LETTERS TO THE EDITOR

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 not mentioned. 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[1]; precursor forms such as progastrin and glycine extended gastrin also have a trophic effect.[2] More recently the autocrine/paracrine pathway, in which tumour cells produce and respond to gastrin, has been shown to be increasingly important.[3] 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,[1 4 5] and further studies have confirmed gastrin expression in human pancreatic cancer cell lines and resection specimens.[4 6] 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,[7] and they have previously been shown to inhibit the growth of gastric, colonic, and hepatocellular cancer cell lines in vitro and in vivo.[8] 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[9]; phase III studies are currently being designed for both pancreatic and colorectal cancer.

Pancreatic cancer has an appalling prognosis. New molecular insights provide encouragement that novel therapeutic strategies may improve the outlook. The immune system 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 of 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, the murine Fc pieces of immunoglobulin are particularly poor at marshalling human defence mechanisms to cause inflammation and tumour eradication and thus, these antibodies proved ineffective in the treatment of most types of human cancer. More recently, however, an effort has been made to "humanise" the antibodies, either by making them as chimeras (essentially murine Fab to bind the antigen, coupled with human Fc), or by retaining only the critical murine amino acids so that the rest of the molecule is human. These techniques are achieved by genetic engineering and sophisticated computer modelling. Principally, such humanised antibodies are less immunogenic than their murine counterpart, but this is not always so, and they should be more active with the human Fc piece, by activating complement and macrophages. However, at present such antibodies and 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.[2] 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 ^{131}I labelled antibodies have been effective in patients who are resistant to other forms of treatment.[3]

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/neu, reacts with molecules present in 20–30% of patients with breast cancer. Her2/neu molecules have a growth effector function and if they can be blocked on the cell surface by the antibody, which inhibits the binding of the ligand (growth factor), the cells die.[4] This has been further illustrated by the use of Gastrimmune against amidated gastrin-17 by Brett and Caplin. Antibodies to other growth factor receptors have also been described, which are proving to be extremely useful in early clinical trials.[4] 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 HAHA (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, or 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 which patients with Dukes's C disease had improved prognoses after receiving 171A antibody, is of interest,[6] although it has still to be established whether the specific or non-specific nature of the antibody was responsible for the improvements. 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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Ring-like elevations in the large bowel: endoscopic signs to distinguish the artefact from true neoplastic lesions

EDITOR,—We read with great interest the article by Martin *et al* (*Gut* 1999;**45**:147) on normal histological findings in small depressed lesions of the large bowel. They described three patients with 7–8 mm depressed rectal lesions, similar to small flat or depressed neoplastic lesions, during sigmoidoscopy (two cases) and total colonoscopy (one case). Specimens taken by extensive biopsy or removed by endoscopic mucosectomy were histologically normal with no evidence of neoplasia. Two weeks later, colonoscopy with chromoscopy in one patient failed to locate the lesion. In contrast to true flat adenomas characterised by rough, reddened central mucosa and an irregular outline, the lesions had normal central mucosa and a regular circular elevation. The authors therefore concluded that flat lesions with a regular circular shape and normal central mucosa are likely to be of little significance, and recommended diagnostic cold biopsy in these cases.

Despite their claim of the first report of normal histological findings in small depressed lesions, we had described similar lesions as ring-like elevations.[1] Histological assessment of biopsy and endoscopic mucosectomy specimens of the elevations revealed slight oedema within the lamina propria. Whereas we observed such elevations predominantly in the ascending colon, their lesions were seen in the rectum. Because cleansing preparation fluid tends to be retained often in the ascending colon and rectum, requiring frequent aspiration, we suspect that their lesions are also pseudolesions caused by suction of the mucosa into a colonoscope forming ring-like elevations.[1] Although they mentioned that suction had not been applied to the mucosa, experienced endoscopists usually aspirate retained fluid unconsciously during colonoscopy. Although histological findings of their lesions showed normal mucosa, we suspect that slight oedema was probably present within the lamina propria of their ring-like lesions. We believe their lesions are the same as ring-like elevations.

Some diminutive polyps disappear during maximal colonoscopic insufflation. This phenomenon is invariably associated with hyperplastic polyps, but not with adenomas.[2] Dye-spraying techniques readily visualise the innumerable fine grooves, the so-called innominate grooves, which remain visible in non-neoplastic lesions and in normal colonic mucosa, but not in neoplastic lesions.[3] Because ring-like elevations usually disappear after vigorous air insufflation and the innominate grooves are always visualised in the elevations, the disappearing phenomenon and the presence of innominate grooves in the lesions serve to differentiate this artefact from true neoplastic lesions.[1] With these endoscopic signs, we can avoid biopsy or removal, and thus the cost of pathological examinations.

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Reply

EDITOR,—We value the comments made by Matsushita *et al* and are grateful to them for bringing to our attention their earlier letter which reports ring-like elevations of the colon thought to be due to suction artefacts.[1] Although we agree with their points regarding the use of suction by experienced colonoscopists, we believe it is unlikely that the lesions we reported were suction related. All of our lesions were initially visualised in the distance, away from the colonoscope tip, and showed no signs of mucosal trauma such as spotted haemorrhage, on close inspection. In addition, there was no histological evidence of increased mucosal oedema to suggest suction trauma.

Maximum air insufflation and observation of these lesions over several minutes was performed routinely, and a striking feature noted was their "fixed nature". We agree that if a normal groove pattern is seen following dye spray and the lesion disappears after air insufflation, then biopsy is unnecessary. However, if lesions fail to disappear, as in the cases we reported, some doubt must remain regarding their nature. In this situation biopsy seems a safe precaution, particularly given the relatively high incidence of advanced neoplasia in true flat adenomas.

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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;**45**: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 gastroenterology trainees to become proficient in ultrasound techniques[1] should send a loud and clear message to the relevant regulatory training bodies. Once ultrasound has been introduced into gastroenterology training programmes in the United Kingdom, such as in Europe[2] or the USA,[3] the questions raised by Shah *et al* would have been partially solved, albeit indirectly.

The purpose of ultrasound guidance in liver biopsy is threefold: (i) to target the liver, (ii) to target the lesion, and (iii) to avoid the gall bladder.[4] In this day and age, it would be unthinkable to perform a blind liver biopsy on a patient who has a discrete liver lesion. However when it comes to diffuse or generalised disease, "X marks the spot" or ultrasound assisted technique should suffice. Although the liver is a large and superficial organ, targeting it, even for diffuse or generalised disease, should not be left completely to chance. In the ultrasound assisted technique, the procedural aspect of liver biopsy is essentially blind subsequent to the initial ultrasound to mark the spot. Therefore becoming proficient in this technique would prevent loss of expertise in the blind approach, and yet the medicolegal position remains sound.

Inadvertent biopsy of the gall bladder can be minimised by allowing the patient to have a light breakfast, as the gall bladder becomes contracted following a meal.[4] However, the more cautious would prefer patients to be fasted, in case they develop a complication requiring operative intervention.

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1 What training do gastroenterologists want in abdominal ultrasound? Results of a national survey of trainees [abstract]. *Gut* 1998;**42**:A61.
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Reply

EDITOR,—Dr Chuah makes some valuable points about the problems of training in gastroenterology in relation to ultrasound. One of the key messages of our article was to differentiate the "X marks the spot" ultrasound technique from the real time ultrasound guided method, which is in standard use within our hospitals. Using this technique, the needle is continuously visualised throughout its time within the liver and therefore there is minimal risk of biopsy of gall bladder or intrahepatic vessels. We consider this to be the safest technique to use but it is also the most difficult method in which to become proficient. Most training schemes for specialist registrars in gastroenterology will have difficulty in accommodating the additional time required to learn this technique.

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BOOK REVIEW

Vitamin D. Molecular Biology, Physiology and Clinical Applications. Edited by Holick MF. (Pp 458; illustrated; $145.00.) US: Humana Press, 1999. ISBN 0 896 03467 4.

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 nmol/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;44:789–99) 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.

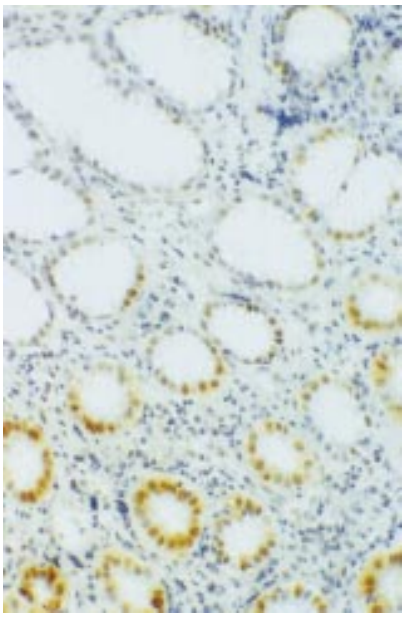

Figure 3(B) H pylori positive chronic gastritis. Original magnification × 250.

NOTES

The Wellcome Institute for the History of Medicine with the 20th Century History of Medicine Group present A Witness Seminar—Peptic Ulcers: rise and fall in the twentieth century

This seminar will be held on 12 May 2000 in London. Registration is £15 (Students/Friends £10) and the closing date is 5 May 2000. For registration/further information: Ms Frieda Houser, The Wellcome Institute for the History of Medicine, 183 Euston Road, London NW1 2BE, UK. Tel: +44 (0)20 7611 8619/8888.

Falk Symposia and Workshops

The Symposium on Hepatology 2000 will be held in Munich, Germany, on 4 and 5 May 2000.

The Symposium on Hiking and Health will be held in Titisee, Germany, on 19 and 20 May 2000.

The Workshop on Hepatobiliary Diseases: Cholestasis and Gallstones will be held in Cluj Napoca, Romania, on 9 and 10 June 2000.

The Symposium on Non-Neoplastic Diseases of the Anorectum—An Interdisciplinary Approach on 1 and 2 October 2000, and the Symposium on Immunosuppression in Inflammatory Bowel Diseases—Standards, News, Future Trends on 3 and 4 October 2000 will be held at Gastroenterology 2000 in Freiburg, Germany.

The Symposium on Biology of Bile Acids in Health and Disease will be held at the XVI International Bile Acid Meeting in Den Haag, The Netherlands on 12 and 13 October, 2000.

The Symposium on Steatohepatitis (NASH and ASH) will be held in Den Haag, The Netherlands, on 14 and 15 October.

The Symposium on Chronic Inflammatory Bowel Diseases—Progress and Controversies at the End of the Century will be held in Bucharest, Romania, on 4 November 2000.

For further information on any of these symposia or workshops, please contact: Falk Foundation e.V.—Congress Division, Leinenweberstr. 5, PO Box 6529, D-79041 Freiburg, Germany. Tel: +49 761 15140; fax: +49 761 1514359; email: symposia@falkfoundation.de

Digestive Disease Week

The Digestive Disease Week will be held at the San Diego Convention Centre, San Diego, California, USA, on 21–24 May 2000. Further information from: DDW Administration, 7910 Woodmont Avenue, 7th Floor, Bethesda, Maryland 20814, USA. Tel: +1 301 272 0022; fax: +1 301 654 3978; website: www.ddw.org