randomised controlled trials which have not required histological evidence of alcoholic hepatitis before allocating treatment.[1 4] The corollary to this is that although alcoholic hepatitis often presents with clinical features of fever, leucocytosis, and hyperbilirubinaemia, there remains a differential diagnosis which may require a biopsy to resolve.[5]

It is important to differentiate between true alcoholic hepatitis and severe liver dysfunction in patients with heavy alcohol consumption because it will influence the choice of intervention. Randomised controlled trials that use GAHS to identify patients with alcoholic hepatitis might be greatly underpowered if the therapy (for example, steroids) is effective in alcoholic hepatitis but ineffective or harmful in other clinical conditions where abnormal clinical parameters might be associated with heavy alcohol consumption. Selection of risk stratification models should be determined by the severity of the adverse effects of the therapy under trial. Those with more severe adverse effects will warrant models with high specificity whereas drugs with minimal side effects will benefit from a model with a high sensitivity. Compared with the DFS, the GAHS has an increased specificity, decreased sensitivity, and improved accuracy, making it suited to the selection of subjects in studies using more toxic therapies.

The utility of the GAHS will depend on the effect of its use in the care of patients. We suggest that the next step in the evaluation of GAHS should be a clinical trial to see if patients randomised to risk stratification with GAHS followed by appropriate interventions have a better outcome than those managed conventionally.

We believe this is an excellent study using robust clinical end points. It is a practical model which can be used easily at the bedside to give valuable prognostic information. Success of future therapeutic trials in alcoholic hepatitis will not only depend on the efficacy of the drug but also the appropriate selection of patients by models and their respective cut off points.

I N Guha, W M Rosenberg
University of Southampton, Liver Unit, Southampton, UK

Correspondence to: Dr I N Guha, Mail point 811, Level D, Southampton General Hospital, Trenoma Rd, Southampton S016 6YD, UK; guhaneil@hotmail.com

IN Guha received grant support from Pfizer.

W M Rosenberg is a consultant for Schering-Plough, Roche, Gilead, Bayer, and Pfizer. He is the Chief Scientific Officer for HepCGen.

Conflict of interest: None declared.

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A proof of concept study establishing *Necator americanus* in Crohn's patients and reservoir donors

The emergence of autoimmunity, including Crohn's disease (CD) where the immune relationship with commensal bacteria is corrupted, has been linked to hygiene.[1 2] A gradual decline in endoparasites is but one argument that might explain this phenomenon.[3] Weinstock and colleagues have successfully tested the pig whipworm, *Trichuris suis*, in patients with inflammatory bowel disease (IBD).[4 5] However, repeated inoculation was required and concern has been raised that aberrant migration could occur.[6] The haematophagous hookworm, *Necator americanus* (NA), is proposed as an alternative. We have tested if CD patients tolerate hookworm infection, and the practical issues associated with establishing reservoir donors (RDs).

Over 700 million people remain infected with hookworms. Infective larvae (L3i) are acquired through skin contact with contaminated soil.[7] Auto-reinfection, direct person to person infection, aberrant migration, and hypobiosis do not occur. Adult worms live in the host small intestine for an average of five years. Infection can be easily terminated with an anthelminthic. Anaemia is the only disease of consequence but is an unusual outcome in properly nourished individuals. Using L3i originally obtained from Madang, Papua New Guinea, but maintained in a healthy researcher in the UK, five CD subjects with longstanding but mostly inactive disease and three RDs each received a carefully measured inoculum (table 1). Subsequently, four additional CD subjects with chronic and mostly active disease were inoculated with L3i cultured from faeces provided by an RD, and the original CD cohort were reinoculated from week 27 to week 30. Ethics approval was granted by the Townsville Health Service District Institutional Ethics Committee. Haematological and clinical measurements are expressed as mean (95% confidence interval).

The inoculation caused a mild itch within five minutes that disappeared after a few days in eight CD subjects and a pruritic rash that lasted two weeks in the RDs, who also developed a painful transient enteropathy. Neither respiratory symptoms nor detectable aberrant migration occurred. In the CD cohort, blood eosinophilia developed from week 5 (mean 2.60×10^9/l (1.89) *v* week 1 0.18×10^9/l (0.10) *v* week 20 0.59 (0.20)). Patent infection had established by week 20 in all cases. CD activity index (CDAI) remained unchanged until week 17, possibly in part due to a hookworm related enteropathy recognisable because of blood eosinophilia and faecal Charcot-Leydon crystals.[8] After 20 weeks, the IBD questionnaire was improved (mean 151 (14) *v* 179 (20)) and the four week cumulated CDAI scores was decreased (mean 141 (31) *v* 87 (15)).[9] Haemoglobin fell marginally (week 1 mean 135.6 (7.8) g/l *v* week 20 129.3 (4.1) g/l). Reinoculation of the five CD subjects first exposed caused no apparent adverse effect. Disease reactivation, as defined by a CDAI >150, occurred in two (CD4, CD5; table 1) after the doses of long term immune suppressive drugs had been reduced. The subject (CD3–7) driven trend was to reduce immune suppression as health improved, a strategy often associated with worsening of symptoms. The five CD subjects first inoculated were in remission at week 45 (fig 1).

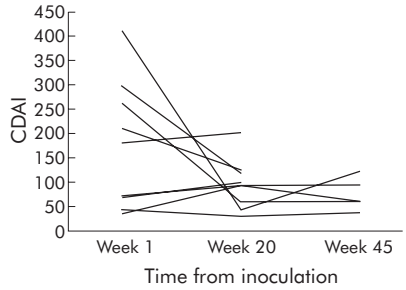

Figure 1 Initial Crohn's disease activity index (CDAI) score for each CD patient versus score at week 20 and at week 45 for the first five inoculated cases (mean 165 (95% confidence interval 145) *v* 64 (25), p = 0.132; mean 165 *v* 75 (29), p = 0.246).

Our pilot study has established a potential for NA, already a fact of life for many millions, as a candidate parasite to inoculate those with autoimmune disease. The natural advantages are lifecycle and migration predictability, ability to control the size of and eliminate a colony, and the parasite's longevity. Inoculation proved safe, even in immune suppressed patients. Our hope that NA would suppress autoreactivity sufficiently to allow immune suppressive therapy to be stopped was unrealistic. Recent and compelling evidence has shown that IBD is self sustaining.[10] It may be that after remission is achieved, endoparasites will offer an alternative or adjunct to immune suppressive therapy, a priority for some people with CD.

J Croese
Department of Gastroenterology, Townsville Hosptial, Townsville, Australia

J O'Neil
Department of Gastroenterology, Royal Brisbane Hospital, Brisbane, Australia

J Masson, S Cooke
Department of Gastroenterology, Townsville Hosptial, Townsville, Australia

W Melrose
School of Public Health, Tropical Medicine and Rehabilitation Sciences, James Cook University, Townsville, Australia

D Pritchard
Boots Science Building, School of Pharmacy, University of Nottingham, Nottingham, UK

R Speare
School of Public Health, Tropical Medicine and Rehabilitation Sciences, James Cook University, Townsville, Australia

Correspondence to: Dr J Croese, Department of Gastroenterology, Townsville Hosptial, Townsville, Q 4814, Australia; jcroese@bigpond.com

doi: 10.1136/gut.2005.079129

Conflict of interest: None declared.

Table 1 Crohn's disease activity index (CDAI) in CD subjects inoculated with infective larvae (L3i). Subsequently, the five CD subjects first inoculated were reinoculated from week 27 to week 30 and four CD subjects with chronic and mostly active disease were inoculated with larvae sourced from one of the authors

	Initial inoculation trial					Reinoculation trial				
	Time (weeks)					Time (weeks)				
ID, age (y), sex	0–4	5–8	9–12	13–16	17–20	27	30	35	39–41	45
CD1 55 M										
Inoculum therapy	25 L3i					25 L3i				
CDAI	79	60	89	77	68		96		93	62
CD2 46 M										
Inoculum therapy	25 L3i					25 L3i				
CDAI	38	114	20	68	48		30			36
CD3 41 F										
Inoculum therapy	25 L3i P5 M15	P5 M15	P5 M7.5			25 L3i P5 M10	P5 M10	P5 M10	M10	M10
CDAI	46	71	85	83	90		36	30	92	95
CD4 34 M										
Inoculum therapy	50 L3i P38 M30	P38 M30	P50 M30	P25 M30	P5 M30	50 L3i P5 M20	P2.5 M20	M20	P25 M30	P20 M30
CDAI	260	230	232	264	118		60	442	60	122
CD5 21 F										
Inoculum therapy	50 L3i P10 M20	P10 M20	P13 M20	P10	P7.5	P5	25 L3i P5	P25 M20	P15 M20	P10 M20
CDAI	144	151	103	79	73		410	180	44	61
CD6 33 F										
Inoculum therapy	50 L3i P15 M20	P10 M20	P5 M20	P5 M20	P7.5 M20					
CDAI	49	32	6	29	100					
CD7 33 M										
Inoculum therapy	50 L3i A150	P25 A150	P5 A150	P5 A150	P8 A150					
CDAI	260	114	96	125	118					
CD8 46 M										
Inoculum therapy	50 L3i M20	M20	M20	M20	M20					
CDAI	145	159	171	152	186					
CD9 44 F										
Inoculum therapy	100 L3i P5 M20	P10 M20	P5 M20	P5 M20	P10 M20					
CDAI	173	127	106	76	125					

L3i, n 3rd stage *N americanus* larvae inoculated percutaneously; P, prednisone n mg/day; A, azathioprine n mg/day; M, methotrexate n mg/week.

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Strong BCL10 nuclear expression identifies gastric MALT lymphomas that do not respond to *H pylori* eradication

Approximately 75% of gastric mucosa associated lymphoid tissue (MALT) lymphomas can be cured by *Helicobacter pylori* eradication.[1] It would be very useful to identify, at the time of diagnosis, the 25% of cases of gastric MALT lymphoma that will not respond to *H pylori* eradication. In general, lymphomas at stage II_E or above do not respond to *H pylori* eradication.[2–4] However, the prognostic value of staging in stage I_E cases is very limited, although tumours that involve the muscularis propria or serosa (stage I_{E2}) show a higher failure rate than those restricted to the mucosa and submucosa (stage I_{E1}).[2–4] Paradoxically, the majority of gastric MALT lymphomas at diagnosis are at stage I_E but 20% of these cases will not respond to *H pylori* eradication.

In a previous study, we have examined the value of t(11;18)(q21;q21) in prediction of the response of gastric MALT lymphoma to *H pylori* eradication. Among the 111 cases of gastric MALT lymphoma studied, t(11;18)(q21;q21) was present in 42/63 (67%) non-responsive cases, including 26/43 (60%) at stage I_E.[5] In contrast, translocation was detected in only 2/48 responsive cases and the two translocation positive cases showed a temporary response to *H pylori* eradication.[5] Based on the same series of cases, we examined the value of t(1;14)(p22;q32)/*IGH-BCL10* in prediction of the response of gastric MALT lymphomas to *H pylori* eradication.

Of the 111 cases examined, 75 including 35 from the complete regression group and 40 from the non-responsive group, had adequate tissue specimens for evaluation of BCL10 staining. Two cases showed strong BCL10 nuclear staining in virtually all tumour cells (fig 1), similar to that seen in t(1;14)(p22;q32) positive cells,[6] while the remaining cases displayed either weak cytoplasmic or weak nuclear staining. Both cases with strong BCL10 nuclear staining were from the *H pylori* eradication non-responsive group; one case (case No 1) had stage II_E disease and showed no response 12 months after *H pylori* eradication while the other (case No 2) had stage I_E disease and showed no response eight months after *H pylori* eradication. As shown in our previous study, both cases were t(11;18)(q21;q21) negative.[5]

To ascertain whether the two cases that showed strong BCL10 nuclear staining were positive for t(1;14)(p22;q32) or variant, interphase fluorescence in situ hybridisation (FISH) with *BCL10* break-apart dual colour probes, *IGH* break-apart probes, *IGκ* break-apart probes, and *BCL10/IGH* dual colour dual fusion translocation probes were performed.[6 7] Both cases failed to show evidence of *BCL10* gene break or amplification. Case No 2 showed an *IGH* break, but FISH with *BCL10/IGH* dual colour dual fusion translocation probes failed to show evidence of *BCL10/IGH* translocation. To further investigate these cases, we performed real time quantitative reverse transcription-polymerase chain reaction of *BCL10* mRNA. Unfortunately, adequate tissue materials were available only in case No 2. The level ($\Delta Ct = 3.4$) of *BCL10* mRNA expression in this case was compatible with that in MALT lymphoma with t(1;14)(p22;q32) (mean 1.60 (SD 2.37)), well above that in those without the translocation (6.94 (1.72)).[6]

To further assess the impact of t(1;14)(p22;q32) on the clinical behaviour of MALT lymphoma, we retrospectively reviewed the clinical presentation of 11 cases, including six from the stomach with known *BCL10* involved translocation (table 1). Of these cases, nine including all those from the stomach, were at stage II_E or above. Although clinical presentation and follow up data were not available in each case, three cases (Nos 1, 2 and 7) presented unusual wide dissemination,