Commentaries

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Is bacterial ash the flash that ignites NASH?

As obesity creeps in epidemic proportions through increasingly inert and affluent “developed” societies, metabolic imbalance has become the commonest cause of liver disease. Fatty liver, although itself benign, predisposes the liver to NASH or non-alcoholic steatohepatitis, a chronic disorder characterised by steatosis, mixed cell type inflammation, focal hepatocyte degeneration, and perivenular or pericellular fibrosis.^{1,2} NASH is slowly progressive, occasionally resulting in cirrhosis with the potentially fatal complications of portal hypertension, liver failure, and hepatocellular carcinoma.^{2,3}

Most cases of NASH appear to have a multifactorial aetiopathogenesis. The predisposing factors include obesity, type II diabetes, insulin resistance, hypertriglyceridaemia, and rapid weight loss, each of which can cause hepatic steatosis. The trigger that sets off injury and inflammation against this background of oxidisable fatty acid excess, and the mechanisms that perpetuate steatohepatitis and fibrogenesis are less clear.⁴ A focus of recent experimental studies has been on biochemical processes that reduce oxygen to reactive oxygen species (ROS); these can potentially damage tissues by the process of oxidative stress. Oxidative stress also increases expression of cellular adhesion molecules, and secretion of chemokines and cytokines, thereby initiating the recruitment of an hepatic inflammatory response.^{5,6}

Weltman and colleagues demonstrated that cytochrome P450 (CYP)2E1 is over expressed in the livers of patients with NASH⁷ as well as in a model of steatohepatitis induced by feeding rats a high fat, methionine and choline deficient (MCD) diet.⁸ Leclercq and colleagues then showed that CYP2E1 catalyses lipid peroxidation in the murine MCD dietary model,⁹ contributing to profound oxidative stress. Alternatively, in Cyp2e1 nullizygous mice, CYP4A enzymes are upregulated and function as alternative catalysts of microsomal lipoperoxidation in experimental NASH.⁹ Other studies have implicated activation of the peroxisome proliferator activated receptor α (PPAR α) in a pathway leading to NASH.¹⁰ Activated PPAR α is a transcription factor that governs expression of the peroxisomal and microsomal (via CYP4A) pathways of lipid oxidation, with consequent over production of ROS.

As opposed to the possible primary role of “biochemical oxidative stress”, it is possible that the inflammatory response can be the primary mediator of liver cell injury in steatohepatitis. This is a favoured mechanism in alcoholic hepatitis in which gut derived endotoxin appears to incite necroinflammatory change,⁶ even in the absence of CYP2E1.¹¹ Endotoxin is a potent releaser of proinflammatory and cytotoxic cytokines such as tumour necrosis factor α (TNF- α). The cell types involved include activated macrophages, including Kupffer cells, lymphocytes, and neutrophils. In alcoholic hepatitis,⁶ and potentially in NASH, such cell types could be recruited to the liver where they not only contribute further to oxidative stress by release of ROS and nitroradicals¹² but also release cytokines that contribute to liver cell injury and hepatic fibrogenesis.

The distinction between NASH and steatosis without inflammation, injury, or fibrosis is never clearer than in the *ob/ob* leptin deficient mouse. This animal exhibits exogenous obesity, diabetes, and a steatotic liver that resembles Swiss cheese without the rind (there is no fibrosis!). In *ob/ob* mice, as well as in other rodent models of uncomplicated hepatic steatosis, administration of endotoxin provokes liver inflammation with focal hepatocyte injury, probably by releasing a shower of TNF- α from Kupffer cells, macrophages, and other cell types.^{13,14}

Until now it has been unclear if these experimental findings have any relevance to the pathogenesis of NASH in the human liver. An earlier clue came from the severe steatohepatitis, occasionally fatal, that occurred after jejunoileal bypass (JIB) surgery for obesity.¹⁵ NASH has also been described in adults during total parenteral nutrition,¹⁶ and in a case of multiple jejunal diverticulae with bacterial overgrowth of the small intestine.¹⁷ In these conditions, metronidazole therapy reduced liver injury in some cases, although use of tetracycline was less effective.¹⁷ Furthermore, in a rat model of JIB liver disease, resection of the redundant intestinal loop with its bacterial flora, or treatment with metronidazole or tetracycline, improved liver disease.¹⁸ The mechanism appeared to be improved absorption of micronutrients, including vitamin E, a critical membrane antioxidant, and possibly essential amino acids required to synthesise the principal cellular antioxidant, glutathione.¹⁸

Despite the dire consequences of severe NASH after earlier JIB, there has seemed little reason to suspect that the intestinal flora has much to do with the usually insidious process of NASH. The report from Adelaide by Wigg and colleagues published in this issue of *Gut* challenges this complacency (see page 206).¹⁹ The investigators studied small intestinal function and serum TNF- α levels in 22 patients with NASH and 23 controls. Using a combined ¹⁴C-D-xylose and lactulose breath test to define small intestinal bacterial overgrowth, they found that half of the patients with NASH had evidence of bacterial overgrowth compared with 22% of controls. Furthermore, serum TNF- α levels were significantly increased in the NASH group compared with controls. These findings entice us to consider the plausible proposal that gut derived bacterial toxins could be involved in triggering liver injury in the context of hepatic steatosis—or to paraphrase the title of this commentary: Do gut bugs trash the stash of liver hash into NASH?

Before accepting this contribution as a real advance towards understanding the pathogenesis of NASH, the limitations of the study should be considered. The patient groups were small and imperfectly matched in some critical variables, such as obesity, diabetes, and hypertriglyceridaemia. A positive ¹⁴C-D-xylose and lactulose breath test was strongly associated with diabetes, as might be expected from the decreased gut motility that commonly results from diabetic neuropathy (albeit that an impressive slowing of gut transit time could not be demonstrated). Could this have biased the findings so that the apparent association with NASH is spurious? To answer this, further studies comparing diabetics with and without NASH are required.

In the Adelaide study, the definition of small intestinal bacterial overgrowth rested on a single parameter, and the apparent high frequency of abnormalities in relatively healthy controls begs the issue of test reliability to define an

apparently subtle form of bacterial overgrowth. The definition NASH may also have been inadequate¹: it requires histological assessment because liver test abnormalities and hepatic imaging do not reliably discriminate between uncomplicated steatosis and NASH. In this study, three of the NASH patients (and all of the controls) were not subjected to liver biopsy, leaving open the opportunity for misclassification of cases.

Despite the finding that TNF- α levels were increased in patients with NASH, Wigg *et al* were unable to demonstrate either a "leaky" infected small intestine (as measured by the lactulose-rhamnose sugar test) or endotoxaemia.¹⁹ At first glance, this seems counterintuitive for the proposal that bacterial overgrowth of the small intestine plays a pathogenic role in NASH. Some plausible explanations for the paradox were suggested: limitations of the limulus assay, binding of endotoxin to plasma proteins, and systemic levels may not reflect portal endotoxaemia. Furthermore, other bacterial products such as peptidoglycan-polysaccharide polymers rather than endotoxin could stimulate release of TNF- α . The latter concept is particularly cogent because *Bacteroides* species rather than aerobic Gram negative bacteria such as *Escherichia coli*, the source of endotoxin, appear to be implicated in the pathogenesis of small intestinal bacterial overgrowth.²⁰ Measurement of peptidoglycan-polysaccharide polymers in patients with NASH would be an interesting direction of investigation in the future.

In the Adelaide study, there was no relationship between body mass index and serum TNF- α levels, but a link between obesity and raised serum TNF- α has been described by others.²¹ Yang and colleagues noted that after endotoxin administration in leptin deficient *ob/ob* mice, hepatic induction of IFN- γ is increased whereas IL-10 induction is inhibited.¹³ IFN- γ increases hepatocyte sensitivity to TNF- α while IL-10 appears to inhibit the tissue response to TNF- α . These findings were interpreted as indicating possible macrophage dysfunction in obesity in a way that could promote steatohepatitis by sensitising hepatocytes to endotoxin.¹³ Guebe-Xabier *et al* have also shown that *ob/ob* mice have a selective reduction of hepatic CD4⁺ NK T cells, and this is associated with and possibly mediated by upregulation of IL-18 and IL-12.¹⁴ Whether these abnormalities of lymphocyte populations and cytokine responses are due to obesity per se or to leptin deficiency (which is not a feature of human obesity) remains to be determined.

NASH can be regarded as the hepatic consequence of the metabolic syndrome (central obesity, insulin resistance, type II diabetes, arterial hypertension, hyperlipidaemia).^{22, 23} Attention has shifted from the reasons for steatosis, much of which is benign or resolves in the advanced stages of cirrhosis, to the mechanisms for hepatocellular injury, inflammation, and fibrosis.^{4, 9, 13} The findings

reported by Wigg *et al*, while not definitive, may provide a new clue to the importance of cytokines in mediating liver cell injury in NASH. Whether the release of TNF- α is a consequence of small intestinal bacterial overgrowth, obesity, or oxidative stress will require further study.

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Hepatocellular carcinoma: is surveillance cost effective?

The development of hepatocellular carcinoma (HCC) constitutes a frequent event during the evolution of patients with liver cirrhosis (3–5% annual incidence rate) and constitutes their main cause of death.¹ Survival is related to tumour stage at diagnosis and to the degree of impairment of liver function. Recent data have shown that

survival after diagnosis is not as poor as reported years ago.² This is due both to advances in diagnosis even in the absence of effective treatment (lead time bias) and to the application of curative treatments (surgical resection, liver transplantation, and percutaneous ablation).² These offer the only chance of cure but their applicability and long term success with five year survival exceeding 50% require the detection of HCC at an early stage, including patients with solitary nodules ≤ 5 cm or up to three nodules each ≤ 3 cm.^{2–5} In contrast, large/multifocal tumours are less likely to benefit from curative approaches and here three year survival falls below 50% regardless of treatment.² The need for detection of HCC at an early stage has prompted

surveillance programmes for patients with cirrhosis. HCC has most requisites for such a policy⁶: the population at risk is known, the disease is highly prevalent, it has a high mortality, and effective screening tests are available and acceptable. However, other conditions are not yet met: the recall policy on raising suspicion is not well defined and, unfortunately, there is no unequivocal proof that treatment improves survival. Radical therapies have never been evaluated in randomised controlled trials but are widely considered "effective" and assumed to improve survival.³⁻⁵ In contrast, randomised controlled trials assessing palliative treatments (that is, chemoembolisation) have shown negative results.² Accordingly, the usefulness of surveillance programmes in cirrhotics is still controversial, leading to the suggestion that they provide a minor benefit in terms of efficacy (years of life saved) and cost effectiveness. The only method to clarify this issue would be to design a randomised controlled trial comparing surveillance versus non-surveillance in a large series of cirrhotics who would be treated if diagnosed with HCC. Such an investigation would be ethically questionable and in addition, almost unfeasible. Ultrasound examination is commonly used for evaluation of cirrhotics, irrespective of the type of symptoms and this would "contaminate" the control arm.

In the absence of randomised controlled trials, how may we estimate the benefits of surveillance? Two approaches are proposed: to conduct follow up investigations or to perform decision-analytical studies using assumptions reported in clinical studies.⁷ Bolondi and colleagues⁸ conducted a follow up study, reported in this issue of *Gut*, recruiting a large series of cirrhotics and applying the most common surveillance policy: ultrasound and α fetoprotein determinations every six months (see page 251). On suspicion, they followed a predefined recall policy to determine the diagnosis and select the most suitable therapy aiming to offer all radical options to patients with early HCC. The outcome of patients under surveillance was compared with that of patients referred to hospital for HCC that was incidentally detected outside their programme. This comparison has allowed a rough estimation of the surveillance benefits but detection of patients with asymptomatic small solitary tumours outside surveillance suggests potential "contamination" of the control group by uncontrolled surveillance within the community physicians who thereafter refer patients with suspected HCC to the tertiary hospital for evaluation and treatment.

As surveillance is aimed at reducing disease specific mortality, comparison of long term survival between both cohorts is crucial. Unfortunately, the difference in survival was significant but not impressive (45% *v* 32% at three years). This may reflect both a lead time phenomenon and a real impact of treatment on survival. Interestingly, the applicability of radical therapies was not significantly different between the two cohorts (69% *v* 54%), although liver transplantation was more frequently applied in the surveillance cohort. Nevertheless, multivariate analysis identified liver function and tumour stage as survival predictors. Tumour stage may be a surrogate of surveillance and thus surveillance may prompt earlier HCC detection not allowing a better therapeutic approach, and this would prevent a marked impact on survival. In

addition to this clinical output, Bolondi *et al* showed that the cost per year of life saved was above US\$100 000, a value largely exceeding the cut off accepted for surveillance by policy makers and health providers.⁹

Do these findings imply that the study is not relevant? The answer is no. Evaluation of surveillance for HCC requires several clinical studies with different designs in different settings. Bolondi and colleagues⁸ describe the outcome of a hospital based programme including all types of cirrhotics and it may be that the clinical impact would be higher in a community based programme. In the latter, the risk of HCC might be lower because of better liver function (the study confirms age, advanced liver disease, and increased α fetoprotein concentrations as the main HCC predictors within cirrhosis) but the applicability of liver resection or transplantation may be increased. Thus a relevant increase in survival could be attained. On the other hand, the cost of each detected HCC in low risk individuals may also rise, and perhaps the unacceptable cost effectiveness ratio would not be modified. Another approach is more intense surveillance (that is, every three months) or the use of different tools. The results of these awaited studies will provide the assumptions to be used for estimation of the benefits and cost effectiveness of surveillance in different scenarios by using statistical techniques such as the Markov model.

Until these data become available, the debate will persist and surveillance will be initiated in cirrhotics, even without evidenced based data. However, this approach does have positive benefits. The diagnosis of patients at a non-advanced stages prompts further refinement of treatments with progressive improvement in long term outcomes. In addition, in the era of genetic profiling, careful recruitment of both clinical and biological data within surveillance will surely introduce molecular concepts into clinical practice. Ultimately, this research will change our understanding of the disease and help us to identify new targets for both prevention and treatment.

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Endoscopic mucosal resection for early gastric cancer

The paper by Ono and colleagues¹ in this issue of *Gut* documents the remarkable results achieved at the Tokyo National Cancer Centre Hospital (NCCH) with endoscopic management of early gastric cancer (EGC) (see page 225). EGCs constitute a much higher proportion of the total number of gastric cancers in Japan than is the case in the West. There are a number of reasons for this: firstly, many asymptomatic subjects in Japan are screened for gastric cancer (usually by barium radiology, followed, if necessary, by endoscopy); secondly, Japanese diagnostic gastroscopy is a much more careful procedure than the “smash and grab” style of endoscopy which is typical in this country: the stomach is inflated to a greater degree, indigo carmine dye spraying is used to examine any suspicious area, and simethicone (to eliminate bubbles and froth) and hyoscine (to paralyse the stomach) are used routinely. There is some evidence that early lesions are missed in the UK: a recent audit in one centre showed that 11 of 81 patients presenting with advanced gastric cancer had undergone endoscopy within the previous two years.²

Is EGC in Japan the same disease as EGC in the West? A recent analysis of published data from Japan and the rest of the world³ concluded that histological type, macroscopic appearance, degree of invasion, and frequency of lymph node metastases are the same in Europe as Japan. Japanese classification of tumour invasion, as Ono *et al* have pointed out, differs, with lesions classified as “high grade dysplasia” in the West called “intramucosal carcinoma” in Japan. A new terminology—the Vienna classification of gastro-intestinal neoplasia⁴—has been proposed in an effort to overcome this discrepancy.

Endoscopic mucosal resection (EMR) for EGCs confined to the mucosa seems a very attractive alternative to surgery. Ono *et al* wish to “promote its use around the world” and their paper is a powerful argument in favour of EMR. Could EMR become a standard therapy for mucosal EGC in this country? EMR demands a high level of endoscopic expertise, as well as a cooperative patient. I have had the opportunity to examine the case from both sides, having visited the NCCH and having played host to endoscopists from the NCCH who worked in our unit over the past few years. I have personally witnessed an EMR at the NCCH which took over three hours to complete (the lesion was large); the patient was lightly sedated with midazolam and remained cooperative throughout. Our patients are less likely to tolerate these procedures as well as the Japanese. Endoscopists from the NCCH carried out a number of EMRs for EGC in our unit in April of this year as part of a “live” demonstration in a course on endoscopic management of early gastro-intestinal cancer, and all patients required a general anaesthetic. As well as anaesthetic input, EMR requires special equipment and a dual channel therapeutic gastro-scope. Although the technique of “strip biopsy” is relatively straightforward, and suitable for smaller lesions, it is more likely to result in resection in multiple fragments which makes histological evaluation of resection much more difficult. (In this series, completeness of resection could not be evaluated in 20%.)

The NCCH endoscopists now prefer the newer technique employing the insulation tipped diathermic knife

(IT knife) which is not commercially available in the UK. This technique is technically much more demanding and time consuming but can be used to resect much larger lesions: I have seen an 8 cm EGC resected with this technique (the patient was unfit for surgery). EMR is not generally suitable however for large lesions: in this series, complete resection was achieved in only 38% of lesions >3 cm.

Alternatives to strip biopsy have been described by other Japanese groups: these include aspiration mucosectomy⁵ and EMR using a ligating device.⁶ Proponents of aspiration mucosectomy claim it is technically easier than strip biopsy.

Japanese endoscopists are expert in assessing depth of invasion of gastric cancers purely on the basis of endoscopic features.⁷ Some criteria, such as size and presence of ulceration, are straightforward, but others, such as the macroscopic configuration (superficial, elevated, depressed, etc) and mucosal fold pattern, are more subjective and may present difficulty for western endoscopists. Ono *et al* “do not use endoscopic ultrasonography (EUS) routinely, as it is not sensitive enough to evaluate minute invasion to the submucosa.” Nevertheless, 15% of resected lesions showed submucosal invasion. I suspect that Western endoscopists would opt for routine use of EUS before embarking on EMR.

Endoscopists inexperienced with EMR will have concerns about complications of bleeding and haemorrhage. Ono *et al* had a relatively high incidence of perforation at 5% (the risk of bleeding is not stated). Remarkably, most of these perforations were managed by endoscopic clipping. Japan has an entirely different medical culture to the UK: litigation and complaints are uncommon, and advice given by doctors is usually accepted without question. British endoscopists will be wari-er of new techniques with potentially serious complications. In this brave new world of clinical governance, who is to determine what an acceptable complication rate should be for a new procedure? The current political climate in the NHS discourages the development of techniques such as EMR. Few centres in this country are likely to diagnose enough EGCs to become expert in EMR, and it would be desirable, therefore, for this technique to become concentrated in a few specialised centres.

Patients with EGC can expect a five year survival rate in excess of 90% with surgery^{8,9}; why then should we in the West embrace EMR? Ono *et al* have pointed out a number of compelling reasons: firstly, EGCs fulfilling the criteria for EMR have a lower risk of lymph node metastasis (0.36%) than the mortality rate from surgery for EGC at their centre (0.5%); secondly, EMR is considerably cheaper compared with conventional surgery; and thirdly, there were no gastric cancer related deaths in this series during a median follow up period of 38 months. Surgery will continue to play a key role in the management of EGC: despite the success of endoscopic therapy, most EGCs at the Tokyo NCCH are still treated surgically.

EMR in this country is likely to develop initially as therapy for EGC in frail patients who would pose a high risk for radical surgery; with increasing experience, we can aspire to the outcomes achieved by the Japanese.

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