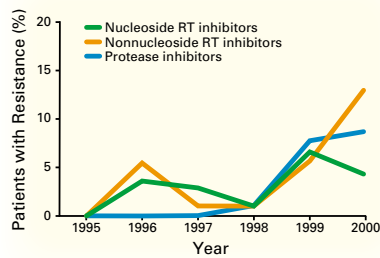




This Week in the Journal

August 8, 2002



Antiretroviral-Drug Resistance among Newly HIV-Infected Patients

In a study of 377 patients with newly acquired human immunodeficiency virus (HIV) infection in 10 cities in North America, the prevalence of antiretroviral-drug resistance increased from 3.4 percent in 1995 through 1998 to 12.4 percent in 1999 through 2000. The frequency of multidrug resistance at presentation also increased, from 1.1 percent to 6.2 percent. After initial antiretroviral therapy was administered, it took longer to achieve viral suppression in those who were infected with resistant virus, and the time to virologic failure in these patients was shorter.

The frequency of drug-resistant virus is increasing among patients with newly diagnosed HIV infections, reflecting a higher rate of transmission of resistant virus. Drug-resistance testing before treatment is now indicated even for patients who are newly infected and have never received antiretroviral therapy.

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“Botulinum toxin A had positive effects on functional disability.”

Intramuscular Injection of Botulinum Toxin for Wrist and Finger Spasticity after a Stroke

Intramuscular injection of botulinum toxin type A has been used to treat patients with spasticity after a stroke, but its efficacy remains uncertain. In this randomized, double-blind, placebo-controlled trial involving patients with spasticity after a stroke, one-time injections of botulinum toxin A into wrist and finger muscles with high flexor tone reduced muscle tone and improved functional disability over a 12-week period. There were no major adverse effects of botulinum toxin injections.

Treatment with injections of botulinum toxin A in wrist and finger muscles appears to be safe and effective in the short term, reducing disability and improving the quality of life in patients with upper-limb spasticity after a stroke.

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PERSPECTIVE

Stroke, Spasticity,
and Botulinum
Toxin

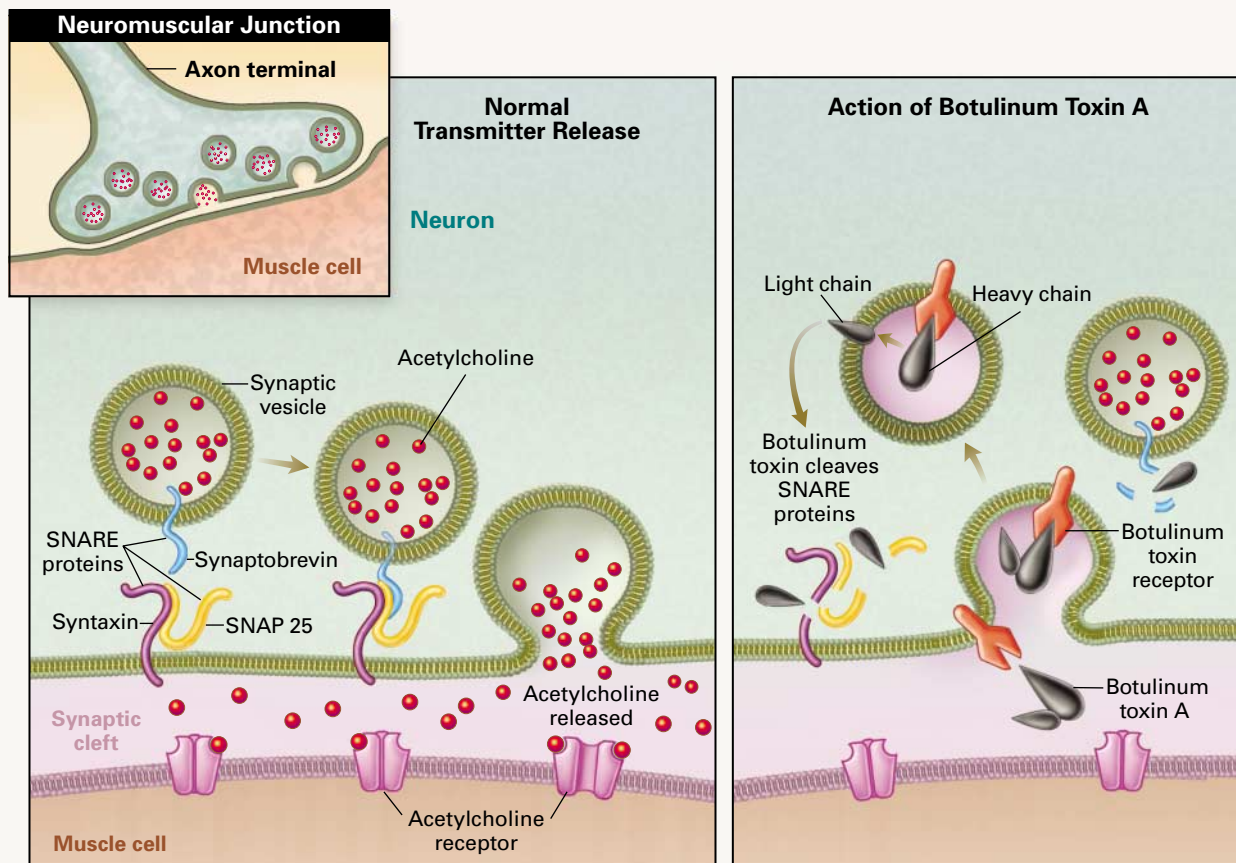
Botulinum toxin is in the news these days. First came September 11 and fears of chemical terrorism. One gram of this “most poisonous poison” could kill a million people were it not for problems of delivery. Then, in April

2002, the Food and Drug Administration (FDA) approved the use of botulinum toxin for the treatment of “frown lines” at the glabella, between and above the eyes. This cosmetic use of the toxin has already attracted the interest of countless people who want to look younger. The toxin is also used to erase “crow’s feet” — wrinkles at the lateral margin of each eye.

In this issue of the *Journal*, Brahear and colleagues (see pages 395–400) report that local intramuscular injections of botulinum toxin can ameliorate disability of the wrist and fingers after a stroke. In

a double-blind, randomized, controlled trial, subjects picked their own “principal target of treatment”: hygiene, dressing, pain, or limb posture. Six weeks after the injections, 62 percent of the subjects who received botulinum toxin reported improvement, as compared with 27 percent of those who received placebo. There were no serious adverse effects. The benefits lasted for at least 12 weeks.

Each year, approximately 750,000 Americans have a stroke. Roughly a third die, making stroke the third leading cause of death after myocardial infarction and cancer. An-



Acetylcholine in nerve terminals is packaged in vesicles. Normally, vesicle membranes fuse with those of the nerve terminals, releasing the transmitter into the synaptic cleft. The process is mediated by a series of proteins collectively called the SNARE proteins. Botulinum toxin, taken up into vesicles, cleaves the SNARE proteins, preventing assembly of the fusion complex and thus blocking the release of acetylcholine.

other third recover, and a third are disabled. Of the approximately 4 million people who have survived a stroke, many have hemiplegia and impairment of the hands.

Two questions arise. To what extent is disability caused by spasticity? Why is botulinum toxin used to treat it?

If the corticospinal tracts on one side of the brain are injured, the immediate effect is contralateral hemiparesis or hemiplegia. If the injury is mild, there may be serious loss of dexterity with only slight weakness. These are the “negative” effects of upper-motor-neuron lesions. Immediately or within days, the “positive” signs appear: overactive tendon reflexes, Hoffmann and Babinski signs, clonus, and hypertonia, or increased resistance of muscle to passive movement. Over time, the spasticity may worsen, causing fixed flexion contractures at the elbows, wrists, and fingers. These complications are the target of therapy. Spasticity is attributable to overactivity of monosynaptic muscle-stretch reflexes, hypertonia, or both.

William Landau, in *Clinical Neurophysiology and Other Arguments and Essays, Pertinent and Impertinent* (Armonk, N.Y.: Futura, 2001), argues that disability in these circumstances arises from the negative symptoms, not from spasticity. It is fruitless, he concludes, to expect functional improvement from the treatment of spasticity. Yet there is a huge literature on anti-spasticity treatments. Physical therapy is one approach. Another is the administration of baclofen or tizanidine to reduce spinal cord reflex activity. Taken by mouth, however, baclofen has limited effectiveness. Therefore, implanted pumps have been used to deliver baclofen directly to the cerebrospinal fluid. This approach is not an option for treating hand

spasticity because cervical cerebrospinal fluid is too close to the brain, which tolerates baclofen poorly. The limitations of oral drug therapy also apply to spasticity of the legs, which has been treated with intrathecal injections of phenol or surgical resection of dorsal nerve roots (rhizotomy) to diminish reflex activity. The multiplicity of treatments is ipso facto evidence that there is no optimal treatment. Moreover, although such treatments have led to improvements in measured joint angles or scales of limb mobility, it has been difficult to demonstrate functional improvement in walking or use of the hands.

Therapeutic use of botulinum toxin bypasses some of these problems. The toxin prevents acetylcholine vesicles from binding with proteins needed for fusion to surface membranes and exocytosis. This inhibitory effect reduces the number of presynaptic transmitter vesicles, impeding neuromuscular transmission and weakening the muscle (see Figure). In contrast to treatment with phenol and rhizotomy, the effects of botulinum toxin are not permanent, persisting only until new neuromuscular junctions are formed in weeks or months. And in contrast to drug therapy, which may induce sedation or somnolence, injections of toxin have only local effects.

The use of botulinum toxin to treat neurologic disease dates back to around 1970, when the toxin was used to reduce the overactivity of extraocular muscles in patients with strabismus. This approach was approved by the FDA in 1989 and rapidly replaced muscle surgery, which had previously been the standard treatment. By 1990, botulinum toxin had also been used — successfully and safely — to treat involuntary-movement disorders attributable to overactivity of local

groups of muscles, including blepharospasm, hemifacial spasm, cervical dystonia (torticollis), and writer’s cramp. These uses of the toxin were welcomed as major therapeutic advances in neurology.

In the past decade, botulinum toxin has been used to treat spasticity caused by cerebral palsy, spinal cord injury, multiple sclerosis, and stroke. Injections in leg muscles are said to help relieve bothersome muscle spasms, allow a caregiver to wash and dress the patient, and relieve pain.

The findings reported by Bra-shear et al. warrant further study because questions remain. Which patients are the best candidates for botulinum toxin? Can functional improvement be expected? Will this treatment help patients regain independence in activities of daily living? Why did so many patients have a response to placebo? The appropriate role of botulinum toxin in the management of spasticity after stroke will surely be tested in more trials to come.

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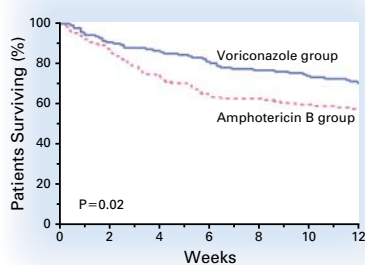
“Factors other than mutations in the CFTR gene can produce phenotypes clinically indistinguishable from nonclassic cystic fibrosis caused by CFTR dysfunction.”

Variant Cystic Fibrosis Phenotypes in the Absence of CFTR Mutations

Classic cystic fibrosis is an autosomal recessive disorder that is caused by loss-of-function mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Clinical manifestations in the airways, pancreas, male reproductive tract, and sweat glands that resemble those occurring in classic cystic fibrosis have been observed in patients with mutations that reduce, but do not eliminate, the function of *CFTR* protein. This study included 30 patients who had no identifiable *CFTR* mutations and who had some features of cystic fibrosis but did not meet a clinical definition of classic cystic fibrosis. The authors conclude that this variant phenotype derives from factors other than mutations in the *CFTR* gene.

If reproducible, these findings suggest that a syndrome with many aspects of cystic fibrosis can arise from mutations in genes other than CFTR.

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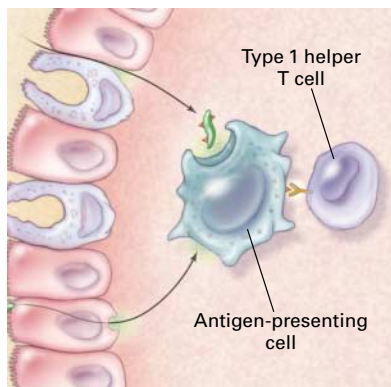


Voriconazole for Invasive Aspergillosis

Invasive aspergillosis is a major infectious complication in patients with prolonged neutropenia and in transplant recipients, and for decades, amphotericin has been the standard treatment. This randomized, unblinded trial involving 391 patients compared voriconazole with amphotericin as the initial treatment for invasive aspergillosis. Those treated with voriconazole had a significantly better response rate and improved survival at 12 weeks (70.8 percent vs. 57.9 percent, $P=0.02$).

Voriconazole represents a major advance in the treatment of invasive aspergillosis. In this randomized trial, treatment with voriconazole, a broad-spectrum triazole, led to improved survival and was better tolerated than amphotericin, with fewer severe adverse reactions.

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Medical Progress: Inflammatory Bowel Disease

Clinical experience has suggested that Crohn’s disease and ulcerative colitis constitute distinct, if not discrete, entities. However, whether these conditions are fundamentally different or are part of a mechanistic continuum is a question with both conceptual and practical implications for management. This review summarizes current understanding of the mechanisms underlying the major forms of inflammatory bowel disease and discusses approaches to therapy.

Inflammatory bowel disease is the result of inappropriate and ongoing activation of the mucosal immune system fueled by the presence of normal luminal flora. This aberrant response appears to be facilitated by defects in both the barrier function of the intestinal epithelium and the mucosal immune system.

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