In a recent study, MARTIN[19] reported the effects of various cations on choline influx, noting that the net transfer of choline obeyed first-order kinetics during the first h. Using the data in Table I from [19], we note that the presence of lithium increases the pseudo first-order rate constant of choline to 0.042 min^{-1} and that this value is independent of choline concentration over the range studied.

In a final series of duplicate efflux studies, we obtained a k_e of 0.085 min^{-1} wherein the supernatant contained a choline concentration of 12 meq/l. Thus we note that choline increases lithium's normal transfer rate for both influx and efflux[20].

Zusammenfassung. Nachweis einer Erhöhung des Li-Austausches in Rinder-Erythrozyten bei Anwesenheit von Cholinchlorid im Extrazellularraum.

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A Comparative Study of Some Anti-Inflammatory Drugs in Wound Healing of the Rat

Anti-inflammatory drugs are widely used in the treatment of various inflammatory skin disorders[1,2]. The rate of wound healing is invariably depressed by these agents[3,4]. A comparative study between steroid and non-steroid anti-inflammatory drugs in wound healing is not yet available.

This study reports the effect on wound healing of phenylbutazone, dexamethasone and a new non-steroid anti-inflammatory drug: 10 undecen-1-thiopseudourea iodide, AHR-1911[5]. This latter drug has been recently reported to be useful in the treatment of several inflammatory skin diseases[6,7].

Materials and methods. We have used albino rats, of either sex, weighing between 300 and 350 g. Under ether anesthesia, an incision 4 cm long was made with a scalpel through the skin of the back previously shaved. The incision was sutured with separate stitches about 0.5 cm apart. A group of rats were adrenalectomized and maintained on normal saline.

The tensile strength of the wound was determined 4 and 6 days after wounding with a tensiometer designed in our laboratory according to the principles already followed by other authors[8]. A brief report about this tensiometer has been previously published[9].

The amount of hydroxyproline was determined in unwounded skin and in wounds 6 and 12 days after operation. Preparation of skin samples was performed according to the method followed by SANDBERG and ZEDERFELDT[10]. Hydroxyproline concentration was measured by the method of MITOMA et al.[11]. Color measurement was determined in a Klett-Summerson photo-electric colorimeter using green filter. Our recoveries ranged between 94–102% for amounts of hydroxyproline added to samples in the range of concentrations studied. Statistical analysis was performed by the Student-*t*-test for non-paired groups[12].

Table I. Effect of phenylbutazone, dexamethasone and AHR-1911 on wound healing of the rat

Treatment	Tensile strength of the wound (g)[a]	
	4th day	6th day
Control	114 ± 3.09	216 ± 5.83
Phenylbutazone, 50 mg/kg	70 ± 2.90 (–39)	139 ± 8.70 (–36)
Dexamethasone, 1 mg/kg	84 ± 2.68 (–26)	155 ± 2.24 (–28)
AHR-1911, 50 mg/kg	92 ± 2.00 (–19)	177 ± 2.51 (–18)

[a] Mean ± S.E. for 5 to 6 experiments. Values for treated groups are different from controls, $P < 0.001$. Percent change of controls in parenthesis.

Table II. Effect of AHR-1911 on wound healing of adrenalectomized rats

Treatment	Tensile strength of the wound (g)[a]	
	4th day	6th day
Control	114 ± 3.09	216 ± 5.83
Adrenalectomized rats	135 ± 4.32[c] (+18)	250 ± 7.88[d] (+16)
AHR-1911, 50 mg/kg	92 ± 2.00[b] (–19)	177 ± 2.51[b] (–18)
AHR-1911, 50 mg/kg Adrenalectomized rats+	98 ± 5.32[d] (–14)	190 ± 7.30[d] (–12)

[a] Mean ± S.E. for 5 to 6 experiments. Values for treated groups are different from controls as follows, [b], $P < 0.001$; [c], $P < 0.01$ and [d], $P < 0.05$. Percent change of controls in parenthesis.

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Table III. Effect of phenylbutazone and AHR-1911 on tissue hydroxyproline content during wound healing of the rat

Treatment	Tissue hydroxyproline content (μg/mg of dried tissue)[a]		
	skin	6th day	12th day
Control	4.30 ± 0.32	3.21 ± 0.18[b] (−25)	5.69 ± 0.21[b] (+32)
Phenylbutazone, 50 mg/kg	4.58 ± 0.20 (+6)	4.25 ± 0.32[c] (+32)	3.78 ± 0.23[b] (−34)
AHR-1911, 50 mg/kg	3.94 ± 0.14 (−8)	4.21 ± 0.12[b] (+31)	4.80 ± 0.12[d] (−16)

[a] Mean ± S.E. for 6 to 8 experiments. Values for treated groups are different from controls as follows, [b], $P < 0.001$; [c], $P < 0.01$ and [d], $P < 0.05$. Rest values are not significantly different, $P > 0.1$. Percent change of controls in parenthesis.

Results and discussion. Table I shows the effect of phenylbutazone, dexamethasone and AHR-1911, at equivalent anti-inflammatory doses, on the rate of wound healing in the rat. Phenylbutazone was the most potent drug in depressing the tensile strength of the wound (36–39%), whereas AHR-1911 was the least potent agent (18–19%). Dexamethasone was intermediate. Lower anti-inflammatory doses of AHR-1911 did not modify the rate of wound healing. The retardation potency on wound healing was as follows: phenylbutazone > dexamethasone > AHR-1911. This depression of the rate of wound healing by AHR-1911 seems to be due to a direct influence on skin and not through adrenal glands stimulation (Table II).

Table III shows that the hydroxyproline content in control rats decreased on 6th day of healing (−25%), while it increased on 12th day of healing (+ 32%). These findings are in agreement with those found by SORENSEN[13]. AHR-1911 as well as phenyl-butazone increased the hydroxyproline content on 6th day of healing to the levels of control rats, but they decreased it on 12th day. Phenylbutazone was twice as potent as AHR-1911 in lowering the levels of hydroxyproline of the wound.

Anti-inflammatory agents have been shown to stabilize the membrane of lysosomes[14] and to prevent the enzymes release from lysosomes during the inflammation phase of wound healing[15]. As a result of this membrane stabilization of lysosomes by anti-inflammatory agents, the hydroxyproline content of the wound increases relatively to levels of unwounded skin. Absolute values of hydroxyproline were decreased on 12th day of healing by both anti-inflammatory drugs (Table III); nevertheless, AHR-1911 had less effect than phenylbutazone on hydroxyproline levels of the wound.

Since hydroxyproline is a specific amino-acid of collagen[16], we assume that the collagen content of the wound is less modified by AHR-1911, and thus the rate of wound healing. These findings might be of importance in therapeutics.

Resumen. Varias drogas anti-inflamatorias incluyendo una droga antiinflamatoria no esteroidea nueva fueron investigadas en heridas producidas en ratas. AHR-1911 resultó ser la droga menos depresora de la cicatrización de las heridas cuando se comparó con la fenilbutazona y la dexametasona. Un menor contenido de colágeno en las heridas fue observado con el uso de AHR-1911.

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[17] Present address: Emory University School of Medicine, Atlanta, Ga. USA.
[18] This study was in part presented at IV Latin-american Congress on Pharmacology and Therapeutics, Caracas, Venezuela, July 9–14, 1972.
[19] AHR-1911 was kindly supplied by Professor N. ERCOLI. Dexamethasone and phenylbutazone were supplied by Merck Sharp and Dohme and Geigy Laboratories, respectively, Caracas, Venezuela.

Open-Field Behavior and Acquisition of Discriminative Response Control in Δ^9-THC Tolerant Rats[1]

If complete tolerance to a drug occurs, no discriminative control based on the presence or absence of that drug in the CNS would seem possible. BUENO and CARLINI[2] have shown that discriminative responding is possible when using a cannabis extract, even after tolerance had been established. Discriminative training started when the rats negotiated a vertical rope as fast as did the controls (tolerance). Our working hypothesis was that if some tolerance occurred, then the cueing effects of tetra-hydrocannabinol (THC) should be weakened and discriminative response control should therefore develop more slowly in tolerant animals as compared to non-tolerant. The present study was undertaken to investigate this, and in addition open-field behavior before and after the presumed development of tolerance was studied.

Materials and methods. 18 male albino Sprague-Dawley rats (300–325 g), from a commercial breeder (Anticimex AB, Sollentuna, Sweden), were used. They

[1] Numbering system according to IUPAC rules. The drug was generously supplied by Dr. T. PETRZILKA, University of Zürich.
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