in areas away from the demyelinated foci. In some of the more actively remyelinating areas, more than 50 percent of the oligodendroglia were labeled. In control animals, labeled endothelial cells and astrocytes were rarely seen, and no labeled cells that could be unequivocally identified as oligodendroglia were seen.

These results demonstrate that cells of the oligodendroglial line can incorporate [^{3}H]thymidine during recovery from virus-induced demyelination. It is unlikely that virus infection directly stimulated nuclear incorporation of thymidine, because this RNA corona virus lacks an RNA-dependent DNA polymerase (*14*). It could be argued that [^{3}H]thymidine incorporation resulted from DNA repair. However, in experimental models in which repair was stimulated by ultraviolet irradiation, thymidine incorporation was limited even after large doses of [^{3}H]thymidine (*15*). In these experiments, the label over nuclei was moderately heavy, which indicates that the labeled oligodendroglia had passed through the synthesis (S) phase of the cell cycle during the period of [^{3}H]-thymidine administration (*11*).

Although hyperplasia of oligodendroglia has been described in both human and experimental tissues (*16*), identifying the proliferating cell populations has proved difficult. In two previous autoradiographic studies (*17*), labeled cells were interpreted to be oligodendroglia; in neither report are the identities of the proliferating cells definitively established. In developing optic nerve of the rat, oligodendroblasts are the major source of oligodendrocytes during myelinogenesis (*7*). Our cumulative labeling technique (*10*) does not allow us to identify the cells giving rise to newly formed oligodendroglia. However, in animals killed 1 hour after a pulse label of [^{3}H]thymidine (*7*), glial cells synthesizing DNA can be identified before they have had time to differentiate. This approach can be used to study the kinetics of oligodendoglial proliferation in several models of demyelinating disease and to evaluate the use of pharmacologic manipulation of proliferation.

Reappearance of oligodendroglia associated with remyelination has been described in vitro (*5*) but not well documented in vivo. Explant cultures treated with antiserums from animals with experimental allergic encephalomyelitis became demyelinated and lost oligodendroglia; withdrawal of the antiserums was associated with remyelination and reappearance of oligodendroglia (*6*). This in vivo study demonstrates regeneration of oligodendrocytes to replace those destroyed by the viral infection. Thus, in this model cell, proliferation appears to be essential to replace destroyed oligodendroglia and to permit successful remyelination in the CNS.

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Behavioral Control of Workers by Queens in Primitively Eusocial Bees

Abstract. *Queens of* Lasioglossum zephyrum, *a primitively eusocial bee, are considerably more active than workers. The queen's behavior stimulates worker activities; removal of the queen results in a marked reduction in activities of other bees. The queen not only activates workers but also directs them by a primitive recruitment behavior suggestive of tandem running of highly eusocial ants.*

Evolution of insect eusociality, in which members of a colony (workers) relinquish all or a portion of their individual fitness to assist another colony member (the queen), has attracted considerable interest (*1*). Two major areas of inquiry are (i) the consistency of apparent worker altruism with the principles of natural selection and (ii) the evolution of social integrating mechanisms. The former problem has received most of the attention while the latter remains relatively unexplored (*2*). The present report attempts to elucidate early steps toward eusociality by considering social integrating mechanisms in an incipiently eusocial species.

Table 1. Queen direction of pollen deposition by workers.

Returns	Number	Percent
Returns from foraging trips with queen leading forager to cell entrance	27	64.3
Returns from foraging trips with queen positioned at cell entrance	10	23.8
No queen involvement in pollen deposition	5	11.9
Total returns to nests	42	100.0

Solitary bees and wasps that provision nests commonly display an invarying sequence of cell construction, provisioning, egg laying, and closure, followed by a repetition of the pattern. Although some solitary species can omit parts of the sequence, it is in the social species that workers possess a large degree of behavioral plasticity. Workers of highly eusocial insects are able to engage in a variety of activities regardless of their sequence and apparently without direction from the queen (*2*). Social facilitation among workers is well documented; trail

and alarm pheromones, communicative dances, and so forth are characteristic of workers in many eusocial insects. In highly eusocial species the queen plays a behaviorally passive role—laying eggs and, in some cases, secreting pheromones which inhibit queenlike behavior in workers. The evolution of relatively unprogrammed workers from their programmed predecessors most likely involves breaking their behavioral repertoire into small, independently executable units.

It is most appropriate to study the evolution of social integration in a primitively eusocial insect such as *Lasioglossum zephyrum*, a small halictid bee that nests in river banks (*3*). A colony generally contains 6 to 20 members during midsummer with castes that intergrade both physically and behaviorally. The bee with the largest ovaries is the primary egg layer and can be designated the queen. Other bees in the nest have smaller ovaries and are less likely to lay eggs. Usually a small number of these workers specialize in pollen collecting; this is one of the most specialized tasks carried out by workers (*4, 5*).

Michener and Brothers (*4*) have hypothesized that the queen's increased general activity and part of her specific behavior might play a role in integrating the colony in *L. zephyrum*. This hypothesis is supported by our investigations; in fact, the queen plays an even larger role than previously thought. The queen appears to disrupt programmed behavioral sequences by restricting certain acts of workers (for example, laying eggs) and actively stimulating other portions of the sequence (for example, pollen collecting).

Brothers and Michener (*5*) found that queens exhibit complexes of activities that differ from those of workers. One characteristic queen behavior is backing away from a worker after meeting it in the tunnel. This stimulates the worker to follow and may be, in part, a dominant-submissive interaction such as occurs in many primitively eusocial insects (*2*).

Our observations indicate that backing and following behavior occurs in several contexts, but commonly takes place when a foraging bee enters the nest carrying a pollen load. A pollen-laden forager is normally met after entering the nest by the queen who then backs down the nest tunnel to the cell being provisioned or backs and then turns and runs to the cell (often a distance of 15 to 25 cm) (Fig. 1). The queen stops just below the entrance of the cell being provisioned and the forager enters that cell and deposits her pollen. Occasionally the queen does not meet the forager but rather positions herself at the entrance of the cell to be provisioned (Fig. 2).

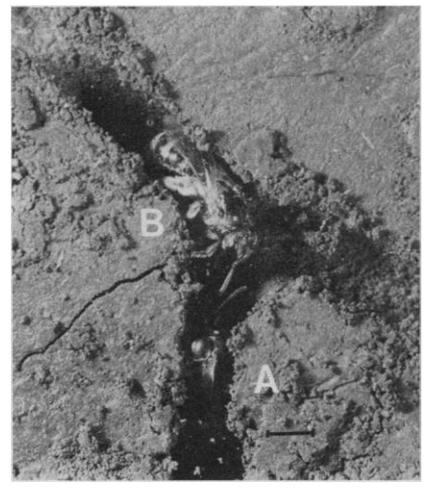

Fig. 1. Queen (A) backing and forager (B) following. Scale bar, 2 mm.

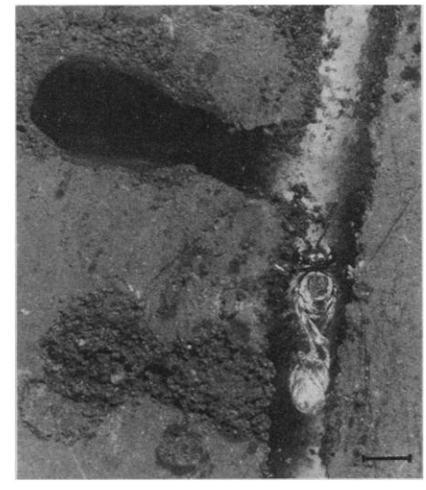

Fig. 2. Queen positioned at entrance to cell. Scale bar, 2 mm.

In 42 observations of ten different colonies, 88.1 percent of arriving pollen-laden foragers were either preceded by the queen to the cell or the queen positioned herself immediately below the cell entrance before the return of the forager (Table 1). In four of the 42 observations, the forager lost physical contact with the backing queen and moved into an incorrect branch burrow (one containing no open cells); the queen reinitiated contact with the worker, which then followed the queen to the correct cell. Four times a part of the nest was disturbed while the worker was foraging, and the queen was diverted and repaired the damage. This resulted in disorientation of the returning bee; one pollen-laden bee spent 8 minutes wandering through the nest before encountering the queen and depositing the pollen in the correct cell. In two other cases the queen was removed from the nest and again the returning forager was unable to locate the cell. Bees unable to locate a cell often deposit their pollen in the burrow (*5*).

The queen, therefore, has a direct behavioral involvement in coordinating this aspect of worker behavior. If the queen is prevented from acting, the worker is unable to carry out the appropriate behavior.

In addition to "directing" certain specific activities, the queen appears to have a general activating effect on the other bees in the nest. In a series of experiments colony activity was recorded, the queen was then removed, and the activity was again measured (Table 2). In some nests replacement queens (former workers that now display typical queen behaviors) were behaviorally recognizable almost immediately; in these colonies activity usually increased slightly when the replacement queen began interacting with the other individuals. In nests where no replacement queen was

Table 2. Activity counts per minute per bee before and after removing the queen. Nests are grouped into those which had a replacement queen before observation terminated and those which did not. Observations were conducted continuously on the day the queen was removed. Minutes of observation are indicated in parentheses. Activity was evaluated by counting the number of bee interactions. Activity counts were adjusted by dividing them by the number of bees in the nest at the time of observation.

Queen replaced				Queen not replaced			
Nest	Bees (No.)	Activity before queen removal	Activity after queen removal	Nest	Bees (No.)	Activity before queen removal	Activity after queen removal
A	5	0.46 (90)	0.52 (60)	F	5	0.27 (30)	0.02 (15)
B	7	.35 (120)	.41 (120)	G	4	.21 (90)	.11 (99)
C	4	.35 (60)	.47 (90)	H	4	.54 (60)	.24 (90)
D	5	.70 (60)	.63 (40)	I	5	.27 (30)	.09 (60)
E	5	.29 (60)	.34 (36)	J	5	.27 (43)	.06 (30)
				K	5	.30 (45)	.13 (120)
Means		.43	.48			.31	.11

evident, activity declined within 30 minutes and remained at a low level; this reduction in activity was significant at the .001 level (paired comparisons analysis of variance). The lowered activity of workers after queen removal indicates that they had been stimulated by her.

While guiding and stimulating of workers by the queen in *L. zephyrum* may suggest that the queen is manipulating other colony members to increase her individual fitness, the gains in inclusive fitness (individual fitness plus influence on fitness of relatives) by the worker that accepts or is subjected to manipulation are unknown. Further research will be required to determine if *L. zephyrum* workers are engaged in a mutualistic association with other colony members, are increasing their inclusive fitnesses by helping the queen raise highly related sisters, or if they are, indeed, oppressed by the queen.

In this report we present evidence for direct behavioral communication from the queen to the workers in colonies of primitively eusocial bees. Such behavior is similar to tandem running of primitive ants (*6*); it is interesting that direct communication among individuals should be important in less advanced forms in such diverse taxa. Perhaps in the initial stages of social evolution as exemplified by *L. zephyrum*, the queen plays an active role in altering patterned behavioral sequences of workers. She may then direct these behaviors as well as influence the general level of colony activity. While this form of behavioral integration may function relatively efficiently in small colonies where the queen can maintain contact with her few workers, in large, highly eusocial colonies the ability of the queen to participate directly in the activities of each worker is limited. This limitation sets the stage for the evolution of integration mechanisms that reduce the behavioral role of the queen and emphasize pheromonal and worker-worker behavioral communication.

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Acute Systemic Effects of Cocaine in Man: A Controlled Study by Intranasal and Intravenous Routes

Abstract. *Nineteen healthy volunteer subjects who regularly administered cocaine to themselves were given placebo and 10 and 25 milligrams of cocaine hydrochloride intravenously and intranasally. A dose of 100 milligrams of cocaine was administered only by the intranasal route. By this route 10 milligrams of cocaine produced no changes different from placebo, and 25 milligrams of cocaine produced physiologic changes only in systolic blood pressure. The 100-milligram dose given intranasally and all of the doses given intravenously produced significant dose-related physiologic and subjective responses.*

We report dose-response and time-course curves for physiologic and subjective effects of cocaine in man. Despite the widespread medical and increasing nonmedical use of cocaine (*1*), there have been no controlled studies of its systemic effects (*2*, *3*). Since cocaine acts systemically as a sympathomimetic (*4*), we measured heart rate, blood pressure, respiratory rate, body temperature, and handgrip strength. We assessed subjective effects by ratings of "high," pleasantness, speeding, hunger, strength, and number of statements rated true on a 36-item Addiction Research Center (ARC) Inventory for acute amphetamine effects (*5*).

Nineteen volunteers between 21 and 42 years of age, who had a history of frequent and regular use of cocaine during the preceding 6 months and had taken no drugs or alcohol for at least 24 hours, participated in the study. All volunteers were free of any illness at the time of the experiment and had no medical history of a condition that contraindicated use of cocaine.

We employed a repeated measures design in which each subject served as his own control. Each subject was given placebo and 10 and 25 mg of cocaine by intranasal or intravenous routes under single- or double-blind conditions (*6*); five subjects received these doses by both routes of administration. The order in which the doses were administered was counterbalanced across subjects. Five of the subjects were also given 100 mg intranasally.

A solution of 0.5 ml of cocaine in bacteriostatic water was instilled into the nostrils, or 1.5 ml was injected intravenously over 90 seconds. The 100-mg intranasal dose was given once by drops and once by flakes (mixed with lactose powder). The flakes were inhaled through a straw. Intravenous placebo consisted of 1.5 ml of bacteriostatic water; intranasal placebo was 0.5 ml of 1 percent lidocaine solution or 5 mg of tetracaine powder mixed with lactose powder. These synthetic local anesthetics mimic cocaine's local effects on the nasopharyngeal mucosa without producing systemic effects.

Heart rate and blood pressure dose-response curves are shown in Fig. 1. The peak changes after cocaine are compared to those after placebo. By the intranasal route, 10 mg of cocaine produced no change different from that produced by placebo, 25 mg produced minimal changes in systolic blood pressure only ($P < .02$), and 100 mg produced significant ($P < .01$) changes in heart rate and in systolic and diastolic blood pressures. The mean magnitude of changes after insufflating cocaine flakes was greater than after instilling the cocaine solution. By the intravenous route, all doses produced significant ($P < .01$) changes in heart rate and systolic blood pressure (*7*). The 5-mm increase in diastolic pressure following intravenous cocaine (10 mg) was not significant.

The onset of these effects (Fig. 2) occurred within 2 minutes of cocaine administration and peaked within 5 to 10 minutes when given intravenously and within 15 to 20 minutes when given intranasally. At the higher doses the effects persisted beyond 30 minutes. The time