## Interferon-α Therapy for Patients with Chronic Fatigue Syndrome

**Colleagues**—The idiopathic chronic fatigue syndrome (CFS) is characterized by prolonged fatigue lasting at least 6 months, of unknown etiology [1]. The cause or causes of CFS are unclear, although there is evidence for chronic infection with Epstein-Barr virus, coxsackievirus, or other viruses and for immune dysfunction [1–5]. There is no established therapy known to be uniformly successful. Interferon-αs have a wide range of antiviral and immunostimulatory properties and have been successful in the therapy of chronic hepatitis B and C and other viral infections [6, 7]. Therefore, these agents seemed a logical choice for a trial of therapy in this common, very debilitating condition.

Twenty adults (14 women, 6 men) with CFS [1] for 1–11 years were randomized by using computer-generated random numbers either to receive immediate therapy (group A, 11 patients) or to be treated after 3 months follow-up (group B, 9 patients). Three megaunits of interferon-α2b (rbe Intron A; provided by Schering-Plough, Mildenhall, UK) was administered subcutaneously thrice weekly for 12 weeks, after which the patients were observed for a further 3 months. One patient was misassigned to group A due to a clerical error. Enrollment was limited to patients with a performance status of ECOG (Eastern Cooperative Oncology Group) I or II (table 1) [8]. At each visit, the patient's activity was graded by the ECOG scale, which has the advantage of large increments between each activity level (table 1).

None of the 9 group B patients recovered significantly during the 3-month pretreatment assessment, although 1 patient decided not to be treated. Therefore, 19 patients were treated (8 group B, 11 group A), of whom 1 group A patient withdrew after 3 weeks of therapy because of side effects (increased fatigue). The remaining 18 patients tolerated 12 weeks of treatment. Therapy was reasonably well tolerated and side effects, which were most prominent 2–4 weeks into therapy, were no worse than those seen during therapy for other conditions [6, 7]. None of the side effects persisted after the end of therapy except mild alopecia, which resolved in 3 months, and mild boils, which persisted for up to a year in 2 women. One patient noticed a transient marked improvement in energy levels for 2 weeks after 2 weeks of therapy. No changes were detected in hematologic parameters, but 2 patients had transient minor rises in aspartate aminotransferase levels during therapy.

At the end of the study, 3 patients were adjudged to have completely recovered, having returned to full, normal activity (ECOG 0; table 1). Two of these patients were seen 12 months later and remained entirely well. Two further patients were improved at the end of follow-up and up to 8 months later, moving from ECOG II to I (table 1). Improvement was first evident 1–3 months after therapy had ended in all 5 patients. The only difference between treatment responders and nonresponders was that 4 of the 5 patients who recovered or improved but only 1 of 15 patients who did not improve had detectable coxsackievirus B IgM antibody in serum. This difference was statistically significant ($\chi^2 = 7.2$, $P < .01$, $\chi^2$ test with Yate's correction). The 4 who improved with treatment all reported an acute virus-type illness at the start of their disease. Two of the 4 coxsackievirus B IgM–positive patients who improved remained IgM-positive and 2 were negative by the end of follow-up.

**Table 1.** Eastern Cooperative Oncology Group (ECOG) status of patients before and after treatment according to end-of-trial condition.

| ECOG grade* | No. of patients: Recovered (n = 3) Before | Recovered (n = 3) After | Improved (n = 2) Before | Improved (n = 2) After | Not improved (n = 15) Before | Not improved (n = 15) After |
|---|---|---|---|---|---|---|
| 0 | — | 3 | — | — | — | — |
| I | 2 | — | — | 2 | 6 | 6 |
| II | 1 | — | 2 | — | 9 | 8 |
| III | — | — | — | — | — | 1 |

* 0 = able to carry out all normal activity without restrictions; I = restricted in physically strenuous activity but ambulatory and able to do light work; II = ambulatory and capable of self care but unable to work; III = capable of only limited self care and confined to bed or chair for >50% of waking hours. (IV = totally disabled and confined to bed or chair.)

This study suggests that a proportion of patients with CFS may benefit from therapy with 3 months of thrice-weekly interferon-α. While the numbers are too small to draw firm conclusions, the temporal relationship of recovery with therapy and the significant association with coxsackievirus B IgM suggests a true treatment response. There are at least two possible explanations for the results of this trial. Some studies have suggested a 50% prevalence of enterovirus infection in patients with CFS [3]. If persisting coxsackievirus B IgM antibodies reflect chronic enterovirus infection, interferon-α may act by suppressing enterovirus replication. However, the evidence for enterovirus infection in CFS is not clear-cut, as at least one study reported an equal prevalence of coxsackievirus IgM positivity in fatigued patients and controls [9]. An alternative explanation is that the positive IgM is due to an aberrant immune response [4, 5], and treatment response relates to the known immunostimulatory properties of interferon-α [6]. Further studies are clearly warranted, possibly using higher doses of interferon-α and stratifying for coxsackievirus B or other enterovirus markers, if we are to ascertain whether this therapy really is of significant benefit for patients with CFS.

The study had the approval of the Royal Free Hospital Ethics Committee and was carried out under a Department of Health Clinical Trials License.

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## Evidence of Direct Transmission of *Escherichia coli* O157:H7 Infection between Calves and a Human

**Colleagues**—Infection with Vero cytotoxigenic *Escherichia coli* (VTEC) serotype O157:H7 is an important cause of hemorrhagic colitis and has been associated with hemolytic uremic syndrome in humans [1]. Outbreaks of infection have been linked to the consumption of certain foods of bovine origin, such as ground beef and unpasteurized milk [2]. Person-to-person transmission has occurred among family members, in day care centers, and in nursing homes [3]. Sources of infection in sporadic cases in humans are rarely determined [4]. Healthy cattle are known to be reservoirs of *E. coli* O157:H7 [5, 6]. However, to our knowledge, there have been no reported cases of direct transmission of *E. coli* O157:H7 from an animal to a human. We describe a case of apparent fecal-oral transmission between calves and a human.

In October 1992, we were informed of a case of hemorrhagic colitis in a 13-month-old previously healthy boy who lived on a farm in southwestern Ontario. The child was hospitalized on 11 October 1992 with bloody diarrhea and vomiting. *E. coli* O157:H7 phage type 23 was isolated from stool. The child was hospitalized for 6 days, receiving supportive treatment; he recovered without complications.

The child's family consisted of the mother, the father, a 9-year-old brother, and a 5-year-old sister. The family raised veal calves in a converted dairy barn on a farm on which they had lived since May 1992. There were no milking cows on the premises. By October 1992, there were 7 Holstein calves aged 1–4 months in the barn. Each calf had been obtained at 3 days of age from a dairy farm ~160 km away. The father and the two older children shared the responsibility of feeding the calves and cleaning the pens. Prior to 6 October 1992, the mother and the 13-month-old child rarely entered the barn, but when they did the child had had no direct contact with the calves. No unpasteurized milk, from any source, was consumed by family members. The father was the only family member reported to have consumed rare beef within the month before his son's illness.

On 6 October 1992, the father suffered a broken ankle and was unable to care for the calves. The mother took over his duties and spent ~½ h/day in the barn feeding calves and cleaning their pens. During this time, her 13-month-old son was placed on the straw beside the calves. The mother noted that the boy frequently touched the calves and put his fingers in their mouths and his.

Fecal samples were obtained from all 7 calves and from all family members on 20 October. All fecal samples were tested in the Vero cell assay and by polymerase chain reaction (PCR) for presence of VTEC. Isolated colonies from positive samples were tested for Vero cytotoxins in the Vero cell assay and toxin-typed by PCR. All isolates of O157:H7, including that obtained from the child on admission, were phage typed [7].

Three of the 7 calves showed evidence of VTEC in their fecal samples by Vero cell assay, PCR, or both. VTEC isolates were obtained from 2 of the 3 positive samples. One isolate was O157:H7 phage type 23; the other was O156:NM. The only family member with evidence of VTEC in the stool was the 5-year-old girl. Serotype O157:H7 phage type 23 was isolated from her stool, although she was not ill at the time. She developed watery diarrhea and stomach cramps on 5 November and was seen by the family's physician, but no stool specimen was obtained. Her 9-year-old brother had similar symptoms on 9 November but was not examined by a physician.

Fecal samples from all of the calves and family members were collected on 16 and 25 November and 12 December and were screened for VTEC. On 16 November, 4 of the 7 calves had positive results by Vero cell assay and PCR. Isolates were obtained from 3 of the 4 samples and included serotypes O103:H2, O?:H40, and O111:NM. The calf that had been shedding O157:H7 phage type 23 on 20 October tested negative for VTEC on 16 November. All human samples tested negative for VTEC on 16 November.

On 25 November, 3 of the 7 calves tested positive for VTEC, and *E. coli* O157:H7 phage type 23 was isolated from 1 of them. VTEC had not been detected in the previous samples taken from this calf. All samples from family members collected on 25

Informed consent was obtained from all patients or their parents.

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