TABLE II. Effect of Hypothalamic Extracts of Porcine, Bovine and Ovine Origin on the Release of Prolactin *in vitro*.

Treatment	Dose SME fragments	Reece-Turner response units* Control	Experimental	Prolactin I.U./100 mg pit Control	Experimental	P†
sheep SME	1	2.2 ± .11	1.5 ± .10	3.00	.49	.001
" "	1	1.6 ± .11	1.0 ± .23	.76	.11	.05
beef SME	.3	1.9 ± .10	1.5 ± .19	1.40	.37	.05
" "	.3	2.0 ± .21	1.3 ± .15	1.99	.41	.05
" "	.5	2.0 ± .2	1.4 ± .15	2.68	.5	.05
" "	.5	2.0 ± .16	1.5 ± .23	2.29	.53	.1–.2
pig SME	1	2.2 ± .31	1.6 ± .29	3.05	.60	.1–.2
" "	1	2.2 ± .16	1.7 ± .12	3.82	.90	.05
" "	.5	1.9 ± .17	1.4 ± .15	1.69	.43	.05
" "	.5	2.0 ± .18	1.4 ± .2	2.25	.42	.05–.1

* Mean ± S.E. † P experimental *vs* control in Reece-Turner Units.

inhibitory effect on prolactin release *in vitro*.

Nicoll and Meites(6) showed that neither oxytocin nor vasopressin influenced prolactin production by rat anterior pituitary *in vitro* indicating that neurohypophyseal hormones are not involved in regulation of prolactin secretion. Talwalker(1) showed that decreases in prolactin activity they observed are not due to inactivation of prolactin and that PIF activity is absent from brain cortex extracts.

These results corroborate and extend the findings of Talwalker, Ratner and Meites(1). The presence of PIF in extracts of hypothalami of large domestic animals makes this activity amenable to purification.

Summary. Rat anterior pituitary halves incubated *in vitro* release prolactin at a comparable rate in 2 incubation media. Addition of hypothalamic extracts of bovine, ovine or porcine origin inhibited release of prolactin *in vitro*.

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Analgesic and Psychotomimetic Properties of Dexoxadrol.* (29840)

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Dexoxadrol (d-2,2-diphenyl-4-(2-piperidyl)-1,3-dioxolane hydrochloride) has been studied extensively in the laboratory, where it displays a combination of depressant and stimulant effects on the central nervous system (unpublished data, Upjohn Co.). These include abolition of the righting reflex, anticonvulsant effects, blocking or depression of the EEG alerting reaction, and parasympathetic blockade. Of particular interest are its high degree of local anesthetic activity and the paradoxical fact that the drug is capable of inducing in mice a condition of "hyperacuity," as demonstrated by an increased response to thermal stimuli and increased writhing after intraperitoneal phenylquinone(1).

Our interest was aroused by reports of clinical pharmacologic experiments wherein

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subjects complained of "numbness." We decided to test dexoxadrol in women suffering from postpartum pain.

Methods. Two hundred and twenty-four women suffering from postpartum pain were randomly allocated to 3 treatments: placebo (lactose) capsules; aspirin, 600 mg; and dexoxadrol, 20 mg. All medications were given by mouth in the form of 2 tablets, and each patient was studied for only one dose of medication. All medications were made up to look alike, and were identified by number only, with a separate number being utilized for each patient. The evaluation of pain relief was accomplished in 2 ways. Patients were asked to categorize their pain prior to medication as very severe, severe, moderate, or slight. After medication they were asked to categorize the pain again, with the 4 categories already described as available designations, plus an additional one of no pain. In addition, the patients were asked to make value judgments as to whether relief of pain had been complete, greater than 50%, less than 50%, or nil. The scoring system for the pain categories was as follows: very severe pain, 4; severe pain, 3; moderate pain, 2; slight pain, 1; and no pain, 0. For the pain relief question, complete relief was scored as 3, greater than 50% as 2, less than 50% as 1, and no pain relief as 0. Side effects, as described spontaneously by the patients, were listed on the interview sheet, with categories for no side effects, nausea, vomiting, vertigo, light-headedness, drowsiness, pruritus, dry mouth, and "other." In several instances the patients' reactions were described in detail because of the complexity of the side effects complained of (see below).

Results. The results by both methods of analysis were essentially similar. The data on pain levels are summarized in Fig. 1, where the pain scores over a period of 4 hours are plotted for the placebo group, and for the 2 active treatment groups. There are no significant differences between the 3 treatments in regard to pre-treatment base level of pain. By the first interview point, *i.e.*, the 30-minute interview, there are significant differences between the active drugs and the placebo. Dexoxadrol is significantly superior

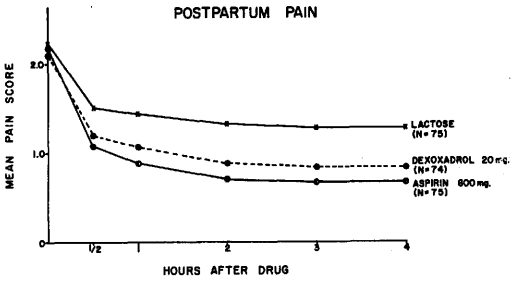

FIG. 1.

to placebo as an analgesic agent (Student's t-test; $P<.05$). Aspirin is also significantly better than placebo ($P<.01$), but does not differ significantly from dexoxadrol. The same situation obtains for the interviews at 1, 2, 3, and 4 hours. Table I summarizes the "pain relief" data.

There was a striking difference between the treatments in regard to side effects. Of 75 patients who received placebo, 2 complained of drowsiness and one of drowsiness and nausea. Of 75 patients who received aspirin, one complained of light-headedness, and one of drowsiness. Of the 74 patients who received dexoxadrol, 19 complained of light-headedness; 5 of drowsiness; one of drowsiness and light-headedness; one of light-headedness, weakness, anorexia, and dyspnea; and 5 showed somewhat more dramatic side effects. Of these 5, one complained of feeling "dopey, weak, and helpless"; one complained of light-headedness and numbness and was observed to weep; one complained of light-headedness, itching, of having "no feeling," being "drunk," and of "not being here." Of the other 2 patients, one stated that she felt drunk, and said that she was "not entirely present." She also said that her "hands had no real feeling" and seemed a bit numb. Four hours after the dose, all that remained was a slight light-headedness.

TABLE I. Postpartum Pain; Mean Pain Relief Scores.

	Hours after drug				
	½	1	2	3	4
Lactose (N = 75)	1.14	1.21	1.34	1.42	1.43
Dexoxadrol, 20 mg (N = 74)	1.55	1.72	1.92	1.97	1.97
Aspirin, 600 mg (N = 75)	1.72	1.92	2.15	2.19	2.19

The final patient was very upset, wept, and tried to get out of bed. She found it difficult or seemed unwilling to explain what was the matter. She said that her upper limbs seemed numb and as if they did not quite belong to her. There was no similar feeling in the lower limbs. She tried to bite her left arm several times as if to convince herself that it really belonged to her. Approximately 1¼ hours after the medication had been given, 50 mg of meperidine were given intravenously and within less than 10 minutes her condition was greatly improved although she still felt "peculiar." By 3 hours after medication the patient was walking around the ward in good spirits. In none of these patients was there any significant fluctuation in blood pressure, respiration, or pulse.

Discussion. At the dose employed in this study, dexoxadrol is an analgesic with a high incidence of untoward side effects, including some that might be called psychotomimetic. One question that immediately arises is whether or not the "analgesia" is really produced by the distracting side effects. This seems unlikely, in view of these facts: 1) very few patients complained of dramatic side effects, 2) complete or partial relief was reported in patients who had no side effects of any kind, and 3) some patients had side effects without obtaining any relief. On the other hand, the highest incidence of side effects of any kind did occur in the 33 patients who obtained complete relief at one or more interview points after administration of dexoxadrol. Fifty-eight per cent of these patients had one or more side effects from the drug, as contrasted with 29 and 31% respectively for the patients who achieved only partial relief during the 4 hours after dexoxadrol, or obtained no relief during this period.

These results seem of interest for at least two reasons. First, the clear-cut analgesia apparent in our study would not have been predicted from animal experimentation, since the laboratory tests suggested, if anything, a *decreased* tolerance to pain. Second, the psychotomimetic effects seen after dexoxadrol are reminiscent of the analgesic and psychotomimetic properties coexistent in such drugs as LSD(2) and as nalorphine(3), cyclazocine (4), and other narcotic antagonists. In this context, anti-morphine effects of dexoxadrol have been reported in mice(1).

Summary. Dexoxadrol, a compound which in animals appears to increase sensitivity to noxious stimuli, and to antagonize certain effects of narcotic analgesics, has been shown capable of relieving clinical pain. Unfortunately, at the doses employed in this study, the analgesic properties are associated with a high incidence of side effects, including psychotomimetic states. The coexistence of analgesic and psychotomimetic properties in dexoxadrol adds this drug to a list of other agents sharing these properties.

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Isolation of the Trachoma Agent in Cell Culture.* (29841)

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After establishment of isolates of the trachoma agent in the yolk sac of embryonated eggs, infection of cell cultures can be readily

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