should exert a powerful electronic influence upon the aromatic ring. In addition, it could provide an acceptor site for hydrogen bonding. Examination of the analgesic activity of (**3**) should thus yield information upon the relative importance of steric vs. inductive influences.

1-Fluorocodeine (**3**) was prepared from 1-aminocodeine[3] via the diazonium fluoroborate, which was obtained as a yellowish powder on carrying out the diazotization in a 1:2 mixture of fluoroboric acid and ethanol. Schiemann-reaction[4], i.e. pyrolysis of this salt, gave acceptable yields (~ 30%) of (**3**) only if performed on a small scale (100–200 mg). However, the method of KIRK and COHEN[5] for photochemical decomposition of diazonium fluoroborates in 50% aqueous fluoroboric acid provided the desired (**3**) in similar yields on a 0.5–1.0 g scale. The compound was isolated by column chromatography on SiO_2 (Merck, 70–350 mesh) with chloroform and chloroform-acetone-diethylamine (5:1:0.5) as eluants; it was purified by recrystallization from acetone-hexane. Colorless crystals, m.p. 176–179°; mol. wt. 317 (mass spec.; calc. for $C_{18}H_{20}NO_3F$, 317). 1-Fluorocodeine had the expected spectroscopic characteristics; the splitting of the NMR-signal from the proton at C-2 into a doublet (1H; δ 6.41, $J = 12$ Hz) by the adjacent fluorine conclusively identifies the compound[6].

The (**3**) obtained by either thermal or photochemical decomposition of the fluoroborate was sometimes accompanied by varying amounts of (**2**); similar replacement of the diazonium group by hydrogen has been observed in other instances[7].

Pharmacological investigation of (**3**) gave the results summarized in the Table. Analgesic activity was determined by the hot-plate method[8]. Clearly, neither the pain-relieving effect nor the other observed parameters were significantly different from those of (**2**). This finding strongly suggests that the decrease in analgesic potency found[1] on introduction of substituents on the aromatic ring of (**2**) and its relatives is caused by the bulk of these substituents; their inductive effect seems to have no detectable influence.

The binding of (**3**) to the narcotics receptor of rat brain has been measured[9] by Dr. WERNER A. KLEE, whom we wish to thank for permission to quote his findings. The dissociation constants oberved for (**3**), (**2**), and (**1**) are 7×10^{-7}, 8×10^{-7}, and 3×10^{-9} *M*, respectively. Here, again, the behavior of (**3**) is thus not significantly different from that of (**2**)[10].

Zusammenfassung. Das bisher unbekannte 1-Fluorcodein wurde durch Schiemann-Reaktion aus 1-Aminocodein dargestellt. Es ist nahezu ebenso stark analgetisch wirksam wie Codein, und wird fast ebenso stark an den Morphin-Rezeptor des Rattengehirns gebunden. Diese Befunde zeigen, dass die früher beobachtete verringerte Aktivität von 1-Chlor-, 1-Brom-, und 1-Acetocodein auf die Raumbeanspruchung der Substituenten zurückzuführen ist.

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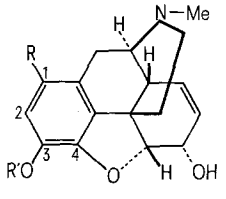

(**1**): R = R' = H
(**2**): R = H, R' = Me
(**3**): R = F, R' = Me

Table I

		1-Fluoro-codeine (*2*)	Codeine (*3*)
ED_{50} (mg/kg)		7.9	7.5
Onset of action		4.0	3.4
Peak of action	(min after	22.8	12.4
Duration of action	administration)	118.8	108.7

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[10] The authors are much indebted to Dr. EVERETTE L. MAY, Laboratory of Chemistry, NIAMDD, for the pharmacological data, and to Dr. K. L. KIRK of the same laboratory for the photochemical experiments.
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Hypersensitivity to Lysergic Acid Diethylamide (LSD-25) and Psilocybin in Essential Headache[1]

The brain modulation of the pain input is partly controlled by monoamines, mainly by 5-hydroxytryptamine (5-HT)[2,3]. An impairment of the modulation following a deficiency of 5-HT, has been recently hypothesized in the mechanism of migraine and other essential headaches (EH)[4,5]. According to the supersensitivity phenomenon, a deficiency of 5-HT could induce an increased reactivity of the specific brain receptors to the same

[1] This study has been carried out with a grant from the National Council of Research, Rome, Italy.
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agonist[6–8]. 5-HT does not pass through the blood brain barrier (BBB) so it cannot be used for exploring a situation of brain supersensitivity. Lysergic acid diethylamide (LSD-25) and psilocybin have an indolic structure with chemical analogy to 5-HT[9]; they pass through the BBB[10] and presumably affect the serotonin receptors. These drugs seemed suitable for detecting a possible 5-HT hypersensitivity in EH sufferers, also in view of the frequent elementary hallucinations such as prodromata of the migraine attacks.

Methods. All subjects were volunteers. 30 normal (non-migraine-headache sufferers) subjects (18 women and 12 men ranging in age from 25 to 60; average age 43.3) were selected among our staff (physicians, biochemists and technicians) and among the patients of our Department of Clinical Pharmacology. Every 3 days at 09.00 h, while fasting, they took, according to a random scheme, an oral dose of LSD-25 (350 ng/kg), psilocybin (20 μg/kg), and placebo. The same oral doses were administered to the EH sufferers. The EH sufferers were divided into 2 groups; the first one of 36 patients (24 women and 12 men ranging in age from 22 to 62; average age 42.4) took placebo and LSD-25 at random, with an interval of 3 days; the second one of 36 patients (20 women and 16 men; between the age of 26 and 58; average age 43.8) received placebo and psilocybin, with the same schedule as the LSD-25 group. Subjects were questioned about their sensations, 4, 8 and 12 h after the drug was administered. The reactions were classified in 3 grades: 0. No reactions. 1. Simple psycho-affective reactions (nervousness, slight anxiety, depression, euphoria). 2. Psycho-affective reactions plus perceptive distortions and/or hallucinations.

Results. a) Placebo. In all, placebo did not provoke psychic reactions. Some vague sensations were not considered. b) LSD-25 (Figure 1). In normal subjects, reaction 0 has been observed in 73%, reaction 1 in 27%, and reaction 2 in none. In EH the results have been 0 in 25%, 1 in 57%, 2 in 18%; in 3 patients the entity of the hallucinations was quite disagreeable and the phenomena were promptly interrupted by an oral dose (25 mg) of chlorpromazine. c) Psilocybin (Figure 2). In normal subjects, reaction 0 has been registered in 86%, reaction 1 in 14%, and reaction 2 in none. In the EH sufferers we obtained reaction 0 and 1 in 41%, and 2 in 18%.

The statistical evaluation, carried out with the Mann-Whitney U test, shows a highly significant difference ($p < 0.001$) between the EH and non-EH groups.

Comment. The greater susceptibility of the EH sufferers to non-hallucinogenic amounts of LSD-25 and psilocybin could be due to a particular BBB permeability to these drugs or to a supersensitivity at the level of the central nervous receptors or both. It is still unknown if LSD-25 acts independently or dependently on its action on 5-HT: if dependently a competitive or mimetic action on 5-HT receptors is under discussion[11–13].

The psychic activity of LSD-25 could also depend on an adrenergic mechanism, since LSD-25 facilitates the catecholamines activity in animal and in man[14,15].

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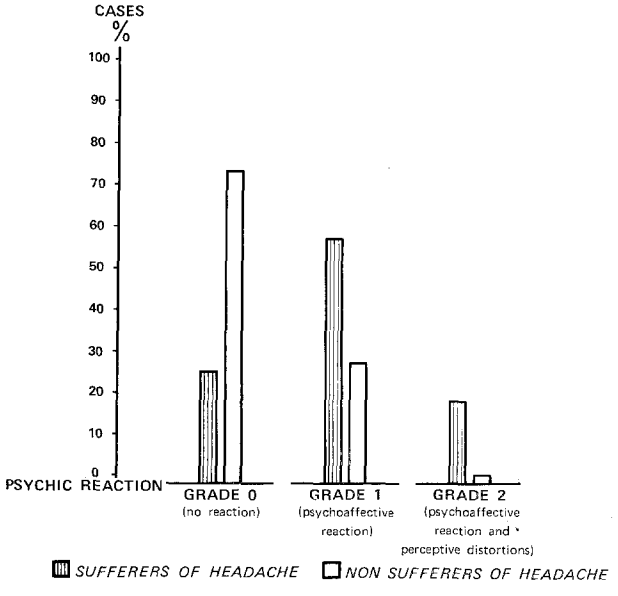

Fig. 1. Migraine-headache sufferers exhibit increased psychic sensitivity to LSD-25, in comparison to non-headache sufferers ($p < 0.001$).

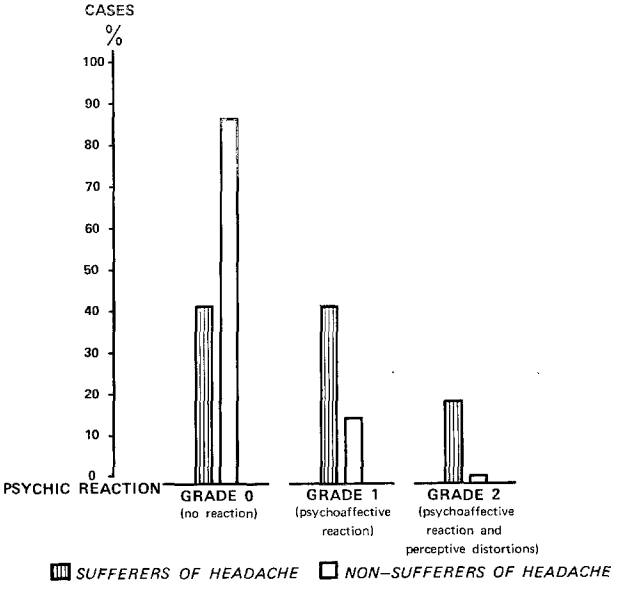

Fig. 2. Migraine-headache sufferers show greater psychic sensitivity to psilocybin, than non-headache sufferers ($p < 0.001$).

The psilocybin hypersensitivity is also in agreement with the hypothesized brain monoamine supersensitivity in migraine-headache; nevertheless the interpretation is more difficult, because of scarse information about the pharmacological mechanism of this drug. However, psilocybin, besides possessing a chemical structure similar to 5-HT, exhibits, like LSD-25, mimetic and antagonist effects on 5-HT[16,17].

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[17] The authors are grateful to Sandoz Pharmaceuticals, Basel (Switzerland), for the supply of LSD-25 and psilocybin, and to Miss Una Hanratty for her assistance in the preparation of this paper.

Riassunto. Usando dosi suballucinogene di LSD-25 e di psilocibina è stato dimostrato che i soggetti sofferenti di cefalea essenziale sono più sensibili dei soggetti normali agli effetti psichici di questi farmaci. Questa ricerca sembra avvalorare l'ipotesi di una condizione di supersensibilità monoaminica cerebrale nelle cefalee essenziali.

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Some Cross-Protection Experiments on the Cholinergic Receptor of Frog Ventricular Strip

The pharmacological characteristics of cholinergic receptors in frog ventricle were first described by Clark[1-3]. The author found that acetylcholine (Ach) produces an inhibitory action on the contractile force. He observed that the antagonistic action of atropine (Atr) persists for a long time after repeated washing away of the drug. Ach did not increase the rate of recovery of the heart from Atr. At all Atr concentrations, the same maximal response could be elicited, provided the Ach concentration was made high enough. The effect of Atr on Ach seems to fit the classical description of competitive antagonism[4]. According to the mass law theory and occupancy assumption, when a maximal response is obtained in the presence of Atr the receptors should be occupied by Ach molecules and Atr molecules should have been displaced. Therefore, if the isolated tissue is washed many times by solution containing high concentration of Ach, it should have regained its original sensitivity to Ach. In fact, however, the decreased sensitivity persisted.

The aim of our study is to obtain further information by cross-protection experiments and to gain some insight into the mechanism of this anomalous antagonism.

Methods. The same method as described earlier[5] was used. In all experiments, Ach was applied at the concentration of 2 µg/ml. The contact time was 2 min. After this, the tissue was washed threefold with fresh solution and allowed to restore the normal ventricular function for about $^1/_2$ h. Atr was used in dose of 40 ng/ml. Phenoxybenzamine (Phe) was added to the bath at the concentration of 250 ng/ml. The contact time of antagonist with the tissue was 1 h. In cross-protection experiments[6], carbachol (Car) was used as the protective agent at the concentration of 20 µg/ml. This drug was simultaneously added to the bath with antagonist. The contact time of antagonist plus Car was 1 h. In such experiments Ach sensitivity of the strip was tested by 3 additions of agonist to the bath before the incubation. After the washout of antagonist plus Car, $^1/_2$ h was waited. Then, the Ach sensitivity was tested again. In each experiment group, the most obvious mean response induced by Ach was accepted as the 100% of Ach sensitivity. Other mean responses were evaluated according to this value. The numbers obtained in this way were graphically plotted versus the time (h).

Results. Ach induced a rapid and reversible negative inotropic effect. The sensitivity to Ach was tested during about 5 h. No any significant change was observed in the effect of Ach (Figure 1, no ago-antagonist) 6 strips were used ($n = 6$).

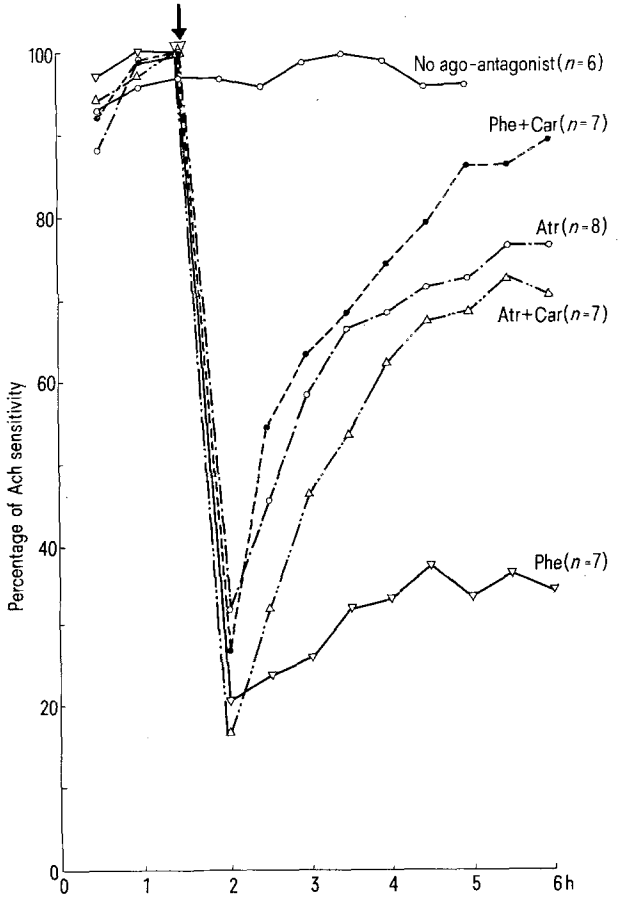

Fig. 1. ↓ 1 h treatment of the strips with antagonist (Phe, Atr) or antagonist plus Car, and then washing with fresh normal solution.

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