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.

The study has also revealed that the lymphatic system of the skin is regionalized so that lymph from one particular area enters the popliteal node in one specific lobe while that from an adjacent area of skin enters a different lobe.

3. The lymph draining the muscle of the lower limb collects in vessels which join the main femoral lymphatic post-nodally.

It was therefore possible to collect pure muscle lymph by cannulating the main femoral lymphatic and ligating the post-nodal lymph vessel close to the node.

The mean control lymph flow from muscle was 21 (μl/100 g)/min whilst that from skin was 240 (μl/100 g)/min. The protein concentration of muscle lymph was 25·5± S.E. of mean 1·9 mg/ml (n=10) while that of skin lymph in the same animals was 23·2±1·9 mg/ml.

After thermal injury there was about a two-fold increase in the protein concentration (37·8±4·7 mg/ml) and a 3–5 fold increase in the flow of skin lymph. On the other hand there was no change in either protein or flow of muscle lymph. This finding indicated that the injury caused an increase in vascular permeability in the skin but not in the muscle.

On the other hand there was a pronounced increase in the lactic dehydrogenase (LDH) activity in muscle lymph (from 0·79±0·2 to 11·18±4 u/ml) indicating that the injury had caused significant damage to the muscle fibres. This cellular damage was probably produced directly and not through reflex nerve activity since maximal stimulation of the sciatic nerve did not produce such a leakage of enzyme into the lymph.

It therefore appears that a different relationship exists between blood vessels and lymph vessels in skin and muscle.

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Potentiation of the biphasic bradykinin response of the guinea-pig ileum

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When the isolated guinea-pig ileum with resting tone is challenged by bradykinin only contractile responses are observed. If, however, the ileum is first contracted by acetylcholine (ACh) or other agonists, and without washing out, bradykinin is added, then a relaxation, immediately followed by a contraction, is seen (Hall & Bonta, 1972). The magnitude of the relaxation, but not of the contraction was found to be dependent on the concentration of the ACh or the percentage of maximum contraction of the ileum (Hall & Bonta, 1973a). The involvement of catecholamines or an action on the adrenergic receptors has been ruled out (Hall & Bonta, 1973b).

It is well known that contraction of some intestinal smooth muscles by bradykinin can be potentiated by a variety of compounds (Walaszek, 1970). These include certain thiols, such as cysteine, 2,3–dimercaptopropanol (BAL) and α-thiol glycerol; and also the mixture of Bradykinin Potentiating Factors (BPF) isolated from the venom of *Bothrops jararaca* (Ferreira, Bastelt & Greene, 1970). There appears to be limited experimental work on the potentiation of the relaxation (Camargo & Ferreira, 1971). We have examined the above potentiating compounds on the biphasic response to bradykinin of the ACh contracted guinea-pig isolated ileum.