

*Leading article*

## Hormonal control of gastric and colorectal cancer in man

Hormonal control of human cancer was first used therapeutically by Beatson in 1895 when he reported response of a massive breast tumour after bilateral salpingo-oophorectomy.<sup>1</sup> Apart from breast cancer several other tumours are now successfully treated with hormones. It has only recently been realised that gut tumours may be under hormonal control.<sup>2–5</sup> Many hormones may affect the growth of gastric and colorectal cancer but significant progress has been made in the area of sex steroids and gastrin. Gastric and colorectal cancer account for over 30 000 deaths each year in the United Kingdom – over 20% of all cancer deaths.

### **Sex steroids**

Gender and parity have been clearly shown to affect incidence and survival in colorectal cancer. The frequency of bowel cancer is increased in nuns<sup>6</sup> and increasing parity decreases the risk, especially of right sided colonic tumours.<sup>7,8</sup> There is an increased incidence of bowel cancer in women with cancer of the breast or reproductive tract.<sup>9</sup> Whilst changes in bile salt metabolism which persist after pregnancy may affect the incidence of bowel cancer, why should this affect survival? The overall prognosis in bowel cancer is better in women,<sup>10</sup> and especially in the parous,<sup>11</sup> so do oestrogens have a protective effect?<sup>12</sup> Oestrogen receptors (OR) have been reported in human large bowel cancers<sup>13–16</sup> and it may well be that oestrogens inhibit growth of OR +ve colorectal tumours.<sup>17</sup>

The effect of androgens has been studied in animal models. In some strains of rats castration can diminish the risk of carcinogen induced bowel cancer.<sup>17,18</sup> Androgen receptors are present on human colorectal tumours<sup>13,19–22</sup> and changes in androgen concentrations produced by dihydrotestosterone or antiandrogens have led to inhibition and stimulation of experimental tumours.

The relationship of gender to the incidence of gastric cancer is well known and oestrogen receptors on human gastric cancer have been reported by several authors. Initially it was thought that few tumours were OR +ve but using immunohistochemical techniques a higher +ve rate is found.<sup>23–25</sup> We recently studied OR status in 100 patients with gastric cancer by an immunohistochemical technique using ERD5 (Amersham) which is a monoclonal antibody directed against a 29 Kda protein found in close association with the oestrogen receptor and found 52% to be positive.<sup>26</sup> Whilst ERD5 status correlates well with OR status by classical biochemical techniques in breast cancer, the relationship in gastric and colorectal cancer is not known.

Early clinical results from Japan suggested a survival benefit in tamoxifen treated patients with gastric cancer but the study was small, historical controls were used and patients received chemotherapy.<sup>27</sup> We randomised 100 patients to receive tamoxifen or act as untreated controls – no benefit in length of survival was seen but ERD5 status was prognostic. Not only did ERD5 positive patients survive for a shorter time, but if treated with tamoxifen they survived for a significantly shorter time than untreated controls. ERD5 negative patients had a longer survival and tamoxifen did not significantly affect prognosis. We have therefore investigated the effect of oestrogens and tamoxifen on gastric cancer cell lines *in vitro* and found that oestrogen and tamoxifen stimulate growth.<sup>28</sup> Hormonal manipulation may thus still benefit gastric cancer patients, but treatment aimed at decreasing circulating oestrogen rather than OR antagonists should perhaps be considered. In Japan some surgeons recommend oophorectomy in premenopausal females with gastric cancer but there are as yet no hard data to support such a policy.

### Gastrin

Gastrin stimulates growth of normal gastric and colonic mucosa. Some gastric and colorectal cancer cell lines are stimulated by exogenous gastrin in *in vitro* culture<sup>29–32</sup> and the growth of xenografts can also be increased.<sup>33–36</sup> Human primary gastric and colorectal cancer cells have gastrin receptors<sup>37–38</sup> and respond to gastrin in early *in vitro* culture.<sup>39–40</sup> Intracellular gastrin has been demonstrated in tumour cells by immunohistochemistry<sup>41</sup> and we have recently shown that a gastrin like substance (which is recognised by an antigastrin antibody and is capable of stimulating growth) is produced by human gastric and colorectal cancer cells in early and prolonged *in vitro* culture.<sup>42</sup>

It seems that autocrine status can be ascribed to gastrin in gastric and colorectal cancer in man. Agents which may prevent the stimulation by exogenous gastrin, or interfere with intracellular gastrin production, release and binding are under investigation. Regression of an 'autocrine' human gastric cancer xenograft has been reported with two compounds.<sup>43–44</sup>

#### ANTIGASTRIN THERAPY?

There are three categories of agent which may be useful in modifying the trophic effect of gastrin on cancer cell growth:

##### GASTRIN RECEPTOR ANTAGONIST

Only one gastrin receptor antagonist is available clinically at present. This compound, proglumide, has been widely used in Europe and Japan for the treatment of duodenal ulcer. Proglumide has been shown to inhibit stimulation of cancer cell lines by gastrin *in vitro* and *in vivo*.<sup>43–45</sup> We are doing clinical studies in gastric and colorectal cancer with proglumide but it is too early to assess results. Proglumide is a relatively weak receptor antagonist but much more potent and specific gastrin receptor antagonists already exist and hopefully will become available for clinical investigations.

##### SOMATOSTATIN

This decreases circulating concentrations of gastrin and inhibits growth of

gastric and colorectal cancer xenografts in experimental animals.<sup>44-47</sup> The mechanism of this effect is uncertain but is probably not caused by decreased serum gastrin concentrations and may be mediated by somatostatin receptors.

#### PROSTAGLANDINS

Some prostaglandin compounds affect metabolism of gastrin in man. Enprostil, an E<sub>2</sub> prostaglandin derivative, affects postprandial release of gastrin. Enprostil significantly slows *in vivo* growth of some cancer cell lines which respond to gastrin. Gastric (MKN45)<sup>43</sup> and colorectal (MC26)<sup>48</sup> cancers respond but serum gastrin concentrations are only transiently affected. It is not yet known whether other prostaglandin compounds have similar actions.

There is now considerable evidence to support the belief that human gastric and colorectal cancers are under hormonal control. Encouraging results have been seen in *in vitro* and animal experiments with compounds which interfere with this process. Whether such preliminary results can be translated into real benefit to patients with gastric and colorectal cancer is the challenge for the future.

D L MORRIS, S A WATSON, L G DURRANT, AND J D HARRISON

*Department of Surgery,  
University Hospital,  
Nottingham*

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