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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18 October 1976

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

course is apparently not related to levels of cocaine in plasma (*8*). There were no significant changes in respiratory rate, body temperature, or handgrip strength at any of the doses.

Subjective effects of 10 mg of cocaine given intranasally were no different from those of placebo. Following 25 mg intranasally, significant changes were observed on the scales of "high" ($P < .02$), pleasantness ($P < .05$), and the ARC Inventory ($P < .02$). The 100-mg intranasal dose and both intravenous doses produced significant ($P < .01$) dose-related changes on all subjective scales except strength. The time course for subjective effects of "high," pleasantness, and hunger are shown in Fig. 2.

There is a direct relation between physiologic and subjective effects. This relation, however, was not consistent for all subjects. For example, more experienced cocaine users rated subjective effects lower than others who had equally large physiologic changes.

After the 25-mg intravenous dose, one subject had a marked affective response (crying) together with a strong "high." We later learned that this individual entered the experimental session feeling depressed. The dysphoric reaction of this subject to cocaine is consistent with a report on the effects of cocaine in depressed patients (*2*).

Each of the 36 true/false items on the ARC Inventory discriminated between placebo and cocaine. The four items that were most frequently rated "true" following cocaine were: (i) I feel as if something pleasant had just happened to me, (ii) I am in the mood to talk about the feeling I have, (iii) a thrill has gone through me one or more times since I started the test, and (iv) I feel like joking with someone. The nine items that best discriminated (*9*) between doses and routes of administration were: (i) I have a pleasant feeling in my stomach, (ii) my thoughts come more easily than usual, (iii) I feel less discouraged than usual, (iv) my memory seems sharper to me than usual, (v) I fear that I will lose the contentment that I have now, (vi) I have a weird feeling, (vii) right now I feel as if all my needs are satisfied, (viii) I feel an increasing awareness of bodily sensations, and (ix) I have a floating feeling. The most frequent spontaneous report of subjects was, "I feel more relaxed." This response is surprising in light of the amphetamine-like properties of the drug. These ten items provide a scale which may be used to assess subjective effects of cocaine.

A biphasic effect from cocaine consisting of an initial euphoria followed by

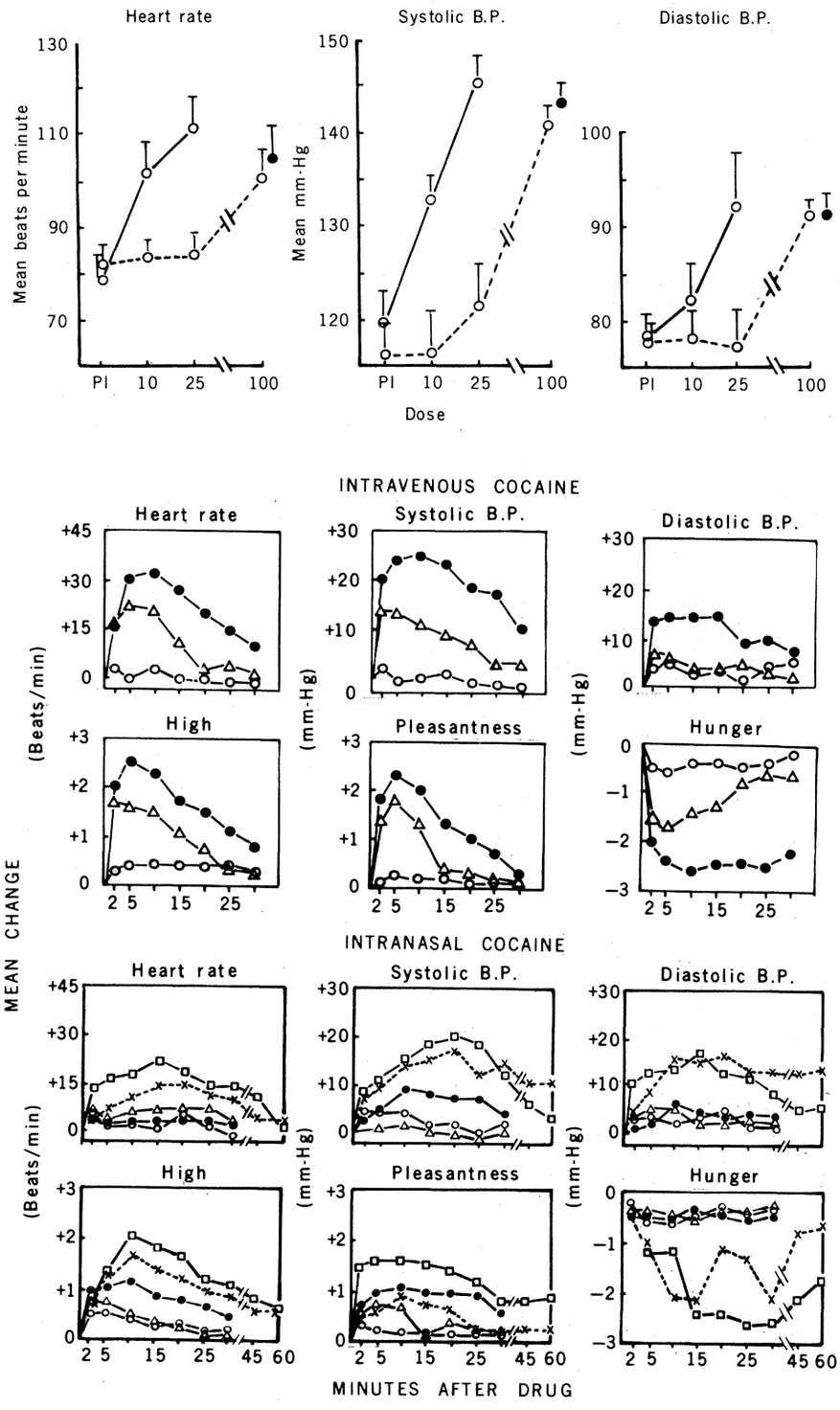

Fig. 1 (top). Dose-response curves for the effects on heart rate, systolic blood pressure, and diastolic blood pressure of placebo (*Pl*), 10 mg (10) and 25 mg of cocaine (25) administered intravenously and intranasally, and 100 mg (100) administered intranasally by drops and by flakes. Each point represents the mean of the peak changes after drug administration for 12 subjects, except points for the 100-mg dose, for which five subjects were tested. Vertical bars indicate the standard error of the mean. *B.P.*, blood pressure; ○——○, intravenous; ○----○, intranasal drops; and ●, intranasal flakes. Fig. 2 (bottom). Time-course curves over a 30-minute observation period for physiologic and subjective effects of placebo, 10 mg and 25 mg of cocaine administered intravenously and intranasally, and 100 mg administered intranasally by drops and by flakes. Each point represents the mean of 12 subjects, except for the 100-mg intranasal doses where each point represents the mean of five subjects. ○——○, Placebo; △——△, 10 mg of cocaine; ●——●, 25 mg of cocaine; x----x, 100 mg of cocaine drops; and □——□, 100 mg of cocaine flakes.

dysphoric effects was reported by four subjects 20 to 30 minutes after the 25-mg intravenous dose, and by two subjects 45 to 60 minutes after the 100-mg intranasal dose. This dysphoria, referred to as "post-coke blues" or "crashing," was characterized by feelings of anxiety, depression, fatigue, and wanting more cocaine.

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1. Accurate estimates of nonmedical use of cocaine are very difficult to obtain. In a 1971 survey of 56,745 students in the 7th through 12th grades in Dallas, Texas, 2108 or 4 percent reported having used cocaine, with 1250 acknowledging that they had used it at least one time during the week the questionnaire was given [J. T. Gossett, J. M. Lewis, V. A. Phillips, *J. Am. Med. Assoc.* **216**, 1464 (1971)]. In 1973 the National Commission on Marihuana and Drug Abuse estimated that nationwide use of cocaine was 3.2 percent for adults and 1.5 percent for youth. A recent national survey estimates that cocaine use among youths 12 to 17 years old doubled between 1972 and 1974 [H. I. Abelson and R. B. Atkinson, *Public Experience with Psychoactive Substances: A Nationwide Study Among Adults and Youth* (Response Analysis Corporation, Princeton, N.J., August 1975)]. A nationwide study in 1974 of a representative sample of men aged 20 to 30 years found that 12 percent of those who live in cities with populations of a million or more reported using cocaine within the preceding year [J. A. O'Donnel, H. L. Voss, R. B. Clayton, G. T. Slatin, R. G. W. Room, *Young Men and Drugs—A Nationwide Survey* (NIDA Research Monograph 5, National Institute on Drug Abuse, Rockville, Md., 1976)].
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6. The initial four subjects were run under single-blind and the remainder under double-blind conditions.
7. The largest effects for an individual subject were as follows. At a dose of 10 mg, one subject's heart rate increased from 70 to 135 beats per minute and another subject's blood pressure rose from 114/68 to 142/116 mm-Hg. At 25 mg, one subject's heart rate rose from 66 to 156 beats per minute and another's blood pressure increased from 114/78 to 176/140 mm-Hg.
8. Plasma levels of cocaine appear to reach peak concentration at 60 minutes following application to nasal mucosa according to C. Van Dyke, P. G. Barash, P. Jatlow, and R. Byck [*Science* **191**, 859 (1976)].
9. These nine items were more frequently rated "true" for higher doses and for the intravenous route of administration.
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21 September 1976

Rod Photoreceptors Detect Rapid Flicker

Abstract. *It is widely believed that human rods cannot detect rapid flicker. With rod-isolation techniques, however, light-adapted rods detect flicker frequencies as high as 28 hertz, and the function relating rod critical flicker frequency to stimulus intensity contains two distinct branches. Human rod vision may, therefore, depend on two independent mechanisms.*

Human vision is mediated by cone receptors in bright light and by rod receptors in dim light (*1*). Because of this, psychophysical measures of temporal resolution contain two distinct regions (*2*). At low, rod intensities, the maximum frequency of visible flicker (or critical flicker frequency, CFF) increases with stimulus intensity, so that observers can see higher frequencies as the flickering stimulus is made brighter. This improvement in resolution terminates in a plateau at about 15 hertz, however, and unless the light stimulates cones, further increases in intensity do not affect CFF. At high, cone intensities, temporal resolution improves again, and cones can detect flicker frequencies above 50 hertz when the stimulus is very bright (*3*).

This suggests that rods achieve their special sensitivity at the price of a sluggish response; that although rods can see dim light, they cannot see rapid flicker (above 15 hertz). The rod response does not stop when cones become active, however; rather it continues, concealed from measurement by the larger cone response. Using techniques that desensitize cones and reveal rod responses (*4*), we have measured rod CFF at high intensities. Contrary to popular belief, rods can detect rapid flicker.

Our experiments required bright, spectrally pure stimuli; these were provided by a 900-watt xenon arc lamp. The test stimulus, which flickered sinusoidally, was a short-wavelength disk seen in Maxwellian view (*5*). It subtended 9° of visual angle and was centered on a deep red (670 nm), 13° background, which was located on the temporal retina, 16° from the fovea (*6*). The test light (but not the background) was obliquely incident on the retina.

These experimental conditions enhanced the rod response in several ways. First, rods are very sensitive to short-wavelength light, but cones are not; the spectral composition of the flickering field, therefore, helped rods and hindered cones. Second, cones are relatively sensitive to red light, but rods are not; the red background, therefore, reduced the modulation depth of the stimulus, as seen by cones, without much affecting its appearance for rods (*7*). Third, rods outnumber cones in the retinal periphery, and they integrate their signals over large areas; the location and size of the stimuli, therefore, facilitated rod detection of the flickering field. Fourth, rods are highly sensitive to obliquely incident light, but cones are not (see below).

Observers adjusted the frequency of the flickering stimulus to determine the highest frequency (CFF) that was visible at each of many intensities (Fig. 1A, open symbols). As expected at low in-

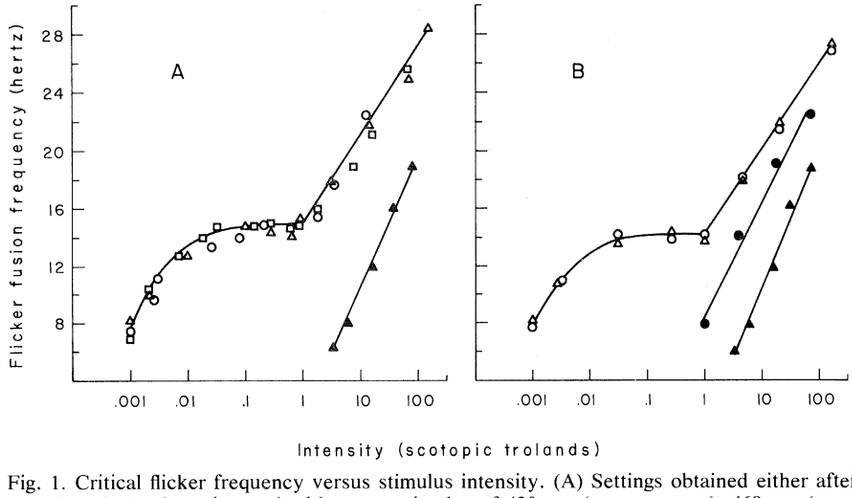

Fig. 1. Critical flicker frequency versus stimulus intensity. (A) Settings obtained either after complete dark adaptation and with a test stimulus of 430 nm (open squares), 469 nm (open triangles), or 520 nm (open circles), or during the cone plateau phase of dark adaptation and with a test stimulus of 469 nm (closed triangles). (B) Settings made after complete dark adaptation (open symbols) and during the cone plateau phase (closed symbols) for a 469 nm stimulus, which struck the photoreceptors either axially (circles) or obliquely (triangles).