ent study shows that an adult-onset, degenerative neurological disorder is associated with abnormal metabolism of the major excitatory amino acid (measured as glutamate) as a result of a partial enzymatic deficiency that probably is genetically determined. These findings raise the possibility that other genetically determined, adult-onset neurological diseases causing nervous system atrophy may also be related to partial enzymatic defects.

Since the metabolic defect is systemic, impaired glutamate metabolism probably occurs in the brain, the organ that has the highest concentrations of glutamate. The susceptibility of the nervous system to abnormal glutamate metabolism may explain why only this system is affected in OPCA patients. Although glutamate does not cross the blood-brain barrier in normal adults, it seems that decreased glutamate catabolism in the nervous tissue could, over many years, cause neuronal damage. GDH is unevenly distributed in the central nervous system (*11*), and it may be associated with the pool of glutamate that is released as a neurotransmitter at the nerve endings (*12*). Decreased catabolism of glutamate at the nerve terminals could result in an increased amount of the neurotransmitter at the synapses, leading to overexcitation and neuronal degeneration.

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Bronchoconstrictor Effects of Leukotriene C in Humans

Abstract. *Maximum expiratory flow rate at 30 percent of vital capacity above residual volume served as an index of airway obstruction in comparing the effects of leukotriene C and histamine administered by aerosol to five normal persons. Leukotriene C was 600 to 9500 times more potent than histamine on a molar basis in producing an equivalent decrement in the residual volume. The leukotriene C response was slow in onset and prolonged, reminiscent of the effects of aerosol allergen challenge in asthmatic allergic subjects.*

The airway constriction that occurs in the setting of immediate hypersensitivity reactions is thought to result from the effects of chemical mediators, released or generated as a consequence of the immunological response, on airway and airspace contractile tissues. Of the mediators identified to date, histamine is an unlikely candidate as a mediator of allergic bronchoconstriction (*1*), whereas a number of lines of evidence suggest that slow reacting substance of anaphylaxis (SRS-A) may be a major cause of this effect (*2*). Recently, it has been recognized that SRS-A is comprised of three leukotriene (LT) constituents—LTC, LTD, and LTE (*3–5*)—which have been shown to be potent mediators of bronchoconstriction in vitro for tissues of humans and lower mammals and in vivo in experimental animals (*6*). In a previous study (*7*) in which LTC was administered by aerosol to two normal persons, bronchoconstrictor activity was reported but the relative potency of LTC to other constrictor stimuli such as histamine was not determined; however, the cough response of the two subjects was so marked that the authors postulated an action of LTC on upper airway irritant receptors.

Five human volunteers (four males and one female, aged 21 to 36 years) without pulmonary disease, without a history of cigarette smoking, and with normal pulmonary mechanics gave informed consent to serve as experimental subjects. At the same time of day on two separate nonconsecutive days, dose-response data were obtained from the subjects as they inhaled aerosols generated from solutions of histamine or LTC with a DeVilbiss No. 42 nebulizer, with a dosimeter set at a constant delivery time (0.8 second) and pressure (20 pounds per square inch). This nebulizer delivers particles with an aerodynamic mass median diameter of 5 μm determined by impact analysis. The subjects inhaled to ~ 60 percent of vital capacity with a 2-second breath hold at the end of inspiration for ten breaths at all concentrations of both agents. Leukotriene C was prepared by total chemical synthesis (*4*); the histamine was obtained from Sigma. Both were diluted in phosphate-buffered saline (*p*H 7.40) within 30 minutes before administration.

Maximum expiratory air flow rate at 30 percent of control vital capacity above residual volume ($\dot{V}_{30}$) was measured from partial expiratory flow-volume (PEFV) maneuvers performed in triplicate immediately before and at defined times after each aerosol inhalation. This particular index was chosen because the full inflation of the lungs required to perform a maximum flow-volume maneuver could have reversed or attenuated the expected airway responses (*8*). All studies were conducted in an integrated-flow (pressure corrected) body plethysmograph according to standard techniques. The concentration of each agent in the nebulizer (expressed in terms of the chemical base) was increased in half-log increments until a 30 percent decrease in $\dot{V}_{30}$ occurred. Flow rates were measured 5 minutes after administration of histamine and 15 minutes after administration of LTC, corresponding to the time of the peak effect as had been determined from preliminary time-response experiments.

On day 3 of the experiment, the reproducibility of the response to a given dose from the cumulative dose-response curve and the detailed time course of the LTC effect was determined. Each subject was required to inhale a dose of LTC that had resulted in a greater than 30 percent decrease in $\dot{V}_{30}$ on a previous

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Table 1. Maximal expiratory flow and density dependence before and after bronchoprovocation with maximum doses of leukotriene C (LTC) and histamine (H).

Subject	$\dot{V}_{30}$-air (liter/sec)*			$\dot{V}_{30}$-HeO_2 (liter/sec)†			Density dependence			EC30‡	
	Control	H	LTC	Control	H	LTC	Control	H	LTC	LTC (μg/ml)	H (mg/ml)
R.L.	1.5	0.9	1.0							19.7	10.0
J.D.	2.8	1.6	1.4	3.8	1.8	2.0	1.36	1.13	1.43	2.7	3.8
N.C.	2.0	1.3	1.1	3.2	2.1	1.4	1.60	1.62	1.27	0.9	1.03
P.W.	2.6	1.6	1.8	3.6	2.0	1.9	1.38	1.25	1.06	16.8	1.8
W.W.	1.9	1.4	1.2	2.5	1.5	1.4	1.31	1.07	1.17	1.2	2.0
Mean	2.16	1.36	1.30	3.28	1.85	1.68	1.41	1.27	1.23		
Standard deviation	0.53	0.29	0.32	0.57	0.26	0.32	0.13	0.25	0.16		

*Maximum expiratory flow at 30 percent vital capacity with subject breathing air. †Maximum expiratory flow at 30 percent vital capacity with subject breathing 80 percent helium and 20 percent oxygen. ‡Interpolated concentration of histamine or LTC required to achieve a 30 percent decrease in $\dot{V}_{30}$.

day of the experiment. The PEFV maneuvers were performed at 1- to 2-minute intervals for 30 minutes. Density dependence of maximum expiratory flow was measured before and after inhalation of the highest concentration of histamine and LTC by comparing flow rates with air and a mixture of 80 percent helium and 20 percent oxygen ($\dot{V}_{30}$-HeO_2) in four of the five subjects. In the experiments with helium, end tidal nitrogen was continuously monitored with a nitrogen analyzer, and the helium-oxygen curves were obtained when the end-expired nitrogen concentration was less than 8 percent, indicating mean complete replacement by the helium-oxygen mixture. Density dependence was calculated as the ratio of $\dot{V}_{30}$-HeO_2 to $\dot{V}_{30}$-air. This technique (*9*) takes advantage of the observation that flow in the central airways is turbulent and, hence, sensitive to gas density, as opposed to flow in smaller peripheral airways, where flow is laminar and independent of density.

There was no statistical difference between the $\dot{V}_{30}$ derived from the cumulative dose-response data and the data for single doses (Fig. 1A). After inhalation of LTC and histamine, all subjects experienced a sensation of chest tightness and manifested easily audible wheezes. Subjects noted no other symptoms after LTC inhalation. Cough and hoarseness developed at all concentrations of histamine with a measurable airway effect, but were absent after inhalation of LTC. The range of concentrations of LTC required to produce a 30 percent decrease in $\dot{V}_{30}$ was 2 to 20 μg/ml. In contrast, a histamine concentration of 2 to 10 mg/ml was required to produce an equivalent reduction in $\dot{V}_{30}$, indicating that the relative molar potency of LTC is 600 to 9500 times that of histamine.

The histamine effect reached a peak approximately 3 minutes after inhalation, and was of short duration, with flow rates returning to or near baseline within 10 to 15 minutes. The LTC effect (Fig. 1B) had a slow onset with significant changes occurring at 10 minutes and the peak effect near 15 minutes; significant changes in $\dot{V}_{30}$ persisted for 25 to 30 minutes after administration. The ratio of helium-oxygen flow rates to air flow rates declined significantly in three of four subjects after histamine and LTC, with a single different subject in each trial showing no change in density dependence with inhalation of either mediator. The mean density dependence decreased significantly after both histamine and LTC inhalation, but the extent of the decreases were similar for the two compounds (Table 1).

The prolonged time course of the pulmonary response to LTC inhalation (Fig. 1B) more closely reflects that observed after antigen inhalation than does the brief response observed after histamine inhalation. The pulmonary response to antigen exposure is frequently characterized by a relatively slow onset and prolonged duration of a predominantly peripheral airway effect, without noted cough or hoarseness of voice (*10*). Subjects complained of cough and hoarseness (signs of upper airway irritation) after inhaling histamine which has documented constrictor effects on the upper airways (*11*), but were free of these symptoms after inhalation of LTC.

Our findings allow an initial insight into the comparative site of airway response to histamine and LTC. When an equivalent decrement in $\dot{V}_{30}$ was obtained, upper airway signs and symptoms were conspicuously absent with LTC, consistent with a more peripheral site of action for LTC compared to histamine. However, we were not able to distinguish between the site of effect of LTC and histamine within the flow-limiting segment (probably peripheral to lobar bronchi at this lung volume) by using density dependence of maximum expiratory flow. Nonetheless, the elicitation of only minimal symptoms in the upper airway by LTC when compared to histamine at comparable and substantial decrements in flow rates is similar to the appreciable degree of asymptomatic pe-

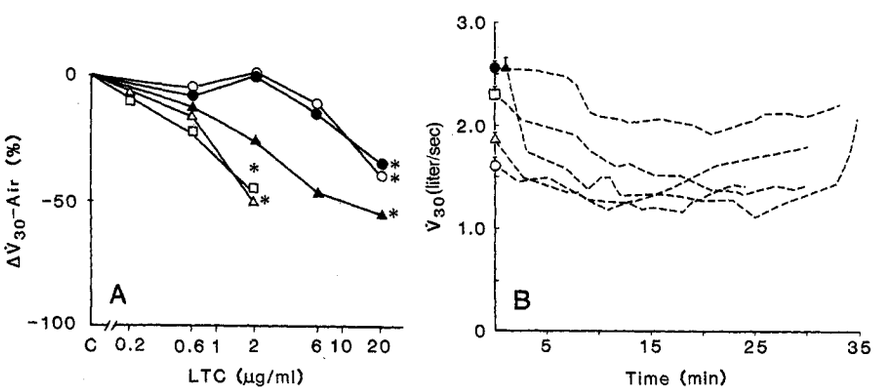

Fig. 1. Individual time courses and dose responses resulting from LTC inhalation. (A) Percentage change from control of maximum expiratory flow rate at 30 percent vital capacity ($\dot{V}_{30}$) while the subject was breathing air. Asterisks indicate the effect of repeated challenge with the highest concentration in each subject. Statistically significant changes ($P < .05$) are those greater than 20 percent for each subject. Symbols represent subjects: ●, R.L.; ○, P.W.; ▲, J.D.; □, W.W.; △, N.C. (B) Time course of response to inhalation of highest dose [shown in (A)] of LTC in each subject. Control values (± standard error of the mean) are shown on the ordinate at zero time. Symbols as in (A).

ripheral airway narrowing commonly observed in individuals with asthma (*12*). The paroxysmal cough response to LTC in two subjects (*7*) is inexplicable in view of the lack of cough in the five subjects reported here.

When prostaglandin $F_{2\alpha}$ was administered to normal subjects by means of an aerosol delivery system similar to that used in this study, a dose of 1200 μg was required to produce an 18 percent decrease in the forced expiratory volume in the first second and symptoms of cough and throat irritation; but no normal subject experienced wheezing or shortness of breath (*13*). In contrast, each of our five subjects experienced a 40 to 50 percent decrease in $\dot{V}_{30}$ and audible wheezing after exposure to less than 20 μg of LTC and were free of cough. Thus, greater potency, a slow and prolonged time-course of action, and a marked peripheral airway effect without signs of upper airway irritation, distinguish LTC from histamine and prostaglandin $F_{2\alpha}$ and are consistent with a role for LTC as a major mediator of allergic airway constriction.

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Oculoparalytic Illusion: Visual-Field Dependent Spatial Mislocalizations by Humans Partially Paralyzed with Curare

Abstract. *In darkness, observers partially paralyzed with curare make large (> 20 degrees) gaze- and dosage-dependent errors in visually localizing eye-level-horizontal and median planes, in matching the location of a sound to a light, and in pointing at a light. In illuminated, structured visual fields visual localization and pointing are accurate but errors in auditory-to-visual matches remain. Defects in extraretinal eye position information are responsible for all errors. The influence of extraretinal eye position information on visual localization is suppressed by a structured visual field but is crucial both in darkness and for intersensory localization if visual capture is prevented.*

Shifts of the image at the back of the eye are produced either by eye movements or by displacements of the visual field of view. Although displacements of the visual field are normally perceived to be displacements, in the presence of eye movements stationary visual fields continue to appear stationary. The observer's use of extraretinal eye position information (EEPI) (*1*) is somehow involved in the difference. Theoretical treatments of EEPI have been unsuccessful in accounting either for the precision and accuracy of visual localization generally or in predicting localization errors (*1*). To further examine the influence of EEPI on spatial localization we attempted to modify the normal quantitative relations between gaze direction and EEPI (whether derived from motor commands directing gaze or proprioceptive feedback from the orbit) by reversibly weakening the extraocular muscles of five adult male human observers through systemic injection of *d*-tubocurarine (*2*). This produced large errors in visual, intersensory, and sensorimotor localizations with magnitudes that systematically depend on degree of muscular weakness, direction of ocular gaze with respect to the head, and most important, the presence or absence of a structured visual field. We have called this the oculoparalytic illusion (OPI) and describe it below.

When the reclining, partially paralyzed observer (Fig. 1g) fixated a single stationary visual target (*3*) at eye level in normal illumination, the target appeared to lie at eye level as it did to unparalyzed subjects. However, as soon as all room illumination was extinguished, the partially paralyzed observer (but not the unparalyzed observer) saw the fixation target slowly descend to a position near the (invisible) floor. Normal illumination immediately restored the appearance of the target to eye level again. This sequence could be repeated as often as desired. When the fixated light was vertically positioned in darkness to a height which the observer reported to be eye-level-horizontal ("one-light experiment"), the settings (*4*) were more than 0.6 m above true horizontal—more than a 20° error at the viewing distance of 1.83 m. When the observer viewed from a position in which his head-and-body were tilted forward the effect was reduced. In a position of still greater forward tilt the light fixated at eye level appeared to ascend to a position near the (invisible) ceiling when room illumination was extinguished; vertical settings of a fixated target to

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