Towards immunotherapy for pancreatic cancer

Editor,—McKenzie and Apostolopoulos’ recent article on immunotherapy for pancreatic carcinoma (Gut 1999;44:767–769) gave an excellent overview. We agree that the poor prognosis of this disease makes it imperative that new agents and novel therapeutic strategies are investigated. However, although this paper discusses classical immunotherapy (where immune competent cells are stimulated to attack pancreatic cancer cells directly), the induction of antibodies directed against growth factors by immunisation (where the immunogen stimulates the immune system to inhibit the growth of tumour cells indirectly) is now a promising field. We are currently undertaking a phase II clinical trial for inoperable pancreatic cancer using one such immunogen, Gastrimmune, which induces neutralising antibodies against amidated gastrin-17 and its precursor glycine extended gastrin-17 (this immunogen is also undergoing a phase II trial for gastric cancer at the University Department of Surgery, Nottingham, UK).

Gastrin has been shown to be a growth factor in a variety of malignancies including colorectal, gastric, and pancreatic cancers in both in vitro and in vivo studies; precursor forms such as progastrin and glycine extended gastrin also have a trophic effect. More recently the autocrine/paracrine pathway, in which tumour cells produce and respond to gastrin, has been shown to be increasingly important. In vitro and in vivo studies have also shown the trophic effect of gastrin and the inhibitory effect of both gastrin receptor antagonists and anti-gastrin antibodies, and further studies have confirmed gastrin expression in human pancreatic cancer cell lines and resected specimens. Thus, there is good evidence to suggest that immunisation against gastrin may be beneficial in the prevention of pancreatic cancer.

We have shown that Gastrimmune induced antibodies inhibit the growth of human pancreatic cancer cell lines, and they have previously been shown to inhibit the growth of gastric, colon, and hepatocellular cancer cell lines in vitro and in vivo. Over 150 patients have now received Gastrimmune in several trials. The side effect profile has been extremely good and the early efficacy data in colorectal cancer has been encouraging; phase III studies are currently being designed for both pancreatic and colorectal cancer.

Pancratic cancer has an appalling prognosis. New molecular insights provide encouragement that novel therapeutic strategies may improve survival. Immunotherapy, which can be employed directly and indirectly to target pancreatic cancer cells, and we hope the promise of these new strategies is fulfilled in the next decade.

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Reply

Editor,—Brett and Caplin have highlighted that our paper was biased towards cellular immunotherapy. We specifically excluded reference to antibodies, but welcome the opportunity to mention these in the context of immunotherapy for pancreatic cancer.

In the early 1980s, murine monoclonal antibodies offered great hope for the diagnosis and cure of cancer, but by the end of the decade, the outlook was pessimistic. Used alone, murine monoclonal antibodies had little effect, mostly because of the occurrence of HAMA (human anti-mouse response) which curtailed the life of the monoclonal antibody in patients by forming immune complexes; furthermore, murine antibodies are less immunogenic than their human counterpart, but this is not always so, particularly if the murine antibody is humanised by genetic engineering and sophisticated computer and macrophages. However, at present such antibodies are in phase I/II trials, and with several exceptions (see later), trials have not been particularly rewarding. We are particularly pessimistic about the use of antibodies, be they humanised or not, against solid tumours in humans, as we are experienced in rejecting grafts and with tumour grafts using antibody and complement. For mucin 1, we have not been able to cause rejection of human MUC1+ tumours in mice by using large amounts of monoclonal antibodies and additional complement, under circumstances which lead to rapid destruction of lymphoid cells.

However, total pessimism now seems unwarranted. Firstly, murine antibodies in lymphoma and leukaemia have been found to be particularly useful in the treatment of these diseases. The antibodies need to be “armed”, especially with isotopes, and using antibodies to CD19 and CD20 “I labelled antibodies in patients effector cells that are resistant to other forms of treatment.”

Furthermore, it takes a long time for appropriate clinical trials to be completed and more patience is needed before abandoning potentially effective treatment. A blanket statement that monoclonal antibodies are not effective in cancer is too broad and this is proved by the use of such antibodies in the treatment of lymphomas; they are particularly sensitive to irradiation and because the patients were immunosuppressed by the disease, they made little HAMA and therefore could be treated successfully.

Antibodies that do not act primarily via their Fc piece by activating complement but have a direct effect on cell surface molecules are another exception. A well known antibody, Her2/ner, reacts with molecules in 20–30% of patients and have growth effect on cell surface antibodies to CD19 and CD20 for lymphoma and leukaemia have been found to be extremely useful in cancer trials. Thus, selective antibodies against growth factor receptors may be useful in the treatment of diseases like pancreatic cancer. It is possible that the antibodies will be immunogenic and a HAMA or HAMA (human anti-human antibody) response will occur, but this can only be shown by a clinical trial. There may also be problems with antibodies obtaining access to tumours not expressing the appropriate molecules as they de-differentiate. However, these are problems of any cellular or humoral immune response, and are no longer regarded as being peculiar to antibodies. Thus, it is appropriate to consider special antibodies and growth factors to be part of immunotherapy for pancreatic cancer.

Finally, the colon cancer trial in patients with Duke’s C disease has improved prognosis after receiving 171A antibody, is of interest, although it has still to be established whether the specific or non-specific nature of the antibody was responsible for the improvement. Nevertheless, phase III trials are now in progress to assess this. It is easier to treat disease by immunotherapy if treatment starts at an early stage. Unfortunately, early diagnosis of pancreatic cancer remains difficult—how can a disease with a relatively low frequency be diagnosed in the absence of symptoms? When the symptoms finally appear it may already be too late for immunotherapy.

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Liver biopsy under ultrasound control: implications for training

EDITOR.—As a gastroenterologist/hepatologist, I appreciate the anxiety expressed by Shah et al (Gut 1999;48:628–629) about having to surrender liver biopsy samples to radiologists as a result of reduced training opportunities. The desire of an overwhelming number of gastroenterologists that the ultrasound-guided biopsy technique be minimised by allowing the patient to have a light breakfast, as the gall bladder becomes contracted following a meal. However, the more cautious would prefer patients to be fasted, in case they develop a complication requiring operative intervention.

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A comprehensive study of vitamin D, this book starts with a brief consideration of the evolutionary aspects of vitamin D and the essential role of photosynthesis of the vitamin in the conservation of calcium in aquatic and land animals. Cutaneous synthesis is the principal source of vitamin D for most healthy people but dietary intake becomes increasingly important in the very young and the elderly. Adequate intakes (formerly called recommended daily allowances) for all age groups, and for pregnant or lactating women, are provided and the central question of how to define vitamin D deficiency is revisited; based on serum parathyroid hormone responses to vitamin D supplementation, a threshold level of intake of 20 ng/ml (50 mmol/l) is suggested.

Vitamin D deficiency is a common side effect of hepatic and gastrointestinal diseases and often results in bone disease; gastroenterologists should, therefore, have some knowledge of the causes, consequences, and treatment of vitamin D related bone disorders. It also has a wide range of actions which are unrelated to its effects on calcium metabolism; receptors for its active metabolite, 1,25-dihydroxyvitamin D, are found in many places including the stomach, thymus, immune system, gonads, and some cancer cells. The antiproliferative and prodifferentiation effects of vitamin D have already been exploited in the development of treatment for psoriasis and other skin disorders and the exciting potential applications of vitamin D in some malignant diseases are discussed towards the end of the book.

Since the pivotal research in the 1960s on the metabolism of vitamin D there has been intense research activity in a number of related areas, including the synthesis and metabolism of vitamin D metabolites and analogues, the molecular biology of the vitamin D receptor, and the mechanisms by which 1,25-dihydroxyvitamin D affects the renal, intestinal, and skeletal transport of calcium. These aspects are covered in considerable detail and occupy about one half of the book; there is also a detailed chapter on the methodology for assays of vitamin D, although the authors do not discuss the usefulness of these assays in clinical practice. The latter part of the book is devoted to clinical issues—for example, rickets and osteomalacia, osteoporosis, inherited defects of vitamin D metabolism, and the pathophysiology of hypercalcaemia associated with the extrarenal production of 1,25-dihydroxyvitamin D, which occurs in conditions such as sarcoidosis and lymphoproliferative disorders. There is also an interesting chapter on the epidemiology of cancer risk and vitamin D. Disappointingly, at least for the gastroenterologist, there is very little coverage of vitamin D deficiency associated with hepatic and gastrointestinal disorders.

The book is well produced and has many illustrations and diagrams; it provides an excellent and comprehensive account of the substantial advances occurring in this area. Furthermore, the chapters are well referenced, many containing over 100 references. This book is not for the gastroenterologist who wishes to extract information about the diagnosis and management of vitamin D deficiency in clinical practice, but will be highly valued by those with a close interest in following the fascinating progress of this hormone.

J E COMPSTON

CORRECTIONS

An error occurred in the keys to figures 4 and 5 of the paper by Yamaoka et al (Gut 1999;45:804–11). Gastritis should be represented by open circles and duodenal ulcer by closed circles. We apologise for any confusion this error may have caused.

The authors of Nardone et al (Gut 1999;44:789–90) have conceded an error. Figure 3(B) was an inverted image of figure 3(A) at a different magnification. The correct figure is published below. The authors regret any confusion this may have caused.

Figure 3(B) H pylori positive chronic gastritis. Original magnification ×250.
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