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Mucosal cell turnover in the upper gut of the mouse and its modification by carbenoxolone

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In 1970 Lipkin claimed that carbenoxolone reduced the rate of mucosal cell proliferation in the acid secreting part of the mouse stomach (fundus) and increased the time these cells took to migrate to the point of exfoliation. Neither effect was apparent in duodenum or colon. This work has now been repeated and extended.

Mice received radioactive [^{3}H]-thymidine i.v. and the radioactivity remaining in the fundic, antral and duodenal mucosae was measured during the six days following this injection. A minimum of 22 mice were used to derive each value.

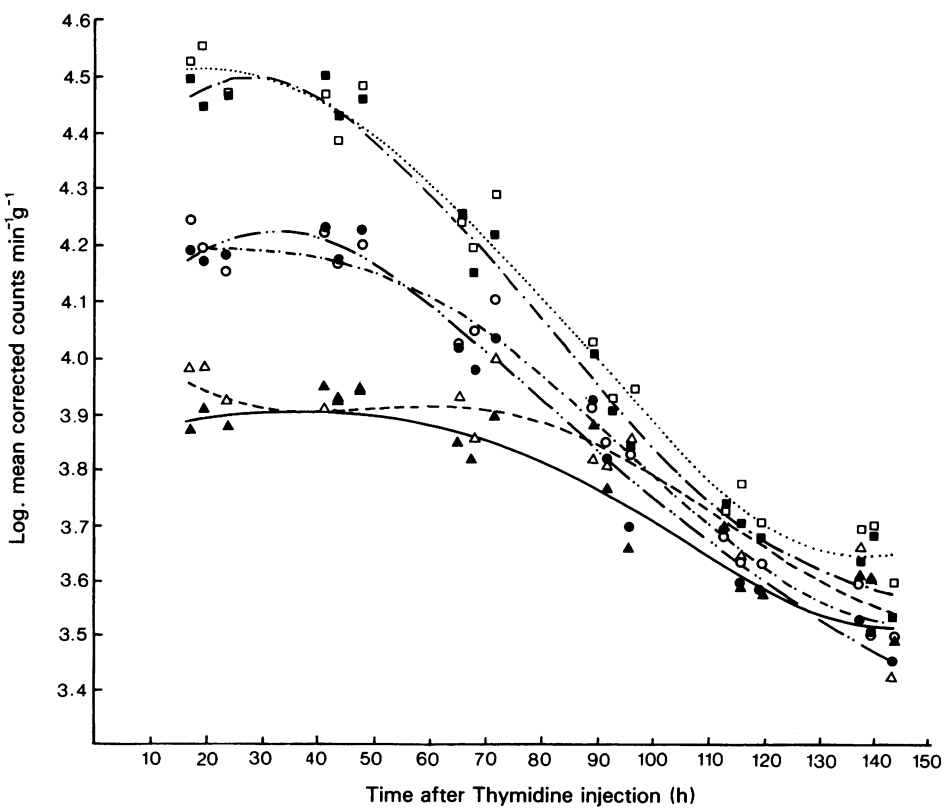

Figure 1 Mouse mucosal cell lifespan. Cells were taken from the (■) duodenal, (●) antral and (▲) fundic mucosae before (filled symbols) and after (open symbols) carbenoxolone.

In each tissue a plateau of radioactivity was followed by an exponential decay slope (Fig. 1). The plateau height is a measure of thymidine uptake and so of mitotic rate, whilst plateau length assesses the cell transit time. The decay slope demonstrates the rate at which mature cells exfoliate into the lumen. Thymidine uptake was greatest in duodenum and least in fundus.

Daily oral pretreatment with 25 mg/kg carbenoxolone from seven days prethymidine until the sampling day did not change the extent of thymidine uptake nor the slope of the decay curve in any tissue. In carbenoxolone treated mice the plateau length was significantly increased (from 66 to 75 h) suggesting that cell migration was slowed. It is unclear if this minimal effect contributes to the therapeutic action of carbenoxolone in gastric ulceration as Lipkin postulated.

When the results of the three tissues were plotted together, it was notable that all the lines tended to converge at the end of the decay slope (Figure 1). This novel finding may suggest that all the tissues maintain a similar absolute number of long lived cells.

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The effects of corticosteroids given at various clock times on cell-mediated immunity to oxazolone

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Skin tests with oxazolone in rats (Pownall & Knapp, 1978), and purified protein derivative of tuberculin in man (Cove-Smith, Pownall, Kabler & Knapp, 1978), have shown circadian variations in cellular immunity. Many drug effects are different at different times of the day (Reinberg, 1976). Further experiments have been carried out with oxazolone in rats to determine whether corticosteroids are more effective as immunosuppressive agents when given at certain clock times.

Dexamethasone (0.1 to 32 mg/kg) was given orally to groups of rats maintained at constant temperature and humidity with light from 10.00 h to 22.00 h alternating with darkness. The ear swelling due to oxazolone application (a sensitive measure of the immune response) was measured 24 h later. The dose-response relationship showed a significant vehicle effect ($P < 0.001$). Table 1 shows transient immunosuppression by methyl prednisolone given as a single intramuscular dose (14 mg/kg) at the time of challenge. The increase in ear thickness at 24 h in both drug-treated groups was similar although the vehicle-treated controls were different ($P < 0.001$). The stronger immune response following challenge at 10.00 h was apparently reduced more than the weaker response to challenge at 22.00 hours. Immunosuppression was not evident at 48 hours. Experiments at other clock times may separate possible circadian variations in the immunosuppressive activity of corticosteroids from the circadian variations in immunity to oxazolone which are evident in the vehicle-treated groups.

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Table 1 Mean (±s.e. mean) increase in ear thickness (μm)

Time	*Group*	*24 h measurements*	*48 h measurements*
10.00 h	vehicle	149 ± 11	140 ± 9
	methyl prednisolone	45 ± 8	157 ± 8
22.00 h	vehicle	80 ± 5	76 ± 7
	methyl prednisolone	47 ± 10	106 ± 14