ASPECTS OF THE RELATIONSHIP BETWEEN
METABOLIC AND PROLIFERATIVE ACTIVITY IN
THE LARGE BOWEL

by

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February, 1990
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ABSTRACT

Studies in this thesis explore aspects of the relationship between metabolism and proliferation of colonic epithelial cells from rats and humans. In rats the physiological perturbation of fasting followed by refeeding has been used to suppress and enhance epithelial proliferation, respectively. Emphasis has been placed on developing and integrating in vivo and in vitro models for both metabolic and proliferative studies.

The major observations from these studies are as follows:

(i) Methods have been developed for the isolation of colonocytes for metabolic studies. Use of the dissociating agent, trypsin, appears to be superior to the conventional use of EDTA and results in a suspension of cells with greater membrane integrity as assessed by metabolic parameters and by light and electron microscopy.

(ii) In the rat colon, crypts were more densely packed and longer in the distal colon than in the proximal colon, an observation which could account for the predilection of the distal colon for carcinogen-induced tumours.

(iii) Various methods were used to assess colonocyte proliferation in vivo and in vitro. All methods showed that fasting followed by refeeding was accompanied by significant increases in proliferation, particularly in the distal colon. The use of bromodeoxyuridine in vivo is a relatively simple and
reliable method of assessing proliferation in the rat colon which avoids the use of radioisotopes.

(iv) Concentrations of SCFA were determined in various regions of the large bowel after fasting and refeeding and showed that levels were highest in the caecum and lower in the proximal and distal colon. In the caecum, acetate, propionate and butyrate were in the approximate molar ratios of 2:1:1. Fasting produced greater falls in the concentrarions of SCFA in the proximal and distal colon than in the caecum, with greater falls in the concentration of butyrate than other SCFA. SCFA concentrations returned towards normal with refeeding for 15 h.

(v) Proliferation in colonocytes was unrelated to absolute concentrations of SCFA but changes in the concentrations of SCFA did accompany changes in proliferation. Changes in the concentration of SCFA may be one factor which influences proliferation.

(vi) Biochemical studies established the presence of the oxidative pentose pathway and the non-oxidative pentose pathway in colonic epithelium. The oxidative pentose pathway is induced by refeeding after a fast. The non-oxidative pentose pathway appears to operate via an L-type mechanism and is uninfluenced by changes in feeding/proliferation.

(vii) A study of the effects of butyrate and glutamine on colonocyte metabolism showed change in the glycolytic, tricarboxylic and oxidative
pentose pathways. The results indicate that colonocytes can use both substrates as alternative and perhaps preferred fuels to glucose.

(viii) The induction of zinc deficiency in rats was accompanied by suppressed proliferation in the distal colon. Zinc may be another factor which influences colonocyte proliferation in rodents and perhaps in man.

The data presented in this thesis provide valuable information with regard to the balance of synthetic and energetic metabolism and their relationship to proliferative responses. The challenge is to investigate the contribution of these parameters in the stepwise setting of cancer formation and to ascertain their importance in modulating these processes.