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A Comparison of the Subjective and Cardiovascular Effects of Cocaine and Procaine in Humans

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FISCHMAN, M. W., C. R. SCHUSTER AND S. RAJFER. *A comparison of the subjective and cardiovascular effects of cocaine and procaine in humans.* PHARMACOL BIOCHEM BEHAV 18(5) 711–716, 1983.—Four normal adult volunteers were given intravenous injections of 16, 32 and 48 mg cocaine, procaine, or saline, once daily in a balanced order. An additional dose of procaine, 96 mg, was also given. Heart rate, blood pressure, and responses on the Profile of Mood States (POMS), Addiction Research Center Inventory (ARCI), and a locally developed drug effects rating scale were measured before and periodically after drug or placebo injection. The profile of action of cocaine was significantly different from that produced by both saline and the lower doses of procaine. Although responses on the ARCI and POMS after all doses of procaine were similar to those obtained after placebo, three of the subjects identified 48 and 96 mg procaine as cocaine, and rated these two drugs similarly at the higher procaine doses.

Cocaine Procaine Human studies Cardiovascular effects Subjective tests

Although the reinforcing properties of cocaine have been extensively documented in the animal laboratory, it is only recently that other local anesthetics have been similarly studied [3, 5, 9, 24]. The findings that some of these (e.g., procaine, chloroprocaine and dimethocaine) can serve as reinforcers in rhesus monkeys has suggested that they might also do so in humans.

Procaine, the first synthetic local anesthetic, is a particularly interesting one. Although not believed to be a drug of abuse in humans, it clearly has central nervous system effects as indicated by its clinical use as an analgesic [13,18] and general anesthetic [11]. In addition, since its introduction as Gerovital H3 in 1956 (see [19] for a review) it has been widely publicized for its beneficial effects in delaying the aging process and reversing some of the symptoms associated with the chronic diseases of old age such as poor memory, cognitive deficits, shortened attention span and decreased alertness.

The present study compared the subjective and physiological effects of procaine with those of cocaine, a unique local anesthetic which is also a psychomotor stimulant. Matched intravenous doses of each, as well as one larger dose of procaine, were administered to four volunteer subjects who showed significant cardiovascular and subjective responses to cocaine. Procaine had no measurable cardiovascular effects in the dose range tested. The higher doses of procaine, however, caused some changes in verbal report of drug effects similar to those seen after cocaine.

METHOD

Subjects

Three male and one female normal adult volunteer ranging in age from 21 to 28 years, with prior histories of intravenous cocaine use participated. Each passed an initial screening consisting of an interview, physical exam, ECG, chest x-ray, urine analysis, and blood chemistry tests. All subjects signed consent forms which described the study, outlined any risks of this procedure, and indicated that cocaine and other drugs structurally similar to cocaine would be administered intravenously.

Procedure

Subjects were housed on the clinical research unit of Billings Hospital for the duration of the study. They participated in testing for approximately three hours each of the ten experimental days, and were free to engage in non-drug recreational activities of their own choice on the ward when not being tested.

Subjects were tested individually and wore appropriate physiological monitoring equipment to measure heart rate and blood pressure. In addition, prior to each session, a teflon intravenous catheter was inserted into an arm vein and attached to a saline solution drip bag. Drug was injected through this catheter. Subjects sat alone in the test room, and were monitored from an adjacent room. The first 30 minutes of each session were designated the baseline recording period. Subjects sat quietly while predrug physiological and questionnaire data were collected. ECG was monitored continuously, heart rate (measured as beat to beat time and averaged every two minutes) and blood pressure (using an Arteriosonde model 1261 Automatic Blood Pressure Monitor, Roche Medical Electronics, Cranbury, NJ; see [2] for details of physiological measurements) were recorded every two minutes, and drug effects questionnaires were filled out. This was followed by a three ml intravenous injection of saline or drug dissolved in saline. The session continued for 120 minutes after drug or saline administration. Questionnaires were filled out at 5, 15, 30, 60, 90 and 120 minutes after injection. These questionnaires included:

(1) Profile of Mood States (POMS). This is an experimental version of the 65-item POMS described and validated by McNair *et al.* [14], and is a 72-item five-point adjective rating scale, the results of which can be factor analyzed into eight mood clusters: Anxiety, Depression, Anger, Vigor, Fatigue, Confusion, Friendliness and Elation. Two derived scores can also be obtained: Arousal is the sum of the Vigor and Anxiety scores minus the sum of the Confusion and Fatigue scores, and the Positive Mood score is made up of the Elation minus the Depression scores.

(2) Addiction Research Center Inventory (ARCI). This is a short form of the 550-item ARCI [4], consisting of 49 items compiled by Martin *et al.* [4], which have been shown to be sensitive to the effects of a number of different stimulant drugs. They were taken from one sedative scale (Pentobarbital Chlorpromazine Alcohol General, PCAG), three stimulant scales (Benzedrine General, BG; Morphine Benzedrine General, MBG; and Amphetamine, A) and one scale measuring dysphoric and psychotomimetic changes (LSD).

(3) Rating. This is a locally developed questionnaire consisting of six lines, each 10 cm long. The lines are labeled "hungry," "down," "sedated," "anxious," "stimulated," and "high." Subjects indicate how they feel by placing a mark along each line labeled, at the left side, "not at all" and at the right side, "extremely."

(4) Drug name. At the end of each experimental session subjects were asked to identify the substance they had received during that session: cocaine, placebo or other.

One intravenous injection was administered each day. Saline was always administered on the first day of the study in order to acquaint each subject with the procedures, and the data from this day were not included in subsequent analyses. During the next eight experimental sessions a series of three cocaine doses (16, 32 and 48 mg) plus a saline placebo and a series of three procaine doses (16, 32 and 48 mg) plus a saline placebo were administered. Two of the subjects received the cocaine series first and the other two received the procaine series first. Doses were arranged according to a modified Latin Square balanced for order, and the dose regimen is indicated in Table 1. On the 10th day of the study all four subjects were given one dose of 96 mg procaine.

TABLE 1
COCAINE AND PROCAINE DOSE REGIMEN

	Subject Number			
Day	68	69	70	71
1	Saline	Saline	Saline	Saline
2	32P	16C	Saline	48C
3	48P	32C	16P	Saline
4	Saline	48C	32P	16C
5	16P	Saline	48P	32C
6	Saline	48P	32C	16P
7	16C	Saline	48C	32P
8	32C	16P	Saline	48P
9	48C	32P	16C	Saline
10	96P	96P	96P	96P

P = Procaine; C = Cocaine.

Data Analysis.

(1) Questionnaires: Results from the two placebo sessions were averaged to obtain placebo session data against which drug data were compared. Scores for each of the POMS, ARCI and Line length subscales were analyzed using separate two-way (Drug × Time) within-subjects ANOVAs. When a significant ($p<0.05$) Drug × Time interaction was found, post hoc analyses (using Fisher's LSD) were conducted to determine which drug or doses significantly differed, and at which times these differences occurred.

(2) Physiological measures: The data collected prior to each drug or saline injection were averaged each day to obtain a baseline value against which the data collected after that injection could be compared.

(3) Data were lost due to equipment failure for one subject after 32 mg cocaine. Therefore, data will be presented only for the effects of 16 and 48 mg cocaine.

RESULTS

Cardiovascular Effects

The cardiovascular effects of intravenous cocaine were generally similar to those reported elsewhere [2,20], with substantial heart rate increases peaking within 15 minutes after drug administration. Procaine, on the other hand, had no significant effects on either heart rate or blood pressure in the dose range tested.

Verbal Report of Drug Effect

In general, when the effects of 16 and 48 mg cocaine were compared with those of placebo, there was a dose-related increase in stimulant-related scale scores on all three of the questionnaires used. Matched doses of procaine, on the other hand, did not have this effect. Analysis of variance indicated that the mean POMS scores after both doses of

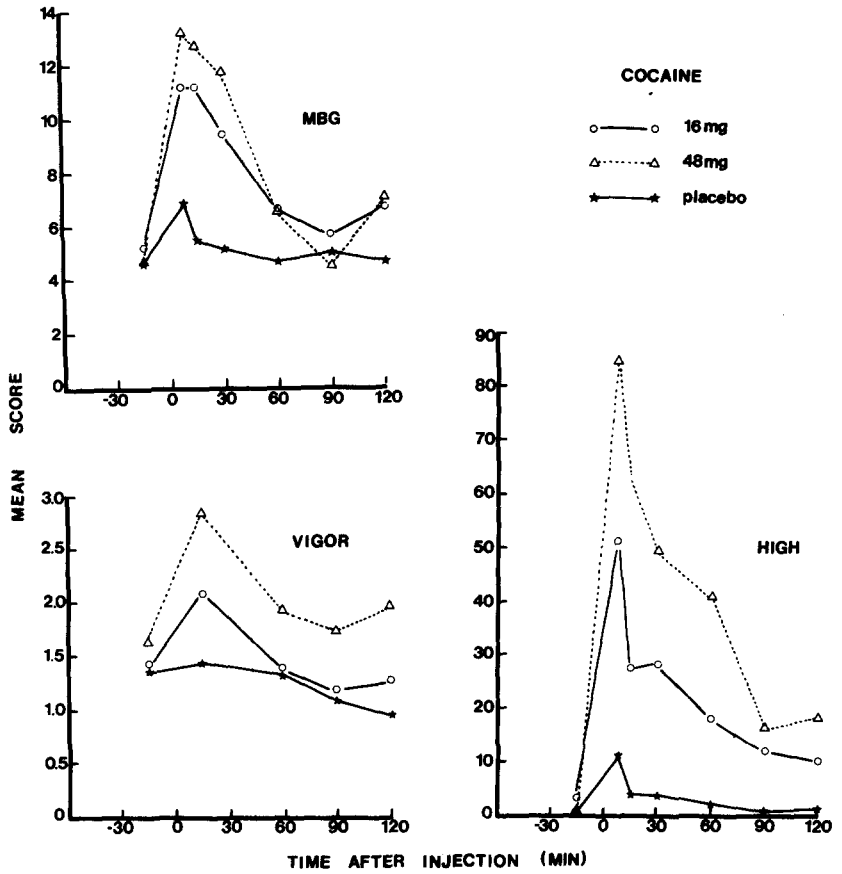

FIG. 1. Effects of intravenous cocaine on verbal report of drug effects. Mean scale score for the four subjects tested is shown for the MBG scale of the Addiction Research Center Inventory, the Vigor scale of the Profile of Mood States and the "High" rating of a locally developed rating scale. Scores on the MBG scale could range between 0 and 16, scores on the Vigor scale could range between 0 and 4, and "High" scores could range between 0 and 100. These questionnaires were administered prior to injection and 5, 15, 30, 60, 90 and 120 minutes after the injection.

cocaine for Vigor, Elation, Confusion, Friendliness, Positive Mood and Arousal were significantly ($p<0.05$, Fisher's LSD) different from placebo at 5 and 15 minutes after cocaine. The Arousal and Vigor scores after 48 mg continued to remain significantly elevated through 60 minutes post-drug. The same dose-related significant increases were seen for ratings of "stimulated" and "high" through 60 minutes post-drug. On the ARCI, the LSD, A and MBG scale scores were significantly elevated above placebo for all doses tested.

Data are presented in Fig. 1 for the POMS Vigor score, the Rating scale "high" score and the MBG score of the ARCI after cocaine. These data are representative of those in which significant cocaine effects were obtained. The significant drug-related increases varied in duration depending on the measures and doses used. These scale scores are very different after procaine administration (Fig. 2). In no case did procaine cause a change in ARCI, POMS or rating scale measures different from that observed following placebo. In addition to the lack of effect on the variables presented in Fig. 2, examination of all scale scores on each of the questionnaires failed to indicate any significant procaine effects.

When the effects of 96 mg procaine were compared to those of 16 mg cocaine, the effects of procaine on Vigor and MBG scores were no different than those obtained after placebo. Both drugs, however, were followed by significant ($p<0.05$, Fisher's LSD) increases in "high" scores as compared to placebo. This was also true for the "stimulated" score.

Subjects were accurate in identifying saline as placebo and cocaine as cocaine. However, 16 and 32 mg procaine were identified as placebo by all subjects. Three of the four subjects tested with 48 and 96 mg procaine called both doses cocaine; the fourth subject called both doses placebo.

DISCUSSION

The present study was designed to evaluate the effects of intravenous cocaine and procaine in matched doses on selected cardiovascular and subjective measures. The data collected clearly indicated that intravenous injections of 16 and 48 mg cocaine had substantial effects on heart rate and verbal report of drug effect as measured by the Profile of

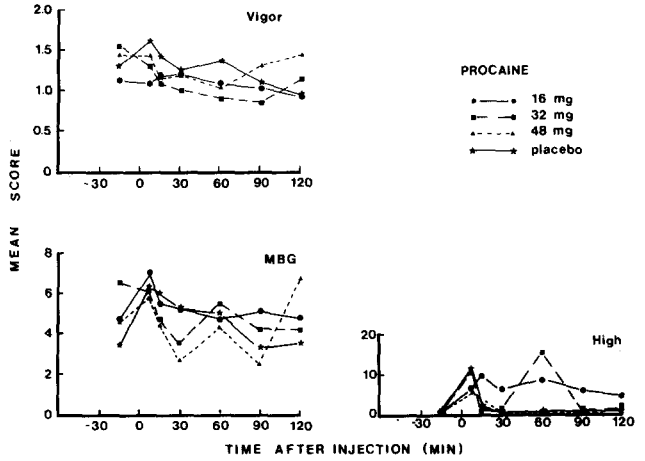

FIG. 2. Effects of intravenous procaine on verbal report of drug effects. See Fig. 1 legend for details.

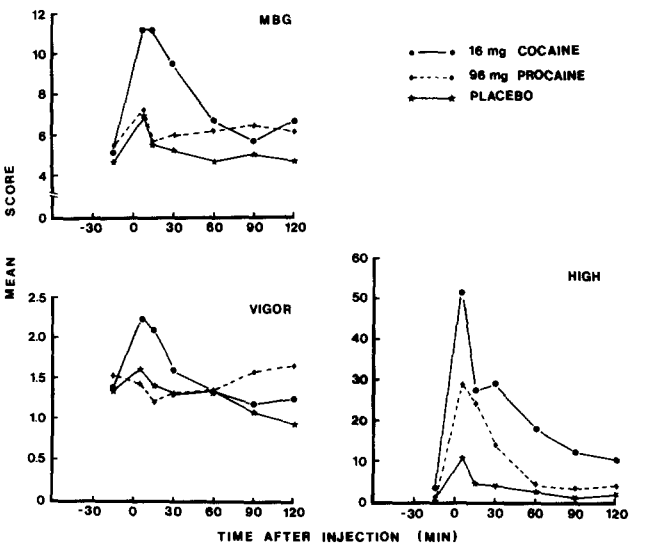

FIG. 3. Comparison of the effects of 16 mg intravenous cocaine with 96 mg intravenous procaine. See Fig. 1 legends for details.

Mood States, Addiction Research Center Inventory, and a locally developed questionnaire assessing measures of "high" and "stimulated." Procaine had no consistent effect on heart rate or the POMS and ARCI measures, but, nevertheless, despite the absence of these potential stimulus cues, at doses of 48 and 96 mg, was identified as cocaine by three of the four subjects, and caused significant increases in the "high" and "stimulated" measures.

It has generally been assumed that the synthetic local anesthetics such as procaine and lidocaine lack cocaine's ability to block reuptake of central monoamines, and are therefore without dependence potential. Recent evidence that at least some of them can maintain responding in nonhuman primates [3, 5, 9, 24] has brought into question this assumption. A second line of evidence from the animal laboratory has also provided support for the similarities between cocaine and at least some of the local anesthetics. Data collected on the discriminative stimulus properties of drugs indicate that various psychoactive drugs produce discriminative stimulus cues which are pharmacologically specific. Woolverton and Balster [25] trained rats to discriminate between procaine and saline, and found that local anesthetics including cocaine, chloroprocaine, dimethocaine, and lidocaine had procaine-like discriminative stimulus properties, while piperocaine and procainamide did not. There are minimal data available on the neurochemistry of the local anesthetics. As has recently been pointed out by Woolverton and Balster [24], some evidence points towards a cholinergic mechanism of action. A few local anesthetics have been shown to act as cholinergic agonists [6] or antagonists [17], and can also be hydrolyzed by cholinesterase [12,21]. On the other hand, drugs which exert their major effects via cholinergic mechanisms are not self-administered intravenously by rhesus monkeys, nor are they likely to have cocaine and amphetamine-like discrimination stimulus properties. Thus the neurochemical basis for the similarity between cocaine and procaine is unclear at this time.

When subjects in the present study were asked to identify the drug they had received, three of the four identified the higher doses of procaine as cocaine. The fourth subject, who identified this dose as a placebo, weighed substantially more than the other subjects, and in order to assess the possibility that his response was based on the lower mg/kg dose that he had received, all subjects were also tested with 96 mg procaine. Again, the same three subjects identified procaine as cocaine while the fourth identified it as placebo. By calling procaine cocaine, the majority of the research subjects indicated that cocaine and procaine share discriminative stimulus properties, a result obtained in the animal laboratory as well. The shared stimulus properties of these two local anesthetics is also indicated by the fact that the "high" and "stimulated" rating scale scores increased after cocaine and procaine but not after placebo. Identification of the shared stimulus properties is not possible from the data collected, but these properties do not appear to include heart rate increases since procaine had no measurable effect on heart rate. To the extent that shared stimulus properties predict shared reinforcing properties, we might expect procaine to serve as a reinforcer in humans.

A traditional approach to the evaluation of a drug's abuse potential is to compare its spectrum of action to that of a known drug of abuse [1,7]. Similarity to the prototype predicts possible abuse potential. It has been pointed out by a number of investigators (e.g., [7,16]) that the major drugs of abuse share the characteristic of causing increases in "well-being" or "euphoria." The MBG scale of the Addiction Research Center Inventory has been interpreted by these investigators as a direct measure of this increase in euphoria. Thus, drug-related increases on the MBG scale should predict high abuse potential. As in earlier studies (e.g., [2]) cocaine caused significant increases in MBG scores as well as LSD and A scale scores. Procaine did not have this effect. The Vigor factor scores of the POMS, shown to increase after oral amphetamine [10], as well as the Anxiety, Elation and Positive Mood factors, increased after IV cocaine but not after procaine. Thus, the profiles of action of cocaine and procaine show only partial overlap in this study, converging in some, but not all of the verbal report measures.

Although procaine appears to have little abuse liability in humans, it has gained popularity in Europe (where it is marketed under the name Gerovital H3) as a drug prescribed for the elderly. In an extensive review of this literature, Ostfeld and his colleagues [19] point out that claims for the efficacy of procaine have been made for the treatment of such complaints as depression, atherosclerosis, parkinsonism, arthritis, high blood pressure and sexual and endocrine function. Because of poorly controlled studies, there is no evidence that the systemic use of procaine is of value in treating the common chronic diseases of the elderly. The only possible exception to this may be its transient antidepressant effect. Studies by Sakalis *et al.* [22] and Zung *et al.* [26] have suggested that chronic systemic procaine may function as a mood elevator in patients diagnosed as depressed. In the present study, although no mood changes, as measured by the POMS, were noted after procaine administration, the population tested were normal volunteers who were tested with procaine once daily for a week rather than depressed patients maintained on drug therapy for 3–4 weeks. The fact that scores on the "high" scale increased, does lend support to the idea that this drug has CNS effects. These results are different from those obtained after intravenous lidocaine. Recent research from this laboratory [27] has shown that lidocaine had no consistent effect on any cardiovascular or verbal report measure in intravenous doses of 16–48 mg. The lidocaine data, along with data from the animal laboratory indicating that rhesus monkeys do not self-administer lidocaine, suggest that lidocaine does not have dependence potential.

Despite at least some similarities with cocaine in humans, and good evidence that it is self-administered by non-human primates, procaine is not thought to be abused by humans. This discrepancy could be due to several factors. First of all, it may well be that what passes for cocaine "on the street" is, in fact, another local anesthetic such as procaine. It is possible that the procaine is a reinforcer and is being used "on the street" in its own right. Procaine is commonly misrepresented as cocaine or mixed with the cocaine that is sold on the street. Cocaine users frequently conduct a test for local anesthesia in which some drug is rubbed on the gums. Cocaine and procaine would both give numbing (or "freezing") effects, thus making possible the use of procaine as a less expensive substitute or filler in the sale of cocaine. It is possible that the presumably inactive "filler" is, in this case, not inactive but is being abused for its own properties. Another factor to be considered in evaluating the abuse potential of procaine is its very short half-life. Procaine has been estimated to have a 7.7 minute elimination half-life in humans [23], and that of cocaine is approximately 40 minutes after intravenous injection [8]. It would thus require frequent injections of drug in order to maintain intoxication. This is precisely what is seen with rhesus monkeys who self-administer large numbers of procaine injections [3,9], but would be far too inconvenient for humans to arrange.

It would appear from these data that procaine shares some stimulus properties with cocaine. Whether procaine shares with cocaine the ability to serve as a positive reinforcer remains to be determined.

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REFERENCES

1. Fischman, M. W. Evaluating the abuse potential of psychotrophic drugs in man. In: *Predicting Dependence Liability of Stimulant and Depressant Drugs*, edited by T. Thompson and K. R. Unna. Baltimore, MD: University Park Press, 1977, pp. 261–284.
2. Fischman, M. W., C. R. Schuster, L. Resnekov, J. F. E. Schick, N. A. Krasnegor, W. Fennell and D. X. Freedman. Cardiovascular and subjective effects of intravenous cocaine administration in humans. *Arch Gen Psychiatry* **33**: 983–989, 1976.
3. Ford, R. D. and R. L. Balster. Reinforcing properties of intravenous procaine in rhesus monkeys. *Pharmacol Biochem Behav* **6**: 289–296, 1977.
4. Haertzen, C. A. Development of scales based on patterns of drug effects, using the addiction research center (ARCI). *Psychol Rep* **18**: 163–194, 1966.
5. Hammerbeck, D. M. and C. L. Mitchell. The reinforcing properties of procaine and *d*-amphetamine compared in rhesus monkeys. *J Pharmacol Exp Ther* **204**: 558–569, 1978.
6. Israel, J. M. and J. M. Meunier. Procaine as an acetylcholine agonist in snail neuron. *J Pharmacol Exp Ther* **211**: 93–98, 1979.
7. Jasinski, D. R. Clinical evaluation of sedative-hypnotics for abuse potential. In: *Predicting Dependence Liability of Stimulant and Depressant Drugs*, edited by T. Thompson and K. R. Unna. Baltimore, MD: University Park Press, 1977, pp. 285–290.
8. Javaid, J. I., M. W. Fischman, C. R. Schuster, H. Dekirmenjiian and J. M. Davis. Cocaine plasma concentration: Relation to physiological and subjective effects in humans. *Science* **202**: 227–228, 1978.
9. Johanson, C. E. The reinforcing properties of procaine, chloroprocaine and proparocaine in rhesus monkeys. *Psychopharmacology (Berlin)* **67**: 189–194, 1980.
10. Johanson, C. E. and E. H. Uhlenhuth. Drug preference and mood in humans: *d*-amphetamine. *Psychopharmacology Berlin)* **71**: 275–279, 1980.
11. Johnson, K. and C. R. A. Gilbert. Intravenous procaine for obstetrical anesthesia. *Anesth Analg (Cleve)* **25**: 133–146, 1946.
12. Kalow, W. Hydrolysis of local anesthetics by human serum cholinesterase. *J Pharmacol Exp Ther* **104**: 122–134, 1952.
13. Keats, A. S., G. L. D'Alessandro and H. K. Beecher. A controlled study of pain relief by intravenous procaine. *JAMA* **147**: 1761–1763, 1951.
14. McNair, D. M., M. Lorr and L. F. Droppleman. *Profile of Mood States (Manual).* San Diego, CA: Educational and Industrial Testing Service, 1971.
15. Martin, W. R., J. W. Sloan, J. D. Sapira and D. R. Jasinski. Physiologic, subjective and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man. *Clin Pharmacol Ther* **12**: 245–258, 1971.
16. Martin, W. R., C. A. Haertzen and B. B. Hewett. Psychopathology and pathophysiology of narcotic addicts, alcoholics, and drug abusers. In: *Psychopharmacology: A Generation of Progress*, edited by M. A. Lipton, A. DiMascio and K. F. Killam. New York: Raven Press, 1978, pp. 1591–1602.
17. Miele, E. and R. P. Rubin. Further evidence for the dual action of local anesthetics on the adrenal medulla. *J Pharmacol Exp Ther* **161**: 296–301, 1968.
18. Mushin, W. W. and L. Rendell-Baker. Intravenous procaine. *Lancet* **1**: 619–620, 1949.

19. Ostfeld, A., C. M. Smith and B. A. Stotsky. The systemic use of procaine in the treatment of the elderly. A review. *J Am Geriatr Soc* **25:** 1–19, 1977.
20. Resnick, R. B., R. S. Kestenbaum and L. K. Schwartz. Acute systemic effects of cocaine in man: A controlled study by intranasal and intravenous routes. *Science* **195:** 696–699, 1977.
21. Ritchie, J. M. and N. M. Greene. Local anesthetics. In: *The Pharmacological Basis of Therapeutics*, edited by A. G. Gilman, L. S. Goodman and A. Gilman. New York: MacMillan, 1980, pp. 300–320.
22. Sakalis, G., D. O. S. Gershon and B. Shopsin. A trial of gerovital-H_3 in depression during senility. *Curr Ther Res* **16:** 59–63, 1974.
23. Seifen, A. B., A. A. Ferrari, E. E. Seifen, D. S. Thompson and J. Chapman. Pharmacokinetics of intravenous procaine infusion in humans. *Anesth Analg (Cleve)* **58:** 382–386, 1979.
24. Woolverton, W. L. and R. L. Balster. Reinforcing properties of some local anesthetics in rhesus monkeys. *Pharmacol Biochem Behav* **11:** 669–672, 1979.
25. Woolverton, W. L. and R. L. Balster. Behavioral pharmacology of local anesthetics: Reinforcing and discriminative stimulus effects. *Pharmacol Biochem Behav* **16:** 491–500, 1982.
26. Zung, W. W. K., D. Granturco, E. Pferffer, H. S. Wang, A. Whanger, T. P. Bridge and S. G. Potkin. Pharmacology of depression in the aged: Evaluation of gerovital-H_3 as an antidepressant drug. *Psychosomatics* **15:** 127–131, 1974.
27. Fischman, M. W., C. R. Schuster and Y. Hatano. A comparison of the subjective and cardiovascular effects of cocaine and lidocaine in humans. *Pharmacol Biochem Behav* **18:** 123–127, 1983.