males, the other parameters did not differ in 'impotent' rats in comparison with 'vigorous' NPA-treated rats.

Discussion. It has been shown that apomorphine provokes repeated penile erections in isolated rat[7,8], reduces ejaculation latency and intromission frequency in sexually experienced male rats[9], and restores ejaculation in 'impotent' rats[10], these influences on sexual behavior being antagonized by specific antagonists of brain dopamine receptors such as haloperidol and pimozide.

Generally speaking, NPA has been found to exert the same behavioral effects as apomorphine, being, however, more potent. In particular we have shown that NPA is much more potent than apomorphine as a SYS und PE inducer than as a SB inducer[1]. Accordingly it was suspected that NPA might strongly influence male rat copulatory behavior. Moreover, since it has been suggested that stereotyped movements might disturb copulatory behavior[10], and since it has been demonstrated that apomorphine doses eliciting SB lost the capability of inducing PE, NPA seems more appropriate than apomorphine for affecting male copulatory behavior, because the ratio between PE and SB-evoking doses is greater for NPA than for APO.

The results presented in this paper show that NPA, like apomorphine, affects copulatory behavior of 'vigorous' male rats reducing LE and IF, and restores copulatory behavior in naturally 'impotent' rats. These effects are produced by 10 $\mu g \cdot kg^{-1}$, i.p., a dose which does not provoke SB. On the other hand, increasing NPA dose to 80 $\mu g \cdot kg^{-1}$, NPA influence on copulatory behavior increased, despite the fact that this dose also caused SB (scored 2.5–3 accordingly to Costall et al.[11]). After this dose, however, whereas stereotype movements were easily observed during the latency before the first mount, they were not observed during mating activity.

In conclusion, NPA resembles apomorphine for its influence on male rat copulatory behavior. In particular the capability of NPA in restoring copulatory behavior in 'impotent' male rats must be carefully considered and evaluated also in the perspective of a therapeutic use.

1 A. Benassi-Benelli and F. Ferrari, Riv. Farmac. Ter., in press (1979).
2 D.A. Dewsbury, Eur. J. Pharmac. *17*, 221 (1972).
3 P. Södersten, D.A. Damassa and E.R. Smith, Horm. Behav. *8*, 320 (1977).
4 D.A. Dewsbury, in: Sexual Behavior: Pharmacology and Biochemistry, p. 169. Ed. M. Sandler and G.L. Gessa. Raven Press, New York 1975.
5 G. Bignami, Psychopharmacologia *10*, 44 (1966).
6 L. Cavalli-Sforza, Analisi Statistica per Medici e Biologi. Ed. Boringhieri. Torino 1976.
7 M. Baraldi and A. Benassi-Benelli, Riv. Farmac. Ter. *6*, 147 (1975).
8 M. Baraldi and A. Benassi-Benelli, Riv. Farmac. Ter. *6*, 361 (1975).
9 E. Paglietti, B. Pellegrini Quarantotti, G.P. Mereu, M. Petta, A. Bonanni and G.L. Gessa, Riv. Farmac. Ter. *8*, 281 (1977).
10 A. Tagliamonte, W. Fratta, M. Del Fiacco and G.L. Gessa, Riv. Farmac. Ter. *4*, 177 (1973).
11 B. Costall, R. Naylor and T. Wright, Arzneimittel-Forsch. *22*, 1178 (1972).

Baroreceptor and sympathetic responses to acebutolol, a β_1-adrenoceptor-blocking agent, in rabbits

A.M. Chevalier-Cholat and A. Friggi[1]

Unité de recherche de cardiologie expérimentale (INSERM U 175), 10, Avenue Viton F-13009 Marseille (France), 6 September 1978

Summary. Baroreceptor activity was increased after i.v. infusion of acebutolol in rabbits with an intact circulation, and in rabbits with a total cardiopulmonary by-pass. In rabbits with an intact circulation, renal nerve activity was reduced.

We have previously studied the responses in rabbits to i.v. infusion of β_1- β_2-adrenoceptor-blocking agents (propranolol, pindolol, timolol). We observed a reduction in renal nerve activity[2–4]; aortic blood pressure and peripheral resistance were reduced and baroreceptor activity was increased in rabbits with intact circulation[4], as well as in rabbits with total cardiopulmonary by-pass[3]. These results suggested a direct vascular action of the 3 drugs.

The purpose of the present work was to compare the effects of a β_1-adrenoceptor-blocking agent (acebutolol) to those of β_1- β_2-adrenoceptor-blocking drugs.

Methods. All methodological details were similar to those already described[3,4]. 15 experiments were performed in New Zealand white rabbits anaesthetized with i.v. urethane. Aortic blood pressure was measured by means of a catheter introduced via the transfemoral artery and connected to a pressure transducer. Aortic blood flow was measured by meaos of an electromagnetic probe inserted around the abdominal aorta. A total cardiopulmooary bypass (TCB) was created in 5 animals. After thoracotomy, the blood from the right atrium was passed through a bubble oxygenator, rewarmed and reinjected into the ascending aorta by means of a pulsatile pump oqerating at a constant frequency. Arterial flow was measured by means of an electromagnetic flowmeter inserted in series between the pulsatile pump and the arterial cannula. Peripheral resistance was calculated by dividing the mean aortic pressure by the mean aortic blood flow.

Baroreceptor activity was recorded from the whole aortic nerve by means of platinum electrodes. After amplification, the nerve activity was counted over a 2-min period with the aid of a digital counter and expressed in counts/sec as a percentage of the activity recorded before the introduction of the drug. The relationship between nerve activity and blood pressure was determined during a control period by bleeding (up to −20 mm Hg), each animal serving as its own control. After reinfusion of the blood, the drug was infused. The activity of the nerve was compared at the same pressure level before aod during infusion of the drug. Efferent sympathetic activity from a left renal-nerve bundle was recorded, counted and expressed as described for aortic nerve activity.

Acebutolol, dissolved in 0.9% saline, was infused into the right jugular vein (3 mg/kg/h in animals with intact circulation) or into the oxygenator (5 mg/kg/h in animals with TCB). The values were expressed as mean ± SEM and the data were compared by means of the analysis of variance.

Results. Peak effects of acebutolol on haemodynamic variables and nervous activities were obtained when the in-

fused amounts reached 0.3–3.0 mg/kg. In rabbits with intact circulation (IC) acebutolol induced a significant decrease in heast rate; no significant effects upon mean blood pressure and peripheral resistance (table), and aortic blood flow were observed. By contrast, in all animals under TCB (at constant arterial reinjection frequency) we noted a decrease in mean blood pressure and peripheral resistance (table); aortic blood flow did not change significantly.

A progressive increase in baroreceptor activity occurred immeciately after the start of infusion of acebutolol in all experiments (IC or TCB). Reductions in renal nerve activity were observed during infusion of acebutolol in rabbits with IC ($-27.0\pm2.3\%$; $n=3$ animals).

Discussion. The present experiments show that acute i.v. administration of acebutolol in rabbits induced an increase in baroreceptor firing and decreased postganglionic sympathetic renal-nerve discharge. Blood pressure and calculated peripheral resistance were reduced under TCB in contrast with the results obtained in rabbits with IC. The increase in peripheral resistance observed under IC in some animals might result from a reflex response to the reduced cardiac output. This interpretation could be consistent with our findings in TCB experiments, where a decrease in peripheral resistance was constantly noted after drug.

Sympathetic renal nerve activity was reduced by acebutolol. Similar results were obtained with β_1- β_2- adrenoceptor-blocking agents[2–4] and with another β_1-adrenoceptor-blocking agent, atenolol[5].

As observed with β_1- β_2-adrenoceptor-blocking agents, aortic baroreceptor firing was increased by acebutolol (and by atenolol; unpublished experiments) in spite of a diminished blood-pressure level. This increase in baroreceptor discharge was probably not caused by the vasodilation, which was not observed in all experiments. It is conceivable that the drug-induced change in aortic nerve activity could be due to an indirect effect mediated via central nervous effects on sympathetic nerve activity to the receptor area. Another possibility would be that inhibition of beta-adrenergic tone by the drugs leads to some contraction of aortic smooth-muscle cells, mimicking the effects of sympathetic activity and noradrenaline upon the baroreceptor area.

In conclusion it is noteworthy that all the β-adrenoceptor-blocking agents studied (with common antihypertensive properties but with different pharmacological patterns) induced an increase in baroreceptor activity. This phenomenon may initiate or contribute to the reduction in sympathetic outflow described at the splanchnic[6,7] and at the post ganglionic[2–5] levels.

Haemodynamic and baroreceptor responses to i.v. infusion of acebutolol (mean ± SEM)

	Intact circulation	Total cardiopulmonary by-pass
Heart rate in	-17.7 ± 4.7	0
beats/min	$n=7$	
(%)	$p<0.001$	
Mean blood	-6.0 ± 7.8	-8.8 ± 3.5
pressure	$n=7$	$n=5$
(mm Hg)	NS	$p<0.01$
Peripheral	$+4.0\pm22.1$	-15.8 ± 4.9
resistance in AU	$n=4$	$n=5$
(%)	NS	$p<0.01$
Baroreceptor activity	$+19.9\pm4.2$	$+14.4\pm9.9$
in counts/sec	$n=7$	$n=5$
(%)	$p<0.001$	$p<0.05$

n: Number of animals, NS: not significant, AU: arbitrary units.

1 We wish to thank Mrs H. Bodard and Mrs F. Raimbault for their technical collaboration and Specia Laboratories for supplying acebutolol. This work was supported by a grant from INSERM (ATP No. 15.75.38).

2 A. Friggi, A.M. Chevalier-Cholat and J. Torresani, C.r. Acad. Sci. Paris *284*, 1835 (1977).
3 A. Friggi, A.M. Chevalier-Cholat and J. Torresani, Eur. J. Pharmac. *45*, 295 (1977).
4 A.M. Chevalier-Cholat, A. Friggi and J. Torresani, Biomedicine *28*, 67 ((978).
5 A. Friggi, A.M. Chevalier-Cholat and H. Bodard, Experientia *33*, 1207 (1977).
6 P.J. Lewis and G. Haeusler, Nature *256*, 440 (1975).
7 N.T. Daskalopoulos and H. Schmitt, Thérapie *30*, 843 (1975).

Embryotoxicity and teratogenicity of Cis-diamminedichloroplatinum

R. Lazar, P.C. Conran and I. Damjanov

University of Connecticut Health Center, Farmington (CT 06032, USA), and Hahnemann Medical College, Philadelphia (Pennsylvania 19102, USA), 10 August 1978

Summary. Cis-diamminedichloroplatinum has lethal, toxic and teratogenic effects on presomitic mouse embryos in doses that are not toxic to adult animals.

Cis-diamminedichloroplatinum (II) (DDP) is a new antitumor compound that has shown promising effects in preclinical and clinical trials[1]. In addition to tumoricidal effects DDP has antimicrobial, immunosuppressive and mutagenic properties. In this paper we report that DDP is also extremely embryotoxic and teratogenic in the mouse.

Material and methods. Timed-pregnant outbred Swiss Webster mice were injected i.p. with freshly dissolved DDP on day 8 of pregnancy. The day the vaginal plug was found was considered to be day 1. Animals were injected with DDP in a single dose of either 13, 8 or 3 mg/kg b.wt. Control animals were either not injected at all or injected with 0.5 ml of saline. Pregnant dams were sacrificed on the 18th day of pregnancy. The numbers of live and stillborn fetuses and early and late resorptions were recorded. Each fetus was weighed. All the fetuses were examined under a dissecting microscope. Every third fetus was fixed in ethanol, cleared in glycerol and stained with alizarin red S for detection of skeletal anomalies. The experimental data were analyzed by use of Student's t-test.

Results. The data on embryotoxicity of DDP are summarized in the table. No maternal death was observed in any of the experimental groups. The live fetuses born to DDP treated dams weighed less than the controls despite the fact that each pregnant uterus contained fewer viable fetuses and that this could have caused more weight gain in