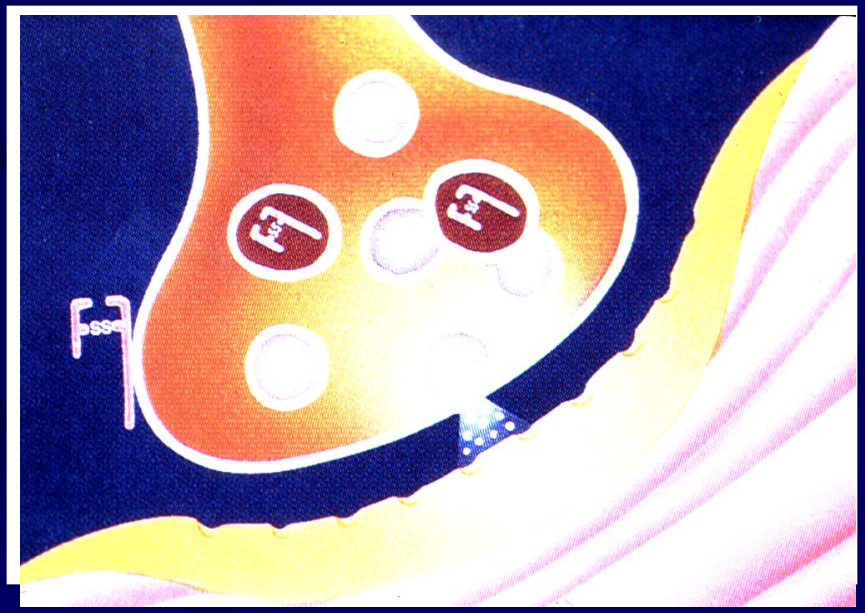
  Botulinum toxin type A first binds to cholinergic nerve ending.



Botulinum Toxin Type A:
Mechanism of Action

- **Internalization:**

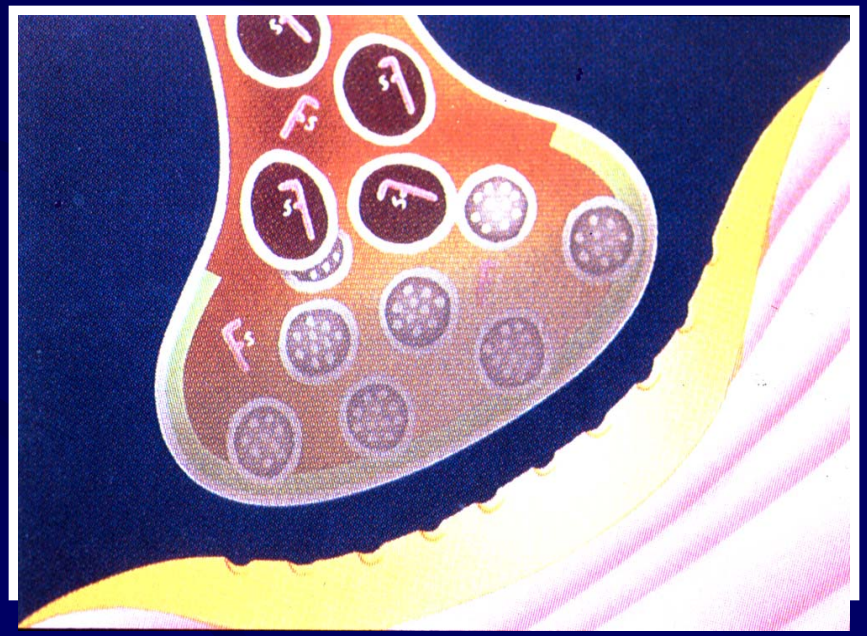
  Botulinum toxin type A is internalized via receptor-mediated endocytosis.



Botulinum Toxin Type A:
Mechanism of Action

- **Blocking:**

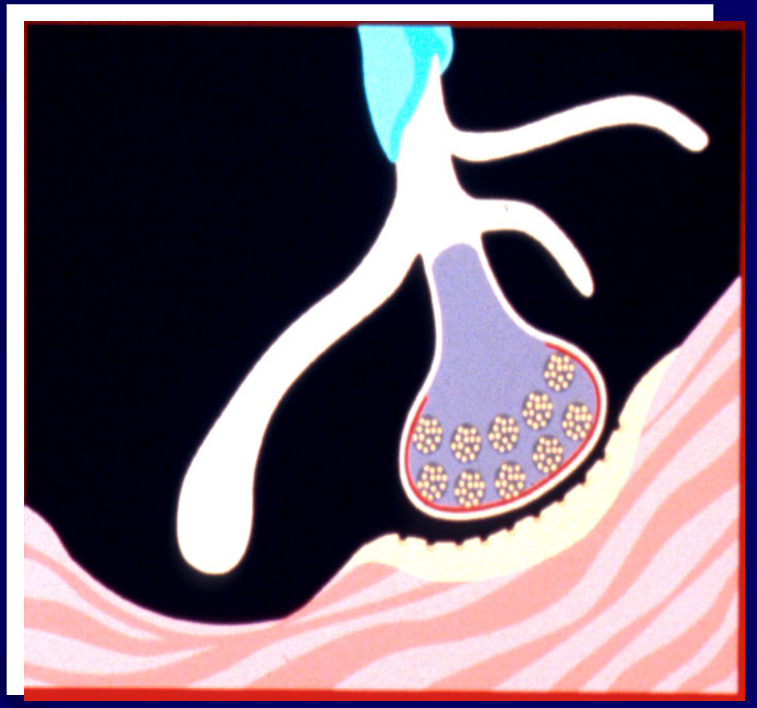
  Once inside cell, botulinum toxin type A blocks release of acetylcholine transmitter. This produces functional muscle denervation.



Botulinum Toxin Type A:
Mechanism of Action

- **Sprouting:**

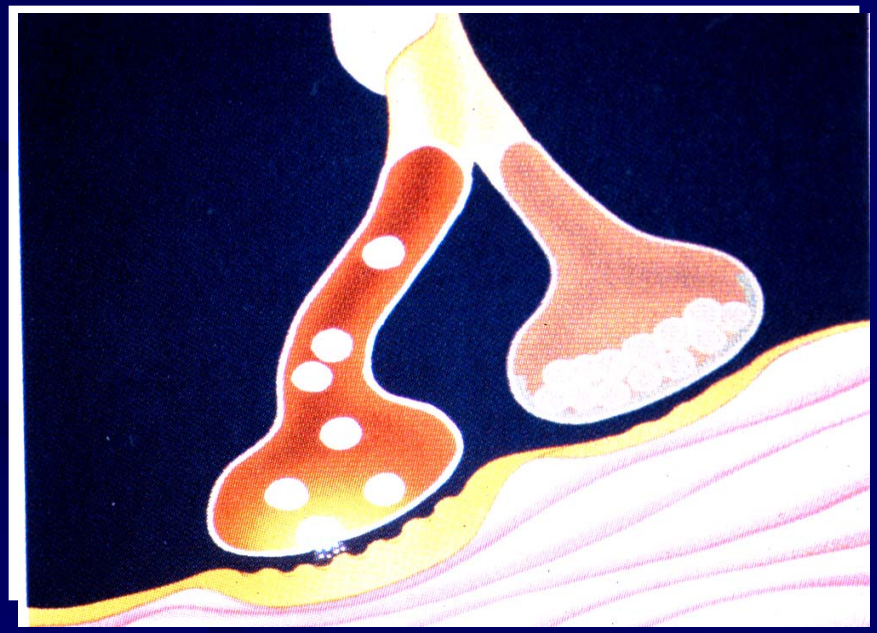
  In muscles treated with botulinum toxin type A, chemical denervation of neuromuscular junction stimulates nerve sprouting.



Botulinum Toxin Type A:
Mechanism of Action

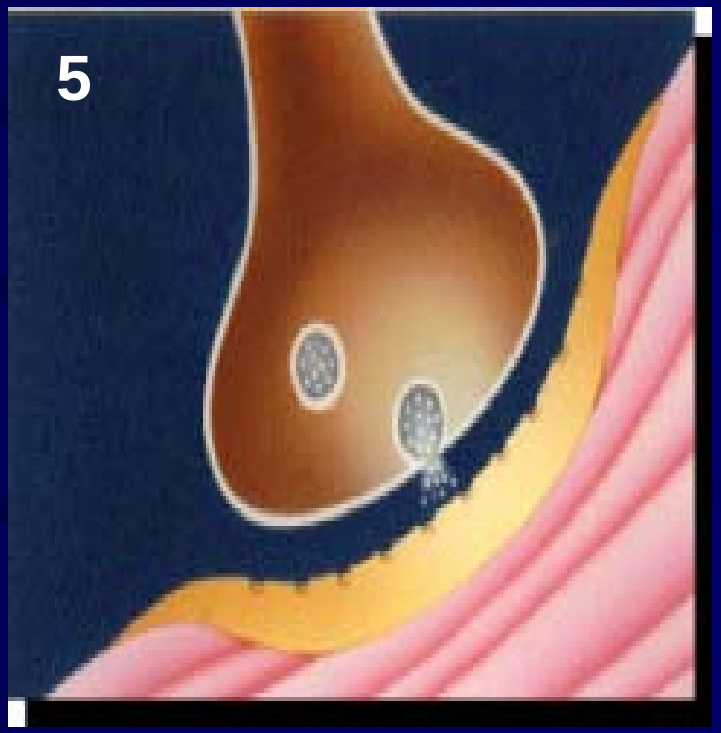
- **Establishing Sprout connection:**

  Single nerve sprout establishes new neuromuscular junction. Muscle tone is restored and spasms return, making it necessary to repeat injections approx. every 3-6 months, depending on individual patient response.



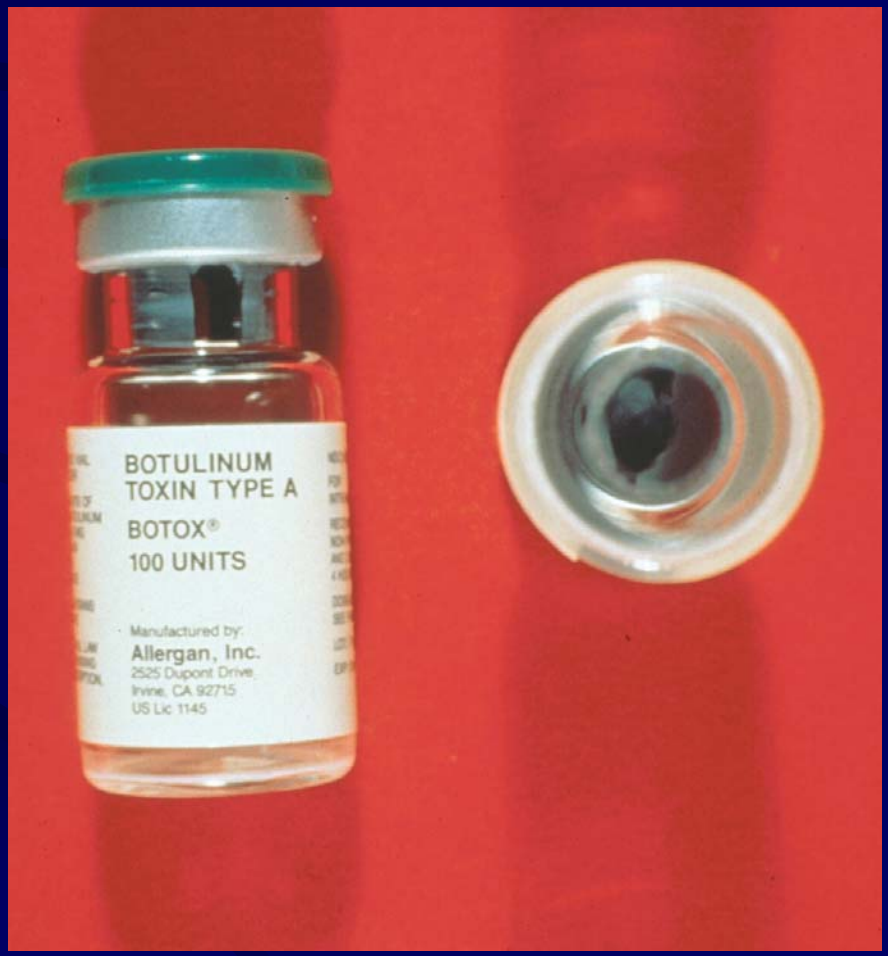
Reestablishment of Neuromuscular Junction

- The sprouted nerve retracts and the original neuromuscular junction is reestablished



BOTOX®:
Commercial Preparation

- Cultures of C. botulinum are established in fermenter, grown, and harvested
- Diluted with human serum albumin
- Freeze-dried in vials of 100 Units



BOTOX®: *Safety*

- In clinical use, dose range = 60-400 Units
- No anaphylactic reactions have been reported
- Not indicated during pregnancy or lactation

Botulinum Toxin Type A:
Possible Adverse Effects

Side effects are a result of the pharmacology and are temporary

- **Resulting symptoms are site specific, *e.g.* weakness in injected and neighboring muscles**
- **Patient may have temporary change in posturing or pain due to re-alignment of nerve-muscle-bone relationships**
- **Patient may report subjective symptoms of weakness and fatigue (‘flu-like’ syndrome) that usually last less than four days**

Botulinum Toxin Type A:
BTX for Spasticity: Patient Selection

- **Pre-injection muscle imbalance is present with identifyable and relatively stronger spastic agonist muscle(s)**
- **Antagonist muscle(s) must be:**
  - **sufficiently powerful for functional control if "agonists" are weakened, or**
  - **capable of hypertrophy and strengthening, if allowed to perform through the appropriate range of motion, or**
  - **acceptable in a flaccid state**

Injection of Botulinum Toxin :
Patient Selection

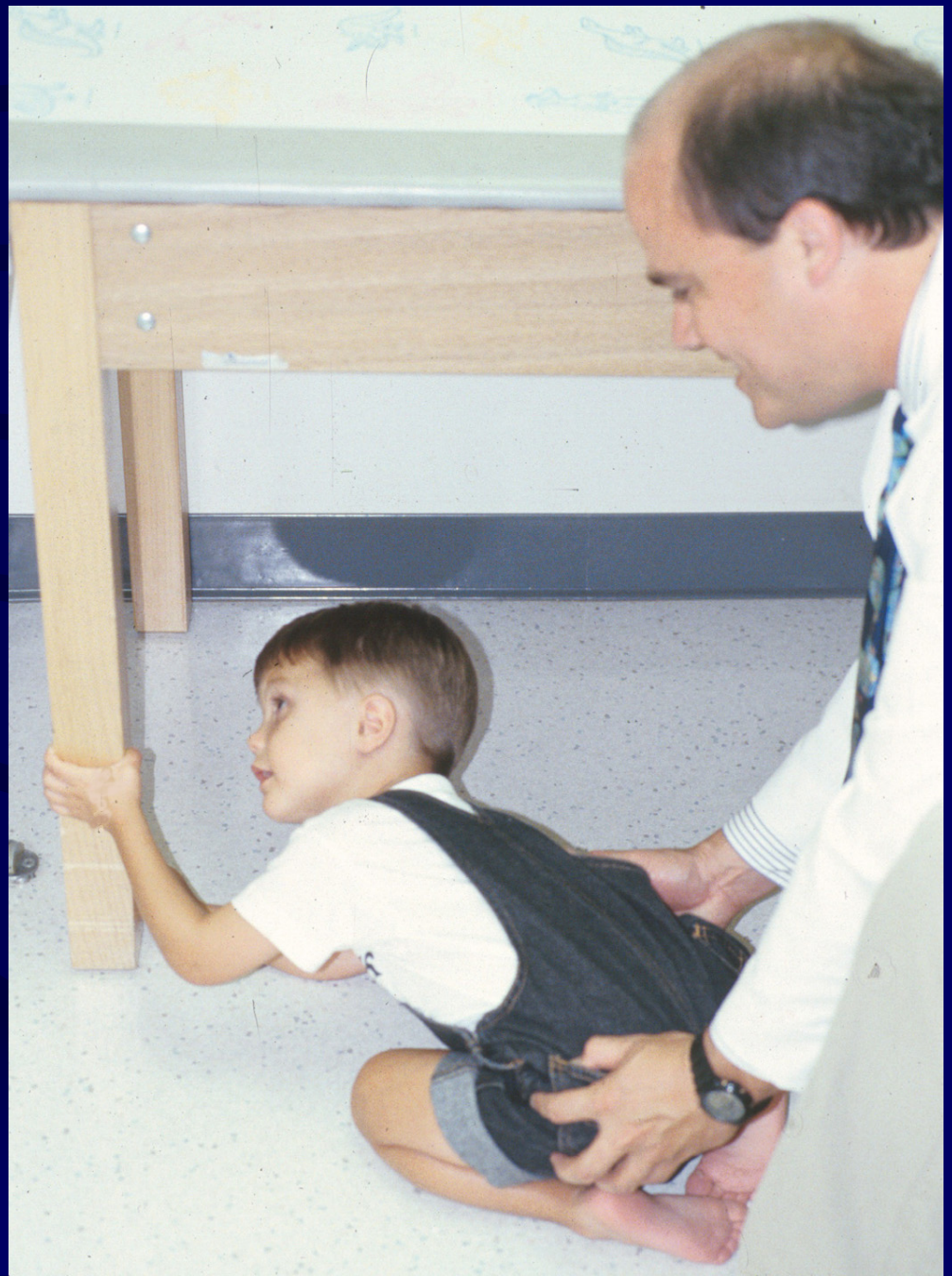
- **No fixed joint deformity present**
- **Weakening spastic limb will not further compromise residual function (including gait).**

Treating Spasticity with Botulinum Toxin

- **Effects are local and dose dependent with minimal distal effect**
- **Selected, graded weakness in injected and adjacent muscles**
- **If too much weakness, strength gradually returns**
- **Can be used in conjunction with other therapies, *e.g.* systemic medications, intrathecal baclofen pump**

Day of Injections

- Administer Versed (Midazolam)
  - dose = 0.25-1.0 mg/kg PO
  - injectable Versed orally or intranasally
  - new Versed syrup
- Effects of Versed



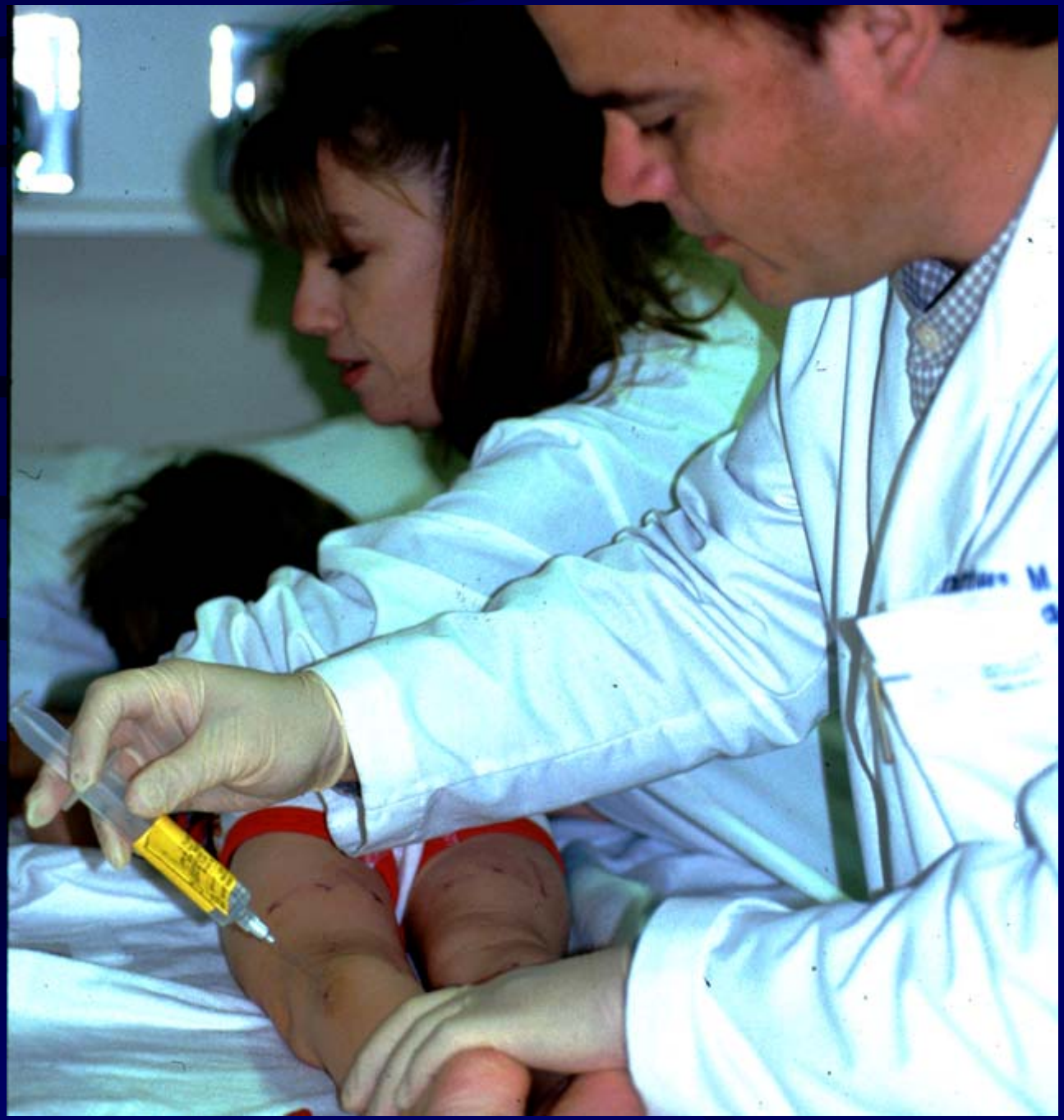

Dodgers
JETS

Day of Injections

- Order BOTOX®
  - dose = 8-12 units/kg
  - diluted in normal saline ≈ 1cc per injection site
  - may also dilute 1-2 cc/100 Unit vial

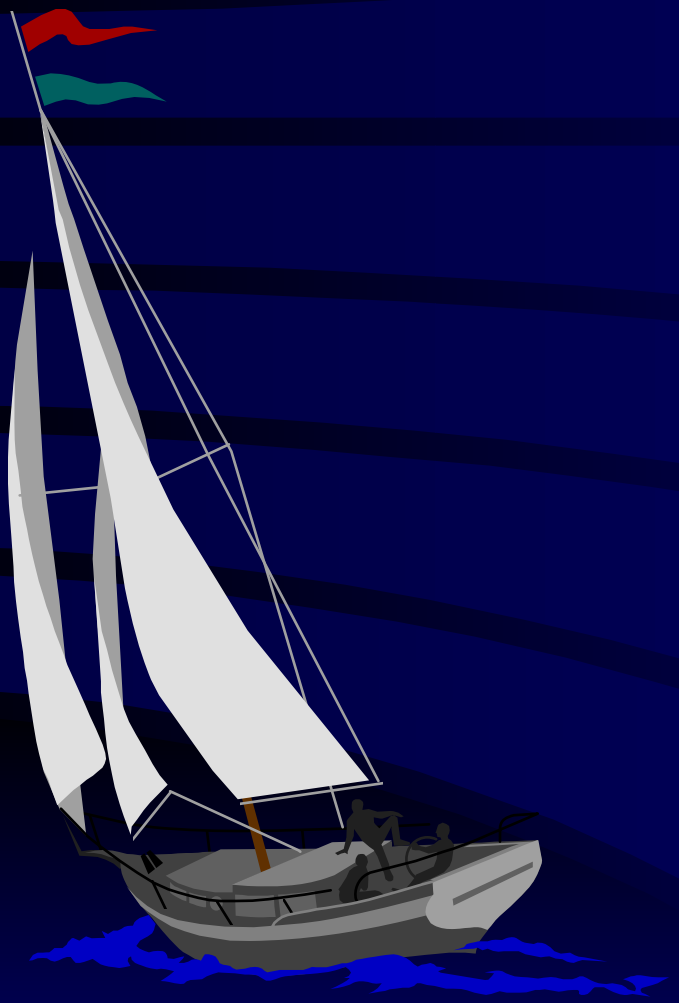
Day of Injections

- Patient to Treatment Room
- Obtain BOTOX®from Pharmacy
- Confirm dosage and sites with MD
- Attach 25g; 1-1.5” needle
- Position patient and prep sites
- Injections given by MD




Post injection serial casting

- Spasticity can be treated by:
  - Oral Medications
  - Nerve Blockade by alcohol or toxin
  - Neurosurgical techniques



Thank You