strengths are all due to the development of the GPDB allowing automated collection of information which is then available for addressing important questions. It is to be hoped that the increasing privacy of information legislation does not restrict and complicate future use of this key database.

The major weakness in this study investigating the association between acid suppressive therapy and the risk of gastro-oesophageal cancer is the relatively short duration of acid suppressive therapy. The longest exposure to the medication was three years and the majority were taking it for less than one year. This cannot be considered to be long term in the time scale of cancer development. *H. pylori* infection is usually acquired in the first few years of life but the cancer which it gives rise to does not usually manifest itself until 50–70 years later. Exposure to anti-secretory medication for at least 10 times the length of exposure examined in the current study would be required before one could make any confident conclusions regarding either adverse or beneficial effects of such treatment on

cancer risk. Hopefully, the authors will be able to use the established database to subsequently examine true long term effects of acid suppressive medication on the risk of gastric and oesophageal cancer.

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Correspondence to: Professor K E L McColl, Section of Medicine, Gardiner Institute, Western Infirmary, 44 Church Street, Glasgow G11 6NT, UK; K.E.L.McColl@clinmed.gla.ac.uk

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Pancreatic cancer

An unfavourable prognosis for pancreatic cancer indicates fields of opportunity

W Greenhalf

Large fields of cancerisation may give more aggressive, but easier to detect, pancreatic ductal adenocarcinoma

Prognosis for patients with pancreatic ductal adenocarcinoma (pancreatic cancer) is notoriously bad. In a study published in this issue of *Gut*, Kim and colleagues¹ make it clear that K-ras mutation in apparently benign pancreatic tissue at some distance from the tumour contributes to poor survival (see page 1598). This could indicate the presence of occult tumour cells in the resection margin but could also indicate that tumours developing in a large field of mutation carrying cells are more aggressive. This offers hope to patients where resection leaves behind no mutant cells in the margin but also suggests that the most aggressive tumours might prove to be the easiest to detect in asymptomatic patients.

A cynical reader might be forgiven for passing over the article by Kim and colleagues.¹ The paper talks of an unfavourable prognosis for patients with pancreatic cancer—cynics will respond with the observation that prognosis for pancreatic cancer is death, how much more unfavourable can it be? The paper also talks about K-ras gene mutations—cynics may groan and remember the many reports on K-ras mutations going back to the 1980s. Some may even remember a happier time when they believed that these mutations might serve as a marker for cancer, a time before it became apparent that such mutations are common in people with benign conditions. Some readers will be tempted to read on when

they notice that the abstract refers to K-ras mutations in resection margins histologically free of invasive cancer; these readers will be rewarded with an optimistic report that may prove of immediate clinical value and furthermore gives some exciting new insights into the different ways in which pancreatic cancer could develop.

Kim and colleagues¹ describe a cohort of 70 pancreatic cancer patients who underwent pancreatic resection of whom 31 were still alive after five years of follow up. Ten year survival (effectively cure) was approximately 20%. This seems extraordinary when compared with the often quoted statistic that the mortality of pancreatic cancer is equivalent to its incidence. The apparent ability of this group to cure what is often described as an incurable disease is also not explicable by misdiagnosis of patients as specimens from the longest survivors underwent independent pathological re-review confirming pancreatic ductal adenocarcinoma. The explanation could be the high quality of care received by patients at the John Wayne Cancer Institute and the UCLA School of Medicine, but although this undoubtedly contributed to survival, many other centres offer equally high standards and the truth is that these values are actually not inconsistent with a number of other recent reports (as the authors point out). In this respect,

Kim's article represents part of the trend which has established that pancreatic cancer can no longer be considered to be an incurable disease in all cases.

Identifying which patients are potentially curable is clearly of more than just academic interest. The obvious explanation of why surgery is not curative is that not all of the tumour was removed. The six month survival benefit previously reported for patients with negative resection margins² is therefore disappointing. The motivation for investigating the K-ras status in the resection margin was to detect occult disease missed by conventional histopathology thus identifying a greater proportion of patients with resection margin positive disease. This could have been criticised because patients undergoing total rather than partial pancreatectomy do not have significantly improved survival³ casting doubt on the importance of local recurrence due to incomplete resection. Kim and colleagues¹ point out that this may be because of metastasis via the retroperitoneal margin of the tumour rather than early systemic metastasis, an argument made more persuasive by the convincing survival advantage they have shown for patients with K-ras negative margins.

If local recurrence, or distant metastasis, originating from incomplete resection of the tumour, is the cause of poor survival, the observations of Kim and colleagues¹ are important; they are also consistent with other reports on the difficulty of detecting occult cells⁴ and the association of poor survival with the presence of molecular markers at apparently clear margins in other tumour types.⁵ However, there are alternative explanations of the results obtained that are perhaps more convincing and even more exciting. The alternative is that the biology of tumours with K-ras positive resection margins are fundamentally different to tumours where the margin is comprised of non-mutant cells. The authors raise the possibility of field cancerisation; this is the theoretical phenomenon whereby a stem cell produces a field of genetically altered cells from which a tumour cell will subsequently arise.⁶ This would potentially explain subsequent development of tumours at other sites within the field (and hence local recurrence) but it is also likely that tumours originating within a large field would have had a longer period of non-neoplastic development than cells originating in a smaller (younger) field. Tumours that have been developing for a longer period will have had more opportunity to have spread metastases before surgery; cancer cells from such tumours may also be more aggressive and/or resistant to chemotherapy.

The evidence for field cancerisation presented in this paper appears to be overwhelming although the authors modestly defer from making a strong statement to this effect. Great effort is taken to ensure that the cells taken at the margin are not histologically abnormal, microdissection being used where necessary. Apologies are made that there is even a possibility of premalignant pancreatic intraepithelial neoplasia (PanIN) lesions in the margin material. As pancreatic cancer is extremely desmoplastic, the proportion of cancer cells to stromal cells is particularly low, even when tumour masses are examined,⁷ yet Kim and colleagues¹ show a high proportion of cells with K-ras mutations in their histologically normal tissue—a higher proportion than might even have been expected in crudely dissected tumour material. Furthermore, the K-ras mutations observed appear clonal—only one type of mutation is observed in each specimen. It is hard to explain these observations on the basis of an occasional occult tumour cell or spontaneous mutation in individual cells at the margin but the observations are entirely consistent with a field of cells derived from a common progenitor cell that carried a mutation.

If field cancerisation explains the presence of K-ras mutations, does the low survival of patients with fields extending beyond the resection margin reflect a second primary within the field? Some evidence is given by Kim and colleagues¹ for local recurrence in a small group of patients with K-ras positive peritoneal margins and in general the peritoneum is a common site of recurrence, even in patients receiving adjuvant therapy.⁸ Recurrence within the remnant of the pancreas is however comparatively rare, particularly in patients receiving adjuvant radiotherapy.⁸ In this respect it is worth noting that adjuvant radiotherapy appears to be less effective in prolonging patient survival than systemic chemotherapy,⁹ suggesting that local recurrence is not a major factor in determining survival. This is supported by the lack of overall benefit in total pancreatectomy compared with partial pancreatectomy³ discussed previously.

If survival is defined by distant metastasis before resection and not by tumour left in the pancreas remnant or a secondary tumour arising in the remnant, why does the presence of K-ras mutant cells in the resection margin make such a large difference to survival? Similar levels of survival have been reported previously in patients with very small tumours¹⁰; this is an important observation and supports the need for early detection, but Kim and

colleagues¹ report no correlation between small tumour size and K-ras mutation status in tumour margins and no survival benefit for patients with smaller tumours. This is presumably because few patients are detected with small tumours and K-ras negative margins do not reflect early detection but instead reflect an independent determinant of survival. Consistent with this, K-ras positive margins are associated with increased neural and lymphovascular invasion and they are also associated with poorer differentiation of the primary tumour, all of which indicates that the nature of the tumour free resection margin reflects biological differences in the tumour.

Is mutation status of the resection margin determined by the nature of the tumour or is it a reflection of the origin of the tumour? Further support for a cancerisation field providing the basis for tumour development, rather than the tumour invading the margin, comes from the observation by Kim and colleagues¹ that not all K-ras positive margins correspond to K-ras positive tumours. Presentation of this observation is understandably muted. We recently presented data on K-ras mutation and p16 promoter methylation in DNA from pancreatic juice supernatant that was not reflected in the DNA from the primary tumour but that nevertheless reflected the presence of the cancer¹¹; this aspect of the work was not uniformly well received. A heterozygous K-ras mutation may be a vital element in establishing a cancerisation field or allowing the field to support further genetic instability but the mutant allele may be lost in those cells within the field that make the next step in becoming tumour cells (as in a small number of cases other mutations will make the K-ras oncogene redundant). Similarly, p16 promoter methylation may be common in the field but be lost along with other CpG island methylation as the cells become cancerous. It is much less likely that overt tumour cells with no K-ras mutation will develop the mutation as they invade the margin region and somehow become occult.

Recent mouse models of pancreatic cancer support the role of K-ras mutations in progenitor cells as being an important, if not essential, element of pancreatic tumorigenesis.^{12,13} This would support the cancerisation field model but how would this fit with the observed difference in survival of patients in the paper by Kim and colleagues?¹ In the mouse models, K-ras mutations are switched on during development of the pancreas and are then expressed in ductal and acinar cells throughout the life of the mouse.

Spontaneous mutation of K-ras in adult human stem cells would be the equivalent developmental path in sporadic pancreatic cancer. Depending on when this occurs, a small or large island of clonal K-ras mutant cells would develop other mutations and epigenetic events within this population could give PanIN lesions and eventually invasive carcinoma. A carcinoma originating in a small field of mutant cells will be likely to have developed earlier in the progression of the K-ras clones than a carcinoma in a large field; the consequence of this for the patient are unclear but it is at least possible that a longer period of preneoplastic development would give a greater chance of selecting mutations that in the context of a cancer cell will give greater invasiveness.

If the paper by Kim and colleagues¹ does indicate that patients with fields of cancerisation will have a better prognosis, then two types of patient will be defined: those with tumours more amenable to treatment and those in whom tumours will develop in a large potentially identifiable region of molecular changes. In the latter case, early identification of risk on the basis of molecular tests may allow early

detection, and nothing in Kim's paper contradicts the notion that early detection will also equate to good prognosis.

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Correspondence to: Dr W Greenhalf, Division of Surgery and Oncology, 5th Floor UCD Building, Daulby St, Liverpool L69 3GA, UK; greenhalf@liverpool.ac.uk

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Hepatitis C

Altered monoaminergic transporter binding in hepatitis C related cerebral dysfunction: a neuroimmunological condition?

D M Forton

There may be a role for disturbed monoaminergic neurotransmission in the pathophysiology of hepatitis C virus associated cerebral dysfunction

Fatigue, depression, and complaints of mild cognitive impairment, such as poor concentration and forgetfulness, are the commonest symptoms reported by patients with chronic hepatitis C virus (HCV) infection.¹ Yet there remains considerable debate as to whether these symptoms are caused by the virus itself. Fatigue is a multidimensional symptom with multiple, sometimes coexisting, determinants which may be biological, psychological, or sociological. It is an

important cause of impaired health related quality of life (HRQL) in HCV infection.² Numerous surveys have documented high prevalences of fatigue but consistently show no relationship with the degree of liver fibrosis, markers of inflammation, or viral load.³ This has led to the conclusion that there is no causal relationship between HCV and neuropsychological symptoms.⁴ Rather, psychological processes associated with diagnostic labelling, social functioning, anxiety about treatment, substance

abuse, and depression have been invoked to account for impairments in HRQL.^{5–6} In contrast, a number of neuroimaging studies, including a single photon emission computerised tomography (SPECT) study published in this issue by Weissenborn and colleagues,⁷ have suggested that measurable abnormalities exist within the central nervous system (CNS) in a proportion of HCV infected individuals (*see page 1624*).^{8–11}

The issue has tended to become polarised between functional and biological arguments, and the likely interaction between physical and psychological factors has been relatively ignored. Attempts have been made to control for relevant confounding factors to determine whether CNS dysfunction relates directly to HCV infection. In a carefully executed study where 300 HCV infected patients were screened for potential risk factors for cognitive impairment such as cirrhosis, psychiatric comorbidity, or previous substance abuse, a highly selected cohort of only 37 patients was identified to have no likely cause for cerebral dysfunction, other than HCV infection itself.¹¹ This small group underwent cognitive testing and patients were found to have significant impairments in learning efficiency, which did not relate to fatigue and depression, which were also