2 compounds. This dose of clomiphene was clearly not effective enough to maintain the uterotrophic effect it had at 3 doses nor to extend vaginal cornification throughout the treatment period as estradiol did. It appears that clomiphene was estrogenic enough to mimic the early effects of estradiol but not to maintain those effects over a long period.

The results add further evidence to the reports[4,5,8] that generalizations concerning the relative estrogenic effectiveness of synthetic antiestrogens should be viewed with caution. These agents which possess at least weak estrogenicity may be as effective or even more so than estradiol in influencing the various indeces of estrogenic sensitivity. Clearly, clomiphene is one of those.

Adrenergic supersensitivity of the pupil in idiopathic headache[1]

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Summary. In idiopathic headache (IH) sufferers, phenylephrine and fenfluramine induce a pupillary dilatation respectively greater and lesser than in controls. The difference may be due to a supersensitivity of the iris alpha adrenoceptors caused by a deficiency of noradrenaline in the iris adrenergic nerve terminal of the IH sufferer. These findings seem to support the hypothesis of a brain receptorial, monoamine supersensitivity in IH.

Idiophatic headache (IH) could be due to an impairment of the central modulation of pain[2]. A deficiency of brain monoamines, 5-hydroxytryptamine in particular, and consequently a supersensitivity of the peculiar postsynaptic receptors, has been suggested to be the main biochemical disorder in IH[3].

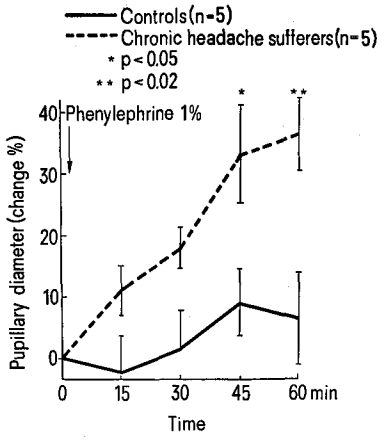

Fig. 1. Pupillary dilatation after phenylephrine 1% instilled in the right conjunctival sac. Each point represents the mean ± SE; *, **, significantly different from the control group.

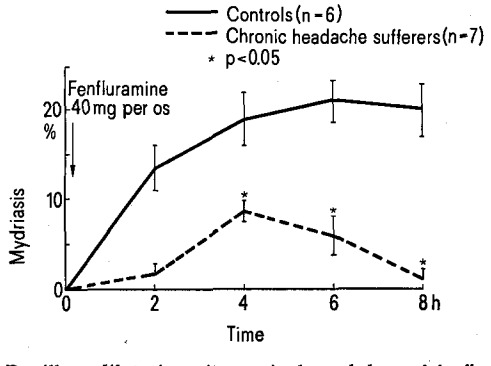

Fig. 2. Pupillary dilatation after a single oral dose of fenfluramine. Each point represents the mean ± SE; *, significantly different from the control group.

Since the pupil innervation is considered as an emanation of the brain, it is therefore possible that the pupil reactivity provides indirect information concerning the monoamine turnover and receptorial sensitivity of the central nervous system.

Materials and methods. 12 drug-free volunteers, sufferers from chronic headache, were studied. Phenylephrine 1% was instilled in 5 of the patients (3 women and 2 men with a mean (± SE) age of 40 (± 19) years, ranging from 35 to 46) in the right conjunctival sac. The remaining 7 patients (3 women and 4 men with a mean (± SE) age of 30 (± 40) years, ranging from 17 to 48) received 40 mg of fenfluramine hydrochloride in a single oral dose.

The control group was composed of 11 healthy drug-free volunteers. 5 controls (2 women and 3 men with a mean (± SE) age of 26 (± 22) years, ranging from 21 to 32) received phenylephrine. The fenfluramine control group was composed of 3 women and 4 men (with mean (± SE) age of 32 (± 18) years, ranging from 20 to 42).

The pupil diameter was always studied in the same light intensity by using the photographic technique of Sneddon and Turner[4,5] with some modifications[6]. The pupil was measured before the drugs; 15, 30, 45 and 60 min after phenylephrine and 2, 4, 6 and 8 h after fenfluramine. Differences between pre- and post-drug values and between headache and control groups were compared by using a trained Student's t-test.

Results. a) Phenylephrine instillation did not induce any statistically significant pupillary dilatation in controls. In IH sufferers, it provoked a statistically significant mydriasis which lasted for at least 60 min. The p-value of the difference between pre-drug and 15, 30, 45 and 60 min after phenylephrine was 0.05, 0.01, 0.02 and 0.005 respectively. The difference between the control and headache group was statistically significant 45 and 60 min after the eye instillation (figure 1).

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b) Oral fenfluramine dilated pupils in controls. This dilatation was statistically significant at 4, 6 and 8 h after the drug with p-value 0.05, 0.01 and 0.05 respectively. There was no significant dilatation of the pupils of IH sufferers after fenfluramine. The difference between the headache and control groups was statistically significant 4, 6 and 8 h after the drug (figure 2).

Discussion. The mydriatric hyper-reactivity to direct alpha adrenoceptor stimulating agent, phenylephrine, seems to indicate a supersensitivity of iris adrenergic receptors in IH.

Fenfluramine mydriasis in controls was similar to that reported by others[7] but in IH sufferers it was significantly less. This difference could be due to a more rapid plasma clearance of this drug or to a changed reactivity of the iris. Fenfluramine precipitates headache[8,9] convincingly by acting on the monoamine turnover[10]. In animals it exhibits peripheral cardio-vascular effects mainly by displacing noradrenaline stores at the adrenergic nerve terminal[11]. If the scarce fenfluramine-induced mydriasis in IH sufferers is due to a poor effect of the drug on the pupil, a reduced release or availability (or both of them) of noradrenaline in the iris nerve terminal can be hypothesized.

In conclusion: We observed on the one hand the hyperreactivity of the iris to an alpha adrenoceptor stimulator, phenylephrine, and on the other a hyporeactivity to a noradrenaline releaser, fenfluramine. Both these suggest a condition of supersensitivity caused by a deficiency of the specific transmitter at the iris adrenergic neuronal site in the IH sufferer.

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Effects of alpha- and beta-adrenergic blockers on the actions of noradrenaline on body temperature in the newborn guinea-pig

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Summary. The effect of NA injected into the lateral cerebral ventricle on T_c was blocked by alpha-adrenergic receptor blockers, but not by beta-receptor blockers, whereas the effect of systemically administered NA was blocked by i.p. administered beta-receptor blockers, but not by alpha-blockers.

Noradrenaline (NA) injected s.c., i.m., i.v. or into the lateral cerebral ventricle increased oxygen consumption and colonic temperature in newborn animals[2–8]. The effect of NA applied centrally[3–5], as well as systemically[7,8], decreased with age and practically disappeared at the age of 3–4 weeks. In contrast, adrenaline having an effect of only a fraction that of NA in the newborn guinea-pig[7], retains its effectiveness on metabolic rate throughout life[9]. For a more penetrating analysis, both NA and the adrenergic blocking drugs were administered systemically and centrally.

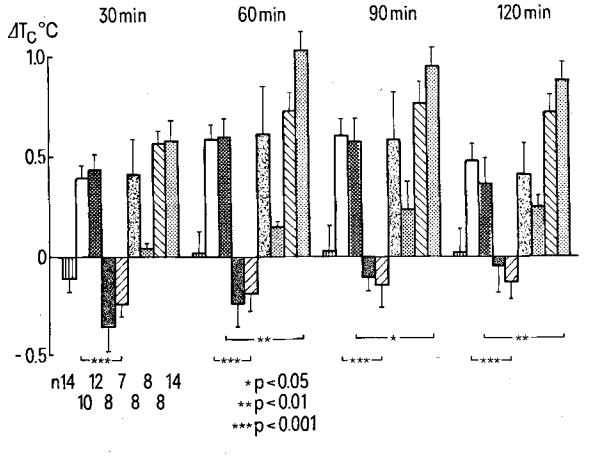

Fig. 1. The effect of 20 µl physiological saline i.c.v. (▥), 100 µg/kg NA i.m. (□), 10 µg NA i.c.v. (■), 1 mg/kg propranolol i.p. (▩), 1 mg/kg propranolol i.p. + 100 µg/kg NA i.m. (▨), 1 mg/kg propranolol i.p. + 10 µg NA i.c.v. (▤), 30 µg propranolol i.c.v. (▩), 30 µg propranolol i.c.v. + 100 µg/kg NA i.m. (▧) and 30 µg Propranolol i.c.v. + 10 µg NA i.c.v. (▤) on colonic temperature 30, 60, 90 and 120 min after NA.

Materials and methods. Colonic temperature (Tc) was measured by copper-constantan thermocouples in a depth of 6 cm at an ambient temperature of 30 °C in unanaesthetized guinea-pigs aged 1–12 days. This age was chosen because within this range the decrease in the effect of NA could be demonstrated, and the increase in Tc was still consistently present at the age of 12 days[3]. The drugs were injected either i.p., i.m., or into the lateral cerebral ventricle (i.c.v.) through the soft skull. Alpha- and beta-adrenergic receptor blockers were injected 30 min before NA. Injections of physiological saline served as controls.

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