patient groups with respect to their ratio of hGR α to hGR β mRNA levels. Unfortunately, among the 12 patients evaluated prospectively, only one turned out to be steroid dependent and one steroid resistant in a two year follow up, allowing no statistical analysis. However, these two prospectively evaluated patients with impaired steroid response did not differ in their hGR β mRNA expression from the steroid responders.

Our findings do not exclude the possibility that hGR protein levels may differ in the respective groups as a result of post-transcriptional regulation. However, quantification of hGR protein levels is difficult and does not provide evidence for the amount of "free" receptor with the ability to bind steroids. Nevertheless, our data indicate that the ratio of PBMC hGR α to hGR β mRNA expression is not correlated with effective glucocorticoid treatment in IBD. Therefore, we conclude—in contrast to Honda and coworkers—that hGR β expression has no predictive value for the efficacy of steroid treatment.

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A non-invasive screen for infectivity in transmissible spongiform encephalopathies

The risk of transmissible spongiform encephalopathy (TSE) infection from endoscopic procedures has been discussed recently in this journal.^{1,2} Subclinical carriers of variant Creutzfeldt–Jakob disease (vCJD), the numbers of whom are unknown, may present a risk

of iatrogenic infection to susceptible patients participating in endoscopy. We report a pilot study, undertaken here on sheep, describing a non-invasive assessment of autonomic function based on heart rate variability (HRV) which may provide a useful screening method for subclinical carriers of certain TSE diseases.

Detection of disease associated prion protein (PrP^d) in the brain stem is used in confirmatory postmortem tests for bovine spongiform encephalopathy (BSE) and sheep scrapie; this protein is also present in humans with vCJD.^{3–5} In scrapie, the timing of PrP^d accumulation in the dorsal motor nucleus of the vagus nerve (DMNX) indicates that this is a likely site of initial neuroinvasion.⁴ Non-myelinated vagal fibres from the DMNX and faster myelinated vagal fibres from the nucleus ambiguus are involved in the control of HRV, which is the millisecond beat to beat change that is distinct from the heart rate. Cardiac vagal tone may be considered to be the sum of low frequency (LF) variation in HRV influenced by vagal efferents from the DMNX, plus high frequency (HF) variations, influenced by the respiratory frequency, resulting from the efferent output from the nucleus ambiguus.⁶ The DMNX contains parasympathetic neurones whose axons communicate directly with the gut, heart, and other viscera and can be implicated in the transport and initial site of infection and subsequent infection in the nucleus tractus solitarius and the nucleus ambiguus.⁴ Thus analysis of HRV may provide an index of vagal

Figure 1 Typical high frequency (HF) and low frequency (LF) filtered tachygrams on which a fast Fourier transformation is done to give estimates of heart rate variability (HRV) in different frequency bands. The reduced HRV is indicated by the flatter lines in the infected sheep.

Figure 2 Box plots (median, upper and lower quartiles, and range) showing heart rate variability (HRV) measures, demonstrating a significant difference (** $p < 0.005$) between biopsy positive and biopsy negative animals (Mann–Whitney test following a Kolmogorov–Smirnov test with Lilliefors significance correction to test for a normal distribution). There is no significant difference in the heart rates of the animals or in the high frequency range of HRV. Within the negative biopsy group, there was no difference in either low frequency or high frequency between the orally challenged and non-infected animals.

dysfunction caused by the presence of PrP^d in brain stem regions before clinical signs become noticeable.

PrP^d has been detected in vCJD rectal samples and implications for potential iatrogenic infection to humans of susceptible genotypes have been drawn.^{1,2} Large scale studies of sheep scrapie show that PrP^d aggregates are consistently present in the recto-anal-mucosa-associated lymphoid tissue (RAMALT) of preclinically and clinically infected sheep.^{7,8} This pilot study investigated the possibility that HRV might also recognise TSE infection in clinically normal sheep, positive for PrP^d in RAMALT biopsies.

Table 1 Summary of the genotypes of the sheep involved in the study

	Negative biopsy	Positive biopsy
Unexposed	2 ARQ/ARQ 1 VRQ/VRQ	–
Oral exposure	4 ARQ/ARQ	3 ARQ/ARQ 3 VRQ/VRQ
Natural exposure	9 ARR/ARR 2 ARQ/ARR 1 ARQ/ARQ	–

ARR/ARR and ARQ/ARR are resistant genotypes.

We recorded HRV data from 25 sheep. Six were clinically normal but PrP^d positive in RAMALT biopsies, and 19 were clinically normal and PrP^d negative in RAMALT biopsies. Among the latter, three were unchallenged controls, 11 were naturally exposed to scrapie infection and of resistant PrP genotypes, one was naturally exposed to scrapie and of susceptible genotype, and four were orally dosed and of susceptible genotypes. Experimentally infected sheep had been dosed with 5 g of a 10% homogenate of a pool from scrapie affected sheep brains.

ECG samples (300 s) were collected and digitised using a commercially available monitor (VariaCardio). ECG R wave timings were obtained to determine variability in the R–R intervals, and an instantaneous tachygram was constructed (fig 1) from which power spectra were calculated.

Power spectral analysis in the 0.032 to 0.138 Hz band (LF), but not the 0.15 to 0.5 Hz band (HF) showed significant differences (LF, $p < 0.005$) between RAMALT biopsy negative and biopsy positive sheep (fig 2). As all positive sheep were asymptomatic, HRV assessment may be a useful preclinical test for TSE infection. This HRV index on its own, used once, may not distinguish between individual rectal biopsy positive animals and controls, as ranges overlapped. However, the negative and positive biopsy groups contained animals of different provenance—the negative biopsy group contained sheep of resistant genotypes, unexposed sheep, and sheep of uncertain infection status; the positive group contained infected sheep at approximately 40–90% of the incubation period. Owing to the small number of sheep investigated here, further large scale studies are needed to refine the methods and aid the interpretation of the results; however, being a live non-invasive screen for TSE infection it has the advantage that repeated measures over time may be taken to strengthen confidence in the interpretation.

We have previously demonstrated a similar reduction in HRV in BSE infected cattle⁹ and in humans incubating vCJD¹⁰ compared with controls. We herewith show that changes in HRV may be a common and early feature of TSE infections. Improved preclinical testing for TSEs using specific signature changes in HRV with respect to time could help minimise the risk of iatrogenic infection from endoscopy and other invasive procedures, and also provide an objective measure of the pathogenesis of the disease.

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Transient elastography in patients with non-alcoholic fatty liver disease (NAFLD)

Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver injury in many countries around the world.¹ NAFLD covers a wide spectrum, ranging from simple steatosis—which is generally non-progressive—to non-alcoholic steatohepatitis (NASH). There are no established non-invasive methods of evaluation for patients with NASH, and until recently liver biopsy was the only method for evaluating liver fibrosis. Transient elastography is a new technique that allows rapid, non-invasive measurement of mean tissue stiffness, which has been shown to be useful for accurate estimation of hepatic fibrosis in patients with chronic hepatitis C.²

We carried out a study to determine the value of liver stiffness measurement with the new medical device called the Fibroscan (EchoSens, Paris, France), based on ultrasound transient elastography, in patients with NAFLD. We carried out liver stiffness measurements in 67 NAFLD patients (mean (SD) age, 50.4 (3.3) years) in whom the diagnosis had