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Effects of Imipramine on Responding Reduced by Methadone

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CLEARY, J., M. NADER AND T. THOMPSON. *Effects of imipramine on responding reduced by methadone.* PHARMACOL BIOCHEM BEHAV **25**(1) 149–153, 1986.—Interactions between methadone and acute and chronic imipramine were studied in pigeons key pecking under a multiple variable interval 15-sec variable interval 150-sec schedule of food presentation. Both drugs decreased response rates at the highest doses. The VI 15-sec schedule was slightly more sensitive to acute drug administration than was the variable interval 150-sec schedule. Acute combinations of the two drugs neither ameliorated nor exacerbated the effects of either drug alone. Chronic imipramine alone had no lasting effect on responding. Unlike acute combinations, chronic imipramine lessened the rate reducing effect of methadone.

Methadone Imipramine Schedule-controlled behavior Pigeons

THE prevalence of depression appears to be higher among people dependent on opiates than among the general population [15,23]. Recently, researchers have reported alleviation of depressive symptoms by administering antidepressant medication to methadone maintained patients [23]. In the laboratory, this combination potentiates analgesia but little else is known about the basic behavioral effects of combined administration of drugs from these two classes. The present study investigated the behavioral effects of the prototypic tricyclic antidepressant imipramine, in combination with methadone, on behavior maintained by positive reinforcement.

While the mechanism of imipramine's antidepressant action is speculative, much is known about its neurochemical effects. Imipramine inhibits reuptake and slows the turnover of norepinephrine and serotonin. It also has cholinergic antimuscarinic activity. Behaviorally, the drug is thought to have little effect in nondepressed humans at therapeutic doses. In most laboratory species, imipramine decreases rates of responding on operant tasks (e.g. [4,10]). However, several investigators have reported increases in rates of operant behavior at relatively high imipramine doses in the pigeon (e.g. [6, 18, 20]). This possibility of increases or decreases in rates of behavior under imipramine recommends the pigeon for use in initial laboratory assessment of imipramine-methadone combinations. In combination studies, the tricyclics generally potentiate narcotic effects. For example, imipramine increases analgesia in several species (e.g. [2,16]). In addition, desimipramine, an active metabolite of imipramine, enhances methadone analgesia and increases amounts of methadone present in brain tissue [12]. Tricyclics also intensify toxic effects during narcotic withdrawal [8].

Methadone and other μ receptor agonists reduce rates of operant responding maintained by positive reinforcers proportional to dose and baseline response rates and inversely related to reinforcement frequency [14,20]. Methadone's rate-reducing effects also vary with schedule contingency, independent of reinforcement rate or baseline response rate [19]. In selecting a baseline for examining methadone's behavioral effects it is useful if a performance can both increase and decrease in rate, and permit comparison of at least two response and reinforcement frequencies. Hence, in the present investigation, operant key pecking maintained under multiple variable interval reinforcement schedules was used.

METHOD

Subjects

Four experimentally naive male White Carneaux pigeons served as subjects. Birds were maintained at 80% of their free-feeding weights by post-session feedings. Water was freely available in the home cage. Subjects were individually housed in a colony room under constant illumination. Temperature was maintained at 24 degrees centigrade.

Apparatus

Experimental sessions were conducted in four commercially available sound attenuating chambers (BRS/LVE, Laurel, MD). Each chamber was equipped with a stimulus panel having 3 keys and a feeder opening which was illuminated during operation. Except for shaping, only the left key was used in the present experiment. White noise was continuously present in the chamber room. Programming of experimental conditions and data recording was accomplished with a single Apple II Plus microcomputer (Apple Computer, Inc., Cupertino, CA) located in an adjacent room.

Procedure

Birds were autoshaped to peck the center key illuminated white, then switched to a continuous reinforcement schedule (CRF) with the left key constantly illuminated red. Under these conditions, each response was followed by 4

seconds access to mixed grain. When birds consistently responded under a CRF schedule, the schedule was changed so key pecks were reinforced under a variable interval reinforcement schedule (VI). Under this schedule responses are intermittently reinforced after intervals of various length. In this case, the average interval was eventually increased to 15 seconds (VI 15") across several sessions. Finally, the key color was periodically changed from red to green illumination and under the green stimulus condition key pecks were reinforced on the average of every 150 seconds (VI 150"). Thus, the terminal schedule for all birds was a multiple variable interval 15 seconds-variable interval 150 seconds (mult VI 15-VI 150).

Under final schedule conditions, the bird was placed in the chamber, and each session started with 30 minutes of darkness followed by feeder presentation and illumination of the house light and left key red (VI 15"). Key pecks had no scheduled consequences during darkness. After 5 minutes under VI 15" the key color was changed to green (VI 150") for 10 minutes, followed by red (VI 15") for 5 minutes and finally green (VI 150") for 10 minutes. Ten seconds of darkness was interposed between each VI schedule component change. Thus, the entire session lasted just over 60 minutes. The VI 150" component was set at 10 minutes instead of 5 to allow the birds to receive at least one reinforcer during this component.

Drug Preparation and Administration

Imipramine hydrochloride (Geigy Pharmaceauticals, Ardsley, NY) was administered at acute doses of 0.3, 1.0, 3.0 and 10.0 mg/kg and chronically at 3.0 and 6.0 mg/kg/day. These doses encompass the therapeutic range of 1.3–4.2 mg/kg/day suggested for humans. Mehtadone hydrochloride was administered at doses of 0.5, 1.5 and 3.0 mg/kg. Doses are expressed in terms of the total salt. Drugs were mixed with 0.9% saline to produce a constant injection volume of 1.0 ml/kg. All injections were given intramuscularly immediately before the start of the session. Since each session started with 30 minutes of darkness, the injection-session interval was effectively 30 minutes. Birds received each dose and all possible combinations of the two drugs in a random order, determined individually for each bird. Birds were administered drugs acutely every Thursday with saline (0.9%) administered at least once during the preceeding 3 days.

Following the determination of acute dose-effect relationships, imipramine was administered chronically to all birds at doses of 3.0 mg/kg/day and 6.0 mg/kg/day. The total chronic daily dose was divided in half and administered at 12 hour intervals. Sessions began just prior to the second daily injection—11 hours after the first daily imipramine injection. This injection schedule was designed to insure assessment of enduring changes induced by chronic imipramine administration. The chronic imipramine-methadone dose regimen was as follows: 14 days of chronic imipramine (3.0 mg/kg/day) alone; 3 weeks during which methadone was administered (0.5, 1.0, and 3.0 mg/kg) once each week in addition to 3.0 mg/kg/day imipramine; 3 weeks drug free; 14 days of 6.0 mg/kg imipramine only; 3 weeks during which methadone was administered at the above doses in addition to 6.0 mg/kg/day imipramine; 14 days drug free; redetermination of methadone alone dose-effect relationship (tolerance determination). In addition, a single 10.0 mg/kg imipramine dose was administered to each bird 12 hours before sessions were begun. This condition assessed possible delayed effect of imipramine under conditions identical to acute administration. Data from this 12 hour presession injection condition are not presented since no bird showed any effects of imipramine 12 hours after acute administration.

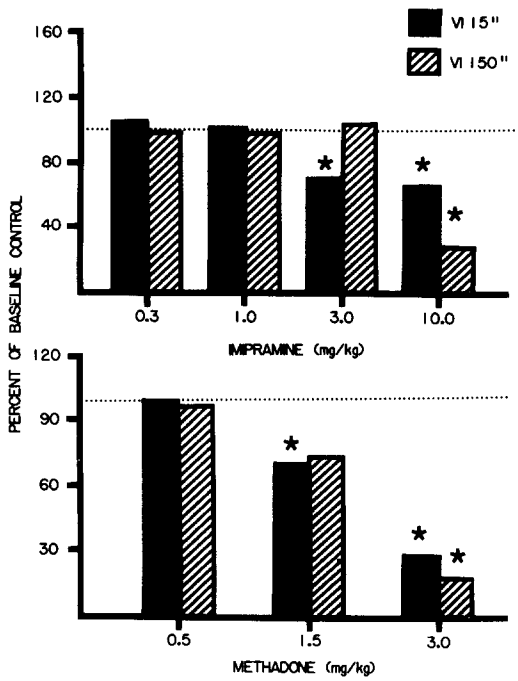

FIG. 1. Effects of acute administration of imipramine and methadone. VI 15-sec SEM=7.7, 19.0, and 26.9 percent at respective methadone doses of 0.5, 1.5, and 3.0 mg/kg and 7.2, 12.0, 31.5, and 27.2 percent at respective imipramine doses of 0.3, 1.0, 3.0, and 10.0 mg/kg. Under the VI 150-sec schedule SEM=5.5, 14.0, and 18.4 percent at the same respective methadone doses and 5.4, 11.5, 52.0 and 11.3 percent under imipramine.

In summary, methadone dose-effect relationships were determined alone, in combination with 4 doses of imipramine, in combination with 2 chronic doses of imipramine, and finally redetermined after a drug free period. Imipramine alone dose-effect relationships were also determined.

RESULTS

As expected, the two VI schedules generated very different baseline key pecking rates. The mean control rates during the acute drug administration phase were VI 15"=47.7 responses per minute and VI 150"=30.9 responses per minute. Following acute methadone administration these rates were 44.65, 32.05 and 9.35 under the VI 15" schedule and 28.05, 21.18 and 5.74 under the VI 150" schedule, at respective methadone doses of 0.5, 1.5 and 3.0 mg/kg. Imipramine administration produced key peck rates of 44.73, 47.08, 33.88 and 34.74 under VI 15" schedule and 28.54, 27.56, 27.58 and 10.66 under VI 150" schedule, at respective doses of 0.3, 1.0, 3.0 and 10.0 mg/kg. There were significant overall dose effects under both schedules (2-way RMANOVA $F(13,78)=5.43, p<0.01$), but no schedule × dose interaction. Specifically, multiple comparison tests (t_{LSD}) showed the 2 highest doses of both drugs produced response rates signifi-

TABLE 1

MEAN RESPONSES PER MINUTE

Methadone dose (mg/kg)	VI 15″ Imipramine dose (mg/kg) 0.0	0.3	1.0	3.0	10.0	VI 150″ Imipramine dose (mg/kg) 0.0	0.3	1.0	3.0	10.0
0.0	47.7	44.7	47.1	33.9	34.8	30.9	28.5	28.0	27.6	10.7
0.5	45.5	48.3	45.2	35.3	19.9	32.0	28.5	28.5	21.2	12.8
1.5	30.6	38.7	30.9	32.0	28.7	25.2	23.9	19.7	3.9	13.7
3.0	12.6	19.0	22.0	16.4	17.2	8.7	9.9	9.5	8.7	14.8

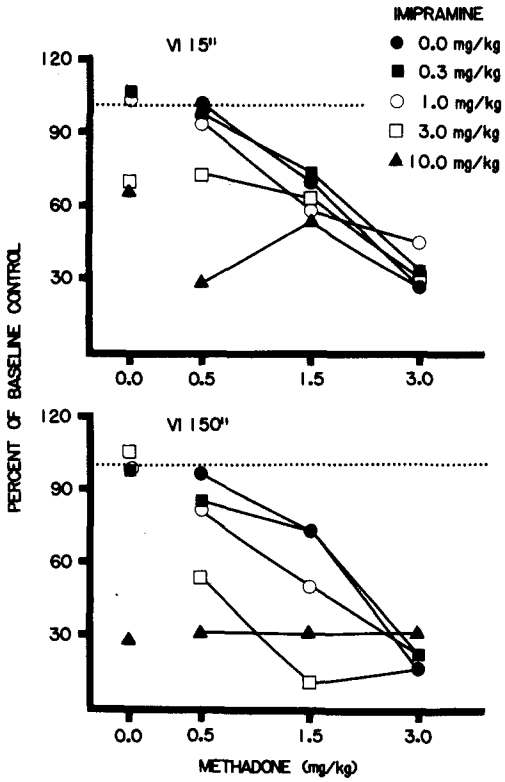

FIG. 2. Effects of combinations of acute administration of imipramine and methadone as a percentage of baseline control rates.

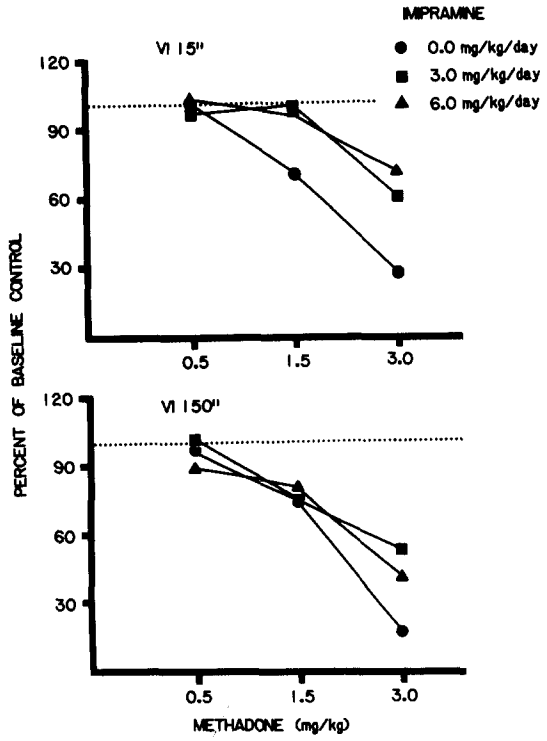

FIG. 3. Effects of chronic administration of imipramine and acute doses of methadone. These data are expressed as a percentage of the mean of the three days preceding methadone administration.

cantly different from baseline rates ($p<0.05$) under the VI 15″ schedule. In addition, response rates under VI 150″ at the highest dose of both drugs were significantly different from drug-free baseline rates ($p<0.05$). Figure 1 expresses these dose-effect relationships as a percent of their baseline control rates.

Table 1 shows the effects of the two drugs, alone and in combination, on group response rates under both schedules. These data are expressed as the mean number of responses per minute for all birds under the specified condition. Baseline rates (0.0 mg/kg) are the mean of the 3 days preceeding drug administration.

In general, imipramine-methadone combinations did not reduce responding beyond the level of suppression for either drug alone. The exception to this lack of additivity can be seen at combinations of 3.0 mg/kg imipramine and methadone under the VI 150″ schedule (Fig. 2). When administered alone, 3.0 mg/kg of imipramine had no effect on the group mean number of key pecks per minute, but variability was considerable (see Fig. 1). More importantly, in terms of the chronic effects discussed below, no dose of acute imipramine increased behavior suppressed by methadone. Reinforcement rate under VI schedules is not directly related to response rate but the drugs, alone and in combination, reduced reinforcement rate in a dose dependent manner similar to reductions in response rate.

Chronic Imipramine Phase

Imipramine chronically administered at 3.0 and 6.0 mg/kg/day had no lasting rate reducing effects under the dos-

ing regimen used. Two of four birds showed rate reductions after initiation of chronic regimen, but this effect quickly diminished. The mean control rate for the last 5 days prior to chronic imipramine was 50.8 and 31.6 responses/minute under the VI 15″ and VI 150″ schedules, respectively. The mean rate for the last 5 days of 3.0 mg/kg/day imipramine under VI 15″ and VI 150″ respectively, was 45.59 and 33.21 responses/minute and 48.50 and 33.20 responses/minute at 6.0 mg/kg/day imipramine.

The results of administering methadone in addition to chronic imipramine are expressed as a percentage of control rates in Fig. 3. The top half of this figure shows that chronic administration of imipramine shifted the methadone dose-effect curve to the right under the VI 15″ schedule. This higher rate and higher density reinforcement schedule was also most affected when imipramine was given alone (see Fig. 1). Although methadone's rate-reducing effects were not ameliorated as drastically under the VI 150″ schedule, chronic imipramine in combination with 3.0 mg/kg methadone produced higher rates than methadone alone in 7 of 8 instances. Also, in contrast to effects under acute administration, methadone given in combination with imipramine did not significantly reduce reinforcement rate at any dose.

Tolerance Assessment

The final phase involved re-establishing the methadone dose-effect curve to assess the degree to which results obtained under chronic imipramine were due to tolerance to the opiate. Methadone was again administered at doses of 0.5, 1.5, and 3.0 mg/kg after a drug-free period of 14 days. This final methadone administration reduced responding to 97%, 98%, and 47% of baseline rate under VI 15″ and 82%,83% and 34% under VI 150″. These results are similar to the original dose-effect curve for methadone except at 1.5 mg/kg under the VI 15″ schedule (see Fig. 1). Thus, the amelioration of methadone's rate-reducing effects at the highest (3.0 mg/kg) dose is due to daily imipramine treatment, not tolerance to the opiate.

DISCUSSION

Both methadone and imipramine produced dose related decreases in response rates similar to those previously reported under a variety of schedule conditions [6, 10, 19]. Significant rate reducing effects were seen under the VI 15″ schedule at lower doses of either drug than under the VI 150″ schedule. Just the opposite effect, in terms of schedule sensitivity, was seen at the highest dose of imipramine. At that dose, key peck rates under the VI 150″ schedule were reduced more (greater percentage reductions and lower actual rates), than rates under the VI 15″ schedule. The significance of these differential schedule outcomes is tempered by increased imipramine-produced variability, especially at these low doses. This increased variability under imipramine has previously been noted by other investigators (e.g., [13]).

When given together, *acute* doses of imipramine and methadone generally did not reduce responding to a greater extent than did the more potent drug given alone. Exceptions to this effect occurred at the lower doses of methadone and the higher doses of imipramine (Fig. 2). Thus, imipramine did not potentiate the narcotic effect on response rate. This is in contrast to imipramine-potentiated narcotic analgesia (e.g [2]) and withdrawal toxicity [8]. More importantly, acute imipramine did not ameliorate the rate-reducing effects of methadone alone in any subject.

In contrast to acute administration, *chronic* imipramine substantially lessened rate reduction due to the highest methadone dose. The imipramine related shift to the right in the methadone dose-effect curve is best seen under the VI 15″ schedule (Fig. 3) but imipramine also lessened methadone's rate-reducing effects under the VI 150″ schedule. This antagonism occurred despite the fact that the active metabolite of imipramine has been shown to increase methadone concentrations in the brain and interfere with methadone metabolism in the liver [12]. Subsequent methadone administration showed this effect was not due to tolerance to the opiate. Why this amelioration of methadone's effects did not occur under the acute dosing regimen is speculative, but such a lack of effect under acute imipramine administration parallels the course of the drug's clinical efficacy. In general, therapeutic effectiveness of tricyclics is not observed until 2 or 3 weeks after treatment begins [1]. This delayed onset may account for the marked difference between imipramine's acute and chronic effects on methadone suppressed behavior in the present study.

Since imipramine affects a variety of neurotransmitters, including norepinephrine, serotonin, acetylcholine, and histamine, speculation concerning a neurochemical mechanism for the effect could take many forms. Of course, the exact neurochemical mechanism of tricyclic antidepression action is unknown and may be unrelated to the methadone interaction demonstrated in the present study. One possible mechanism involves the tricyclic's ability to potentiate synaptic norepinephrine by blocking its reuptake. Several authors have associated increased norepinephrine function with increased activity levels [5,17] or attributed stimulant-like activity to noradrenergic synaptic transmission [1].

Investigators have previously reported a beneficial interaction, in terms of improved depression rating scores, when methadone-maintained patients are treated with a tricyclic antidepressant [7, 21, 23]. In general, these studies showed doxepin, a tricyclic with considerable sedative properties, an effective adjunct to methadone therapy. Imipramine has also been evaluated clinically in combination with methadone, but, while all patients in the study improved, the imipramine group was not significantly better than the placebo group [9]. When methadone patients improve under tricyclic therapy, the positive effects may be attributed to the tricyclic's action on the patients' underlying depression or, in some cases, to doxepin's anxiolitic properties [23]. However, the lowered key pecking rates induced by methadone in the present study probably have few characteristics in common with human states of depression or anxiety. Thus, this amelioration of methadone's rate reducing effects may indicate the presence of an additional mechanism of beneficial pharmacological interaction independent of clinically defined depression.

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REFERENCES

1. Baldessarini, R. J. Drugs and the treatment of psychiatric disorders. In: *The Pharmacological Basis of Therapeutics*, 6th edition, edited by A. G. Gilman, L. S. Goodman and A. Gilman. New York: MacMillan, 1980, p. 420.
2. Bhattacharya, S. K. Imipramine-induced potentiation of morphine analgesia in rat: Role of brain monoamines. *Indian J Med Res* **68:** 849–854, 1978.
3. Bradley, P. B. and B. J. Key. A comparative study of the effects of drugs on the arousal system of the brain. *Br J Pharmacol* **14:** 340–349, 1959.
4. Cook, L. and R. T. Kelleher. Drug effects on the behavior of animals. *Ann NY Acad Sci* **96:** 315–335, 1962.
5. Cooke, J. D. and S. M. Schanberg. The effects of metamphetamine on behavior and on the uptake, release and metabolism of norepinephrine. *Biochem Pharmacol* **19:** 1165–1179, 1970.
6. Dews, P. B. A behavioral output enhancing effect of imipramine in pigeons. *Int J Neuropharmacol* **1:** 265, 1962.
7. Goldstein, B. J., C. D. McCoy, D. C. McBride and A. F. Jacobson. *Treatment of Depression Among Herion Addicts Receiving Methadone*. Final report to National Institute of Drug Abuse. NIDA Grant No. 5R01J02035, 1982.
8. Jhamandas, K., M. Sutak and S. Bell. Modification of precipitated morphine withdrawal syndrome by drugs affecting cholinergic mechanisms. *Eur J Pharmacol* **24:** 296–305, 1973.
9. Kleber, H. D., M. M. Weissman, B. J. Rounsaville and C. H. Wilbur. Imipramine as treatment for depression in opiate addicts. *Arch Gen Psychiatry* **40:** 649–653, 1983.
10. Kornetsky, C. A comparison of the effects of desipramine and imiparmine on two schedules of reinforcement. *Int J Neuropharmacol* **4:** 13–16, 1965.
11. Lewinsohn, P. M. The behavioral study and treatment of depression. In: *Progress in Behavior Modification*, vol 1, edited by M. Hersen, R. M. Eisler and P. M. Miller. New York: Academic Press, 1975.
12. Liu, S.-J. and R. I. H. Wang. Increased analgesia and alterations in distribution and metabolism of methadone by desimipramine in the rat. *J Pharmacol Exp Ther* **195:** 94–104, 1975.
13. McKearney, J. W. Effects of tricyclic antidepressant and anticholinergic drugs on fixed-interval responding in the squirrel monkey. *J Pharmacol Exp Ther* **222:** 215–219, 1982.
14. McMillan, D. W., P. S. Wolf and R. A. Carchman. Antagonism of the behavioral effects of morphine and methadone by narcotic antagonists in the pigeon. *J Pharmacol Exp Ther* **175:** 443–458, 1970.
15. Rounsaville, B. J., M. M. Weissman, K. Crits-Christoph, C. Wilber and H. Kleber. Diagnosis and symptoms of depression in opiate addicts: Course and relationship to treatment outcome. *Arch Gen Psychiat* **39:** 151–156, 1982.
16. Saarnivaara, L. Analgesic effect of some sympathetic drugs and their effects on morphine analgesia in rabbits. *Ann Med Exp Biol Fenn* **47:** 180–190, 1969.
17. Sulser, F. and P. L Mobley. Regulation of central noradrenergic antidepressant treatments. In: *Neuroreceptors: Basic and Clinical Aspects*, edited by E. Usdrin, J. M. Davis and W. E. Bunney. London: J. Wiley & Sons, 1981.
18. Terrace, H. S. Errorless discrimination learning in the pigeon: Effects of chlorpromazine and imipramine. *Science* **140:** 318–319, 1963.
19. Thompson, T., J. Honor, S. Verchota and J. Cleary. Interval and ratio reinforcement contingencies as determinants of methadone's effects. *Pharmacol Biochem Behav* **21:** 743–747, 1984.
20. Thompson, T., J. Trombley, D. Luke and D. Lott. Effects of morphine on behavior maintained by four simple food reinforcement schedules. *Psychopharmacologia* **17:** 182–192, 1970.
21. Titievsky, J., G. Seco, M. Barranco and E. M. Kyle. Doxepin as an adjunctive therapy for depressed methadone maintenance patients: A double blind study. *J Clin Psychiatry* **43:** 454–456, 1982.
22. Vaillant, G. E. A comparison of chlorpromazine and imipramine on behavior of the pigeon. *J Pharmacol Exp Ther* **146:** 377–384, 1964.
23. Woody, G. E., C. P. O'Brien, A. J. McLellan, M. Marcouici and B. D. Evans. The use of antidepressants with methadone in decreased maintenance patients. *Ann NY Acad Sci* **398:** 120–127, 1982.