A CLINICAL PREFACE

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In 1970-71 three things came together: First, strabismus surgery had reoperative rates of 40% in some categories, and we were systematically looking for alternatives. Second, we had developed electromyographic techniques and equipment to localize injections of anesthetic in human eye muscles for physiologic studies. We applied this in animals to test the effects of locally injected alcohol, enzymes, enzyme blockers, long-acting anesthetics and snake neurotoxin. Third, the chapter by Drachman in Simpson's 1971 book, *Neuropoisons*, showed that he could induce local paralysis with botulinum toxin. The idea of using botulinum toxin clinically had been floating around for several years (Bach-y-Rita, Crone, Jampolsky and Maumanee probably all had it independently), but it had seemed too wild to consider until then. Schantz supplied Drachman and nearly the whole experimental world with toxin, using at the Food Research Institute the crystalline type A technique developed by Lamanna in 1946 and later modified by Duff in 1957 at Fort Detrick. Schantz generously supplied toxin for our experiments, published in 1973, in animals (later, humans) on dosage, duration of effect, pharmaceutical methods of freeze-drying and so on. The long reluctance of FDA to issue an IND for clinical trial was overcome by the intercession of David Cogan, whose awesome reputation and logic availed, and clinical studies began in 1977. By 1982 we had injected the eye muscles for strabismus and nystagmus, the lid muscles for retraction and blepharospasm, and the limbs and neck for dystonia, as predicted in 1973. At that point safety and efficacy seemed substantial. The subsequent contributions of over 200 clinical investigators then expanded the knowledge base rapidly. The groups at Columbia University, Houston, NINCDS and Vancouver deserve special mention, and excellent work from Moorfields (London) was the basis for the Porton development.

The valuable clinical attributes of botulinum toxin are its specificity for motor nerve terminals and its long duration of action. In appropriate doses one can block most muscle groups without any other effect. The immune response problem will be overcome by more potent preparations (less protein), and other serotypes of botulinum toxin are on the way as alternatives for the few patients (less than 40) documented to produce antibodies to botulinum toxin type A.

Weakness of adjacent muscles due to drug diffusion can be reduced by protective antitoxin injection of those muscles. Prolonging clinical action is the major challenge and will be very valuable to patients. Loading the nerve terminal with a mixture of more than one

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serotype of toxin to take advantage of several types of nerve terminal receptors or of separate enzymatic effects in the nerve terminal, and conjugating the heavy chain receptor portion to other toxin molecules are some of the ways this is being approached.

Clinicians and their patients are grateful to the basic investigators and their colleagues whose work underlies the valuable addition of botulinum toxin to treatment of neurological disease. This symposium brings together these clinical and basic science groups, whose continued interdependent work should extend this beginning. We are grateful to Bibhuti DasGupta for such a success.