TABLE 1. *Serum phenytoin levels, phenytoin half-lives and HPPH:DPH ratios in 6 patients on sulthiame, and repeat estimations one month after sulthiame was stopped*

Patient (age and sex)	Dose of phenytoin (mg/day)	Dose of sulthiame (mg/day)	Serum phenytoin (μM)		Phenytoin half life(h)		HPPH:DPH ratio	
			Before	After	Before	After	Before	After
FW (23M)	150	600	20	10	34·2	18·2	40·8	74·0
RC (43M)	300	400	46	23	31·2	16·6	28·6	81·4
CH (28F)	300	600	78	43	46·3	22·5	14·3	27·7
WP (44M)	300	600	82	46	66·4	40·6	12·0	16·4
MS (25M)	300	400	142	56	77·0	41·2	13·5	40·2
PH (22M)	300	600	180	112	79·4	45·6	4·6	5·2
*Mean			72·9	37·7	51·9	28·3	19·0	40·8
**Significance of difference			<0.05		<0.05		<0.05	

*Means for serum phenytoin level and half-life based on logarithmically transformed data,

**Wilcoxon's test for pair differences.

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Anti-nociceptive effects in N-substituted cyclohexylmethylbenzamides

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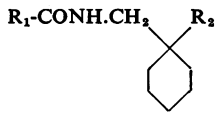
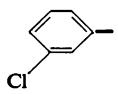
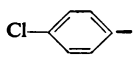
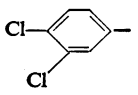
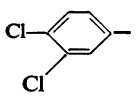
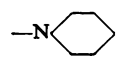
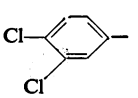
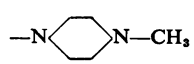
In the mouse, certain N-substituted cyclohexylmethylbenzamides markedly inhibited writhing induced by phenylquinone and the nociceptive responses to being placed on a hot plate (55° C) (Table 1). The results indicated that these compounds possessed analgesic activity and [3,4–dichloro–N–{1–(dimethylamino)cyclohexyl] methylbenzamide (AH 7921) was selected for detailed study in higher species.

In the conscious dog the minimal oral effective doses of AH 7921, morphine and codeine required to completely suppress the pain response to electrical stimulation of the dental pulp (Neat & Peacock, 1971) were $1{\cdot}25 \pm 0{\cdot}8$, $1{\cdot}25 \pm 0{\cdot}3$ and $3{\cdot}5 \pm 0{\cdot}6$ mg/kg respectively. In a similar test using the conscious rhesus monkey the minimal anti-nociceptive doses of AH 7921, morphine and codeine were $13{\cdot}8 \pm 1{\cdot}2$, $\leqslant 5{\cdot}0$ and $11{\cdot}3 \pm 0{\cdot}8$ mg/kg respectively. Anti-nociceptive doses of AH 7921 caused no overt behavioural effects in the mouse, dog or monkey but higher doses (50 mg/kg orally) caused slight central nervous system depression. The addictive liability of AH 7921 was next investigated.

AH 7921 was administered orally to rats, 5 mg/kg 3 times a day increasing to 20 mg/kg 3 times a day over 5 days. On the fifth day the animals were challenged with naloxone, 0·25 mg/kg s.c., which caused an abstinence syndrome similar to that produced in animals that had received morphine on a similar dosage schedule. In the rhesus monkey single doses of AH 7921, 5–10 mg/kg s.c., completely alleviated the abstinence syndrome in morphine-dependent animals. In addition, AH 7921, 7·5 mg/kg s.c. twice daily, increasing to 30 mg/kg s.c. twice daily over 30 days, produced physical dependence in naïve monkeys which was demonstrated in two ways. Nalorphine, 2 mg/kg s.c., induced an abstinence syndrome typical of that seen following morphine withdrawal in morphine-dependent monkeys. Secondly, on terminating AH 7921 treatment abstinence signs appeared over a period of 24–48 h. AH 7921 would be classed as a narcotic

TABLE 1. *Anti-nociceptive effects of some N-substituted cyclohexylmethylbenzamides in the mouse*



AH no.	R_1	R^2	Phenylquinone test ED50 mg/kg orally	Hot plate test ED50 mg/kg s.c.
7563		$-N(CH_3)_2$	15·3 (7·6–31·0)	15·5 (5·4–42·0)
8533		$-N(CH_3)_2$	> 100	≃ 60
8532		$-N(CH_3)_2$	16·0 (8·4–34·0)	9·5 (4·3–24·5)
8529		$-N(CH_3)_2$	7·3 (3·3–16·1)	5·0 (1·7–15)
7921		$-N(CH_3)_2$	0·85 (0·4–1·7)	2·5 (1·2–6·4)
7959			> 100	> 100
8507			> 1000	> 100
Morphine			1·1 (0·7–1·8)	2·8 (1·1–4·8)
Codeine			5·8 (2·9–11·6)	17·0 (9·1–32·0)

analgesic having high addictive liability. These findings are relevant to the relationship between structures of morphine-like compounds and addictive liability.

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The offset of morphine tolerance in rats and mice

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It seems likely that, in animals rendered tolerant to morphine, the rate of reversion towards the level of responsiveness to morphine seen in naïve animals reflects the recovery from the underlying metabolic perturbation. Reports on the rate of offset of opioid tolerance are sparse and conflicting; Goldstein and Sheehan (1969) estimated the half life of levorphanol tolerance in mice as 16 h, whereas Cochin and Kornetsky (1964) report that in rats significant tolerance to morphine was retained for more than one year. A difficulty experienced in measuring the level of morphine tolerance arises from the fact that the test procedure necessarily involves the administration of an opioid analgesic which then reinforces the phenomenon being measured, but this can be circumvented by