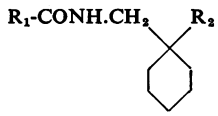
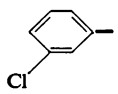
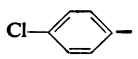
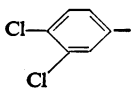
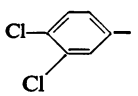
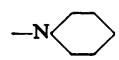
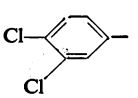
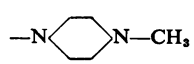
TABLE 1. *Anti-nociceptive effects of some N-substituted cyclohexylmethylbenzamides in the mouse*



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

the simultaneous administration of a protein synthesis inhibitor with the opioid (Cox, Ginsburg & Osman, 1968 ; Cox & Osman, 1970).

Tolerance to morphine was induced in young male rats (100–150 g) using a variety of dosage regimens of morphine, methadone and diamorphine. At intervals up to 20 days after the final dose of the tolerance inducing treatment, responsiveness to the analgesic effect of morphine was tested by a paw pressure method during a 6 h intravenous infusion of morphine (5 [mg/kg]/hr) and cycloheximide (200 [μg/kg]/hr). The steady state level of analgesia was expressed as an analgesic index (Cox, Ginsburg & Osman, 1968). The plot of the log analgesic index against time after cessation of the tolerance inducing treatment showed that from the fourth day up to the 20th day, the points were well fitted by straight lines of which the slopes were apparently constant for all the tolerance inducing treatments given, whether with morphine, methadone or diamorphine, the mean slope corresponding to a half life of $13{\cdot}4 \pm 0{\cdot}16$ days (mean $\pm$ S.E., 6 observations). In contrast, during the first three to four days of withholding the drug there was a more rapid loss of tolerance at rates that appeared to vary with the intensity of tolerance and the inducing drug. Preliminary observations in mice using a hot plate method of testing analgesia suggest a similar pattern with the offset rate in the slower second phase of the same order as that found in rats. Administration of naloxone (1 mg/kg S.C.) to rats on the day of drug withdrawal did not alter the pattern of the subsequent offset of tolerance.

In two experiments in which rats were treated daily with triiodothyronine (150 μg/kg S.C.) from the fourth day after withholding morphine the half life of tolerance offset, measured from the eighth day onwards, was reduced to 6·0 and 6·5 days. However, such treatment with triiodothyronine did not affect the responsiveness of naïve animals to the analgesic effect or the capacity of morphine to induce acute tolerance.

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Skin and muscle lymph from the rabbit hind limb

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In earlier experiments, rabbit hind limb lymph collected from the femoral lymph vessel was examined after various injuries (Lewis 1969 ; Boyles, Lewis & Westcott 1970 ; Jasani & Lewis 1971). This lymph drained both skin and muscle and all of it was thought to pass through the popliteal node. However, when comparing changes in pre- and post-nodal lymph, Lewis & Yates (1972) found that the muscle-derived lymph did not pass through the node.

The detailed anatomy of the lymphatic system of the rabbit hind limb has been subsequently studied by following the pathways of injected dyes. Three lymphatic beds were found.

1. The superficial and deep tissue of the foot and ankle are drained by lymph vessels which run with the deep veins to the popliteal node.
2. The superficial lymph vessels of the medial skin from mid-calf to the groin enter the inguinal node while those of the lateral skin drain into the popliteal node.