Feeding was observed during the day and at night (*14*). From 197 feeding observations, *Pocillopora* comprised (numerically) slightly over 85 percent of the prey. A variety of other scleractinian corals, and the hydrocoral *Millepora*, were also eaten by *Acanthaster*. Several large massive colonies of *Pavona* present along the reef base were preyed on extensively during 1970 and 1971. However, all of 22 colonies examined recently (21 September 1972) showed small areas of live coral (less than 1 percent of the surface area) which had survived. The patches of living coral were usually present in narrow depressions and fissures. Parts of large massive corals (*13*) or whole small colonies in inaccessible positions on the reef floor (*15*) also survived attack on western Pacific reefs. Such surviving colonies are probably important in reef recovery both in terms of their ability to regenerate over grazed surfaces and for eventual restocking of decimated bottom areas.

From the data presented on the abundance of living corals [6100 m^2 of *Pocillopora* (*16*)], horizontal reef growth (21.4 percent per year), and the feeding rate of *Acanthaster* (5.4 m^2 of living coral per year per individual), it is possible to make some reasonably precise predictions on the outcome of continued feeding by this predator. Figure 2 shows the projected growth trend of the Uva Island *Pocillopora* reef at three different population densities of *Acanthaster* over a 5-year period. The present population size of *Acanthaster*, comprising 36 individuals total (26 individuals per hectare), is estimated to result in the destruction of 194 m^2 of coral per year, or 3.2 percent of the reef surface standing crop. If the mortality and recruitment of corals is assumed to be in balance, it is seen that horizontal reef growth more than compensates for the coral destruction due to *Acanthaster*. This analysis also suggests that reef growth would probably not be interrupted by low plague densities of *Acanthaster* (65 individuals per hectare). However, it is predicted that reef destruction would occur rapidly at ten times the present population.

In conclusion, it is apparent that *Acanthaster* represents only one of several factors tending to limit the formation and progression of coral reefs. Further, the number of *Acanthaster* present on the majority of coral reefs investigated (*17*) would appear not to exceed the carrying capacity on the basis of the present analysis. Until more accurate data are available on the growth dynamics of coral reefs, in my opinion it would be imprudent to continue supporting the extermination of *Acanthaster*, except in those areas where it can be demonstrated to constitute a real threat to the continued existence of reefs.

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Nerve Growth Factor: Enhanced Recovery of Feeding after Hypothalamic Damage

Abstract. *A single intraventricular injection of nerve growth factor (NGF), given at the time of brain damage, facilitated the course of recovery from the lateral hypothalamic anorexic syndrome in male rats. In the second and third weeks after the trauma, NGF-treated rats ate more food, regained body weight more rapidly, and fed more vigorously in response to intraventricular administration of norepinephrine than untreated controls. After full recovery, rats that had been treated with NGF were resistant to reinstatement of the hypothalamic syndrome by 6-hydroxydopamine. NGF may facilitate behavioral recovery by promoting the development of supersensitivity to norepinephrine and possibly also by stimulating the growth of regenerating noradrenergic neurons in the brain.*

Nerve growth factor (NGF), a protein with structural similarities to insulin (*1*), is aspecific stimulator of growth and differentiation of peripheral sympathetic and sensory cells (*2*). Although the effects of NGF in the periphery have long been recognized, its action on the central nervous system has only recently been detected. Using histochemical fluorescence methods, Björklund and Stenevi (*3*) demonstrated that NGF stimulates the sprouting and growth of regenerating noradrenergic neurons in the brain. After transection of noradrenergic axons in the caudal hypothalamus by a transplant of iris tissue, a single intraventricular injection of NGF given at the time of damage led 7 days later to a striking increase in the number of newly formed sprouts in and around the transplant. It was suggested that "NGF could be used to accelerate, increase the magnitude of, or improve the final result of, regeneration of central catecholamine neurons" (*3*).

We report here for the first time evidence of the behavioral activity of NGF. This work complements the histochemical studies of Björklund and Stenevi (*3*) and provides, at the same time, some new information about the processes that may underlie the recovery of function after brain damage.

Our experiments were concerned specifically with the recovery of feeding after hypothalamic damage. Feeding may be abolished for several weeks by mechanical or electrolytic destruction of the lateral hypothalamus on both sides (*4*). However, if death is prevented by forced feedings and appro-

priate nursing care, feeding gradually recovers even if most of the neurons in the lateral hypothalamus are apparently destroyed (*5*).

We have been able to temporarily reverse the lateral hypothalamic anorexic syndrome by administration of norepinephrine in the lateral ventricle (*6*). The immediacy and strength of the reversal, taken together with earlier evidence that noradrenergic neurons play an important role in the regulation of feeding (*7*), strongly suggested that the anorexic syndrome may be attributed at least in part to a deficit in noradrenergic function; the deficit arises, presumably, from the damage to ascending noradrenergic pathways in the lateral hypothalamus (*8*). We also observed that the reversal of the lateral hypothalamic syndrome by norepinephrine followed a definite time course. For the first several days after the placement of large lesions, norepinephrine failed to induce feeding. During the second and third week, however, at about the time that some spontaneous feeding is observed, total recovery of normal intake and even overeating could be induced by a single 10-μg dose of norepinephrine. This time course coincides with that observed in studies of the regenerative sprouting of catecholamine neurons after axonal transection (*9*), and it also coincides with the time course of development of denervation or disuse supersensitivity (*10*). It therefore seems plausible to suggest that at least two mechanisms, the development of supersensitivity to norepinephrine (*11*) and the regeneration of damaged noradrenergic neurons, may be involved in the recovery of feeding after hypothalamic damage.

To test these ideas, we attempted to facilitate the recovery process by administration of NGF, an agent that stimulates regeneration of noradrenergic neurons in the central nervous system. Twenty-five male rats, weighing 400 to 500 g, were housed in separate cages and observed until their normal daily intakes of Purina Lab Chow (27.2 $\pm$ 0.9 g) and water (51.1 $\pm$ 2.8 ml) were established. All rats then received lesions in the lateral hypothalamus on both sides by a direct anodal current of 2 ma for 10 seconds; at the same time, a cannula for intraventricular injections was permanently implanted in the lateral ventricle (*12*). Immediately after the implantation, 13 control rats received an intraventricular injection of Ringer-Locke solution (20 μl), and 12 experimental rats received NGF (4 μg of the 2.5*S* or β subunit of NGF dissolved in 20 μl of Ringer-Locke solution). A highly purified sample of lyophilized, salt-free NGF prepared from mouse submaxillary gland was provided by W. A. Frazier and R. A. Bradshaw of the Washington University School of Medicine (*1*).

Table 1. Facilitating action of norepinephrine on the intake of sweetened milk. Numbers indicate mean intake (milliliters) $\pm$ S.E.M. in a 45-minute test. Indicated substances as hydrochloride salts were dissolved in 10 μl of Ringer-Locke solution and injected in the lateral ventrical immediately before the test. Not significant, n.s.

Treatment group	Rats (*N*)	Milk intake (ml)				
		Day 14: no injection	Day 15: *l*-norepinephrine (10 μg)	Day 16: no injection	Day 17: dopamine (10 μg)	Day 20: Ringer-Locke (10 μl)
Nerve growth factor	12	10.1 $\pm$ 3.2	36.2 $\pm$ 4.8	14.5 $\pm$ 2.9	22.9 $\pm$ 2.8	23.7 $\pm$ 3.3
Ringer-Locke solution	13	9.2 $\pm$ 2.2	19.2 $\pm$ 4.5	10.4 $\pm$ 2.9	15.9 $\pm$ 3.1	14.5 $\pm$ 3.0
		n.s.	$P < .01$	n.s.	n.s.	$P < .05$

Feeding and drinking were virtually abolished in nearly all cases for the first 4 days after the trauma, and body weights dropped precipitously (Fig. 1A). During this initial phase, NGF appeared to retard feeding and to accelerate weight loss. On day 4, for example, no rat that had received NGF had yet started to feed spontaneously, whereas 3 of the 13 controls had. By the end of the first week, however, these small differences had disappeared and food intake, weight loss, and the number of spontaneous feeders in the two groups were almost identical.

In accordance with the histochemical results of Björklund and Stenevi (*3*), significant effects of NGF emerged between the second and third weeks. Between day 7 and day 14, the rats treated with NGF had a mean weight gain of 27.6 $\pm$ 12.0 g, whereas the control rats suffered a mean weight loss of 6.4 $\pm$ 14.8 g ($P < .05$, single-tailed test; the large standard errors probably are due mainly to individual variation in lesion damage and capacity for recovery). Over the same period, the mean daily food intake of the NGF-treated rats increased by 16.6 $\pm$ 3.6 g, while that of the controls increased only by 6.8 $\pm$ 4.3 g ($P < .05$, single-tailed test). On days 8 and 9, all rats were given access overnight to milk (1 part Borden's sweetened condensed milk and 2 parts water). The introduction of this highly palatable liquid food on day 8 stimulated strong feeding in many

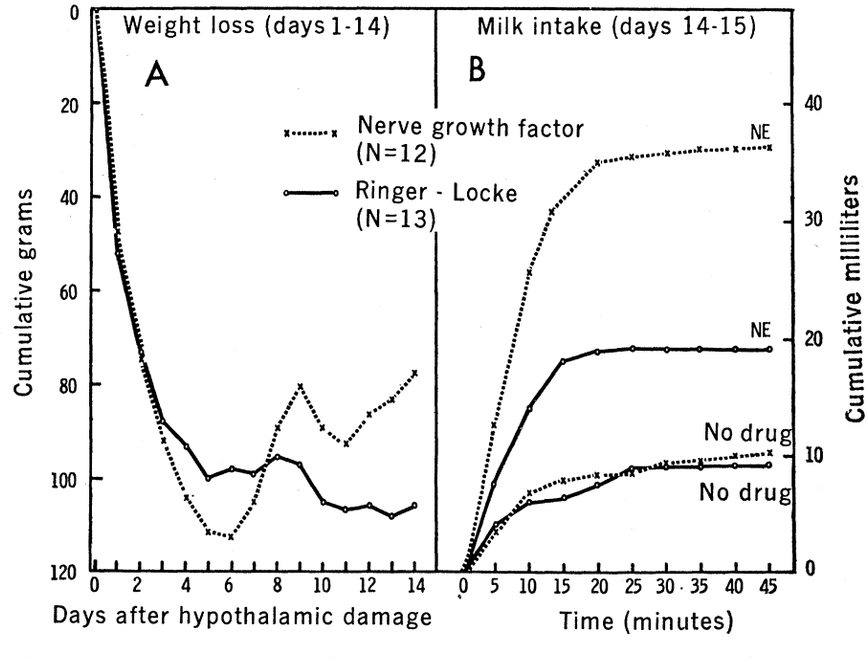

Fig. 1. (A) Cumulative loss of body weight after lateral hypothalamic lesions. Access to sweetened milk was allowed overnight before days 8 and 9. (B) Intake of sweetened milk in 45-minute tests immediately after an intraventricular injection of 10 μg of *l*-norepinephrine hydrochloride (*NE*) or no treatment (*No drug*). Curves are plots of cumulative intake in successive 5-minute periods.

rats, but the effect was more pronounced in those treated with NGF; 10 of the 12 rats in the NGF group, but only 5 of the 13 controls, consumed 20 ml or more. The mean intake of milk (milliliters) in the two tests was as follows: day 8, NGF 55.6 ± 9.2 compared to control 29.7 ± 10.6, $P < .05$, Mann-Whitney U test; day 9, NGF 66.9 ± 6.7 compared to control 53.2 ± 11.6, not significant.

During the third week of recovery, responsivity to exogenous norepinephrine was assessed in a 45-minute milk-intake test. Consistent with (*6*), intraventricular administration of 10 μg of *l*-norepinephrine increased the intake of milk in rats recovering from hypothalamic damage. In the group treated with NGF, however, the effect of norepinephrine was potentiated; the experimental rats fed voraciously and consumed, on the average, almost twice as much milk as the controls (Fig. 1B and Table 1). Neurochemical specificity is suggested by the observation that dopamine had no greater effect than a control injection of Ringer-Locke solution in either group.

In experiment 2, six additional rats received NGF and five controls received Ringer-Locke solution immediately before hypothalamic damage. Bilateral lesions were placed in all rats as in the first experiment, but 1.5 mm more dorsally. As a result, no rat in the control group failed to eat or drink even on the first day after the trauma; on this day, the mean intakes of food and water were 49.3 and 84.6 percent, respectively, of the levels prior to the operation. In contrast, the animals treated with NGF were severely anorexic (mean intake of food in grams: NGF 3.7 ± 1.4 compared to control 13.4 ± 2.7, $P < .01$) but only moderately adipsic (mean intake of water in milliliters: NGF 24.7 ± 6.3 compared to control 39.6 ± 6.9, not significant). A smaller, but still substantial, anorexic effect of NGF was observed on the second day; no significant effects on food or water intake were noted on subsequent days. Thus, in two experiments, NGF selectively blocked feeding for at least 2 days after intraventricular administration at the dosage studied. Although other explanations are possible, this observation suggests that NGF may specifically interfere with noradrenergic activity in the feeding system (and elsewhere) in the initial phase of its action.

In experiment 3, we attempted to reinstate the lateral hypothalamic syndrome in rats that had recovered from the effects of the lesions by administration of 6-hydroxydopamine, a specific toxin of catecholamine neurons (*13, 14*). The 11 rats used in experiment 2 and 8 additional rats that received lesions as in experiment 1 (3 treated at the time of lesion placement with NGF and 5 with Ringer-Locke solution) were challenged 2 months after surgery with an intraventricular injection of 6-hydroxydopamine hydrochloride (25 μg dissolved in 10 μl of Ringer-Locke solution containing 0.1 percent ascorbic acid). This dose of 6-hydroxydopamine produces a selective depletion of brain norepinephrine in rats with no lesions (*14*). On the day before the injection of 6-hydroxydopamine, the intake of food and water was similar in the two groups (*15*). On the day after the injection, individual food and water scores were reduced in all cases, but the reductions were significantly greater in magnitude in the control group than in the group that had been treated with NGF. (Mean intake of Purina Lab Chow in grams: all rats, NGF 16.8 ± 3.2 compared to control 8.6 ± 1.9, $P < .025$; rats from experiment 2 only, NGF 19.0 ± 4.1 compared to control 9.6 ± 1.4, $P < .05$, single-tailed test; mean intake of water in milliliters: all rats, NGF 29.1 ± 3.9 compared to control 16.4 ± 2.6, $P < .01$; rats from experiment 2 only, NGF 33.0 ± 3.9 compared to control 20.2 ± 3.6, $P < .05$.)

The above results show that a single administration of NGF facilitates the recovery of feeding after lateral hypothalamic damage, enhances the feeding response to norepinephrine, and confers long-term protection against reinstatement of the lateral hypothalamic syndrome by 6-hydroxydopamine. These effects of NGF on behavior may be mediated by more than one mechanism. On the one hand, it is conceivable from the histochemical work (*3*), and from the early studies on peripheral noradrenergic cells (*2*), that NGF may stimulate the regeneration of reversibly damaged neurons in the noradrenergic feeding system. Apart from our behavioral findings, however, there is no evidence that such regeneration leads to functional synaptic connections. On the other hand, the observation of increased responsivity to norepinephrine and decreased responsivity to 6-hydroxydopamine in NGF-treated rats suggests that NGF may promote supersensitivity to norepinephrine. In this regard, the possibility that NGF impairs noradrenergic function on a short-term basis is pertinent, because other agents that antagonize or deplete norepinephrine also induce supersensitivity (*10*). Whether or not the action of NGF involves both supersensitivity and new growth, and whether or not these processes are functionally interrelated, is purely a matter of conjecture at this point. Nevertheless, we may speculate on teleological grounds that supersensitivity to norepinephrine permits the receptive cell to function on a temporary basis with a minimum noradrenergic input until the regeneration of permanent new connections is completed.

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