The Chronic Mononucleosis Syndrome

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In January 1985, two reports captured the attention of the lay and medical communities by suggesting that a chronic illness characterized by fatigue is associated with unusual serological responses to Epstein-Barr virus (EBV) antigens [1, 2]. Those reports unleashed countless demands for serological testing and consultations by infectious disease specialists. In the ensuing three years the merits and deficiencies of the hypothesis that EBV infection is associated with chronic fatigue have been further explored. I have been charged with placing the existing data into a more manageable perspective. To do so I address a series of issues: whether chronic EBV infection exists; what EBV and a recently described human herpesvirus may have to do with chronic fatigue; the diagnostic value of EBV serological testing; and the utility of acyclovir therapy for treating patients with chronic fatigue. In addition, I reflect on the “outbreak” of chronic fatigue reported in Lake Tahoe in 1985 [3, 4].

Chronic EBV Infection

The human herpesvirus named for Epstein and Barr is a ubiquitous pathogen that chronically infects virtually everyone by early adulthood [5]. Following acute infection, which is mostly an asymptomatic event, the virus persists in B lymphocytes and salivary glands. Virus is routinely detected in the saliva for months after acute infection and intermittently thereafter for life.

In contrast to the carrier state and intermittent reactivation of the virus, which are clinically “silent” processes, chronic infection can be symptomatic. There are well-known malignant syndromes in which EBV is believed to participate: African Burkitt’s lymphoma, nasopharyngeal carcinoma, and thymic carcinoma. Other disorders associated with EBV include the hemophagocytic syndrome, lymphocytic interstitial pneumonia in children with AIDS, and oligoclonal lymphoproliferation in bone marrow or organ transplant recipients [6-8]. Additionally, EBV is implicated in oral hairy leukoplakia in homosexual men with AIDS [9]. Viral sequences and proteins are detected in the involved tissues, and a recent therapeutic trial found the lesions to respond to treatment with an analogue of acyclovir (J. Greenspan, personal communication).

Another form of symptomatic, chronic EBV infection is a rare, severe illness [10-13]. The patients typically exhibit both humoral and cellular immune abnormalities that appear to be acquired during primary EBV infection. Hematologic complications include anemia, thrombocytopenia, or leukopenia. Chronic persistent hepatitis, interstitial pneumonia, uveitis, or malabsorption due to lymphocytic infiltration of the small bowel are also seen. Adenopathy and hepatosplenomegaly are prominent in some patients.

Two particularly well-studied patients with severe, chronic EBV infection were reported by Schooley et al. [12], who noted that, in addition to the above clinical features, there were extraordinarily elevated titers of antibodies to some EBV antigens. Not being a cytopathic virus in the classic sense, it is difficult to assess the quantity of EBV in tissues; thus, EBV’s contribution to the pathogenesis of these severe infections remains unclear. We have recently detected, by in situ hybridization, high levels of EBV RNA in the involved tissues of a few such patients (K. D. Croen, S. E. S., unpublished observations). Perhaps that technique will help clarify the role of EBV in chronic illnesses.

On the basis of the observations to date, it is possible to develop criteria for diagnosing severe, chronic
Table 1. Suggested criteria for diagnosing severe, chronic EBV infection.

I. Severe illness of greater than six months' duration that:
1. Began as primary EBV infection OR
2. Is associated with grossly abnormal EBV antibody titers (IgG to VCA, \( \geq 1:5120 \); antibody to EA, \( \geq 1:640 \); or antibody to EBNA, <1:2) *

AND

II. Histological evidence of major organ involvement, such as:
1. Interstitial pneumonia
2. Hypoplasia of some bone marrow elements
3. Uveitis
4. Lymphadenitis
5. Persistent hepatitis
6. Splenomegaly

AND

III. Detection of increased quantities of EBV in affected tissues by:
1. Anticomplementary immunofluorescence for EBNA OR
2. Nucleic acid hybridization

* VCA = viral capsid antigens, EA = early antigens, and EBNA = Epstein-Barr nuclear antigens.

Some patients with severe, chronic EBV infection have not only extraordinarily high antibody titers to the viral capsid antigen (VCA) and to early antigens (EA) but, on occasion, lack antibodies to all known Epstein-Barr nuclear antigens (EBNA) or to just one of them (EBNA-1) [13, 14]. Antibodies to EBNA-1 classically appear within the first several weeks of acute EBV infection. Among hundreds of sera tested, Miller et al. [13] noted the absence of antibodies to EBNA-1 long after primary EBV infection in only 12 instances. Eight of these were patients with severe illness, seven of whom had high titers of antibodies to other EBV antigens (table 2). The remaining four individuals, however, suffered intermittent low-grade fevers, recurrent sore throats, and chronic fatigue and had normal physical or laboratory findings, including titers of antibodies to the other EBV proteins.

The question posed by such patients is whether they represent a milder form of chronic EBV infection, one that has been called "chronic mononucleosis." Unfortunately, the features of this mild illness are nonspecific and overlap with those of many other physical and psychological disorders. For individuals in whom illness began with acute EBV infection or is associated with a failure to make antibodies to EBNA-1, it is tempting to suspect chronic mononucleosis. The vast majority of patients with similar complaints, however, do not exhibit those historical or serological features and in the absence of other provable diagnoses must be considered to have chronic fatigue of unknown etiology.

Table 2. Characteristics of patients who lack antibodies to EBNA-1.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age/sex</th>
<th>AIM*</th>
<th>Clinical manifestations</th>
<th>VCA</th>
<th>EA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18 y/F</td>
<td>+</td>
<td>Fever, pneumonia, anemia</td>
<td>20 480</td>
<td>10 240</td>
</tr>
<tr>
<td>2</td>
<td>17 y/F</td>
<td>-</td>
<td>Fever, pneumonia, leukopenia, uveitis</td>
<td>5120</td>
<td>2560</td>
</tr>
<tr>
<td>3</td>
<td>8 y/F</td>
<td>-</td>
<td>Thrombocytopenia, hyper IgG</td>
<td>( \geq 1280 )</td>
<td>( \geq 1280 )</td>
</tr>
<tr>
<td>4</td>
<td>27 y/M</td>
<td>+</td>
<td>Neutropenia, hyper IgE</td>
<td>10 240</td>
<td>2560</td>
</tr>
<tr>
<td>5</td>
<td>5 y/M</td>
<td>+</td>
<td>Pneumonia, ascites, hyper IgG</td>
<td>40 960</td>
<td>20 480</td>
</tr>
<tr>
<td>6</td>
<td>2 mo/F</td>
<td>-</td>
<td>Fever, leukopenia, thrombocytopenia</td>
<td>320</td>
<td>160</td>
</tr>
<tr>
<td>7</td>
<td>5 y/F</td>
<td>+</td>
<td>Uveitis, chondritis, sinusitis</td>
<td>2560</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>10 d/F</td>
<td>-</td>
<td>Fever, anemia, hepatosplenomegaly</td>
<td>10 240</td>
<td>160</td>
</tr>
<tr>
<td>9</td>
<td>31 y/M</td>
<td>+</td>
<td>Fatigue, lymphadenitis</td>
<td>40</td>
<td>&lt;20</td>
</tr>
<tr>
<td>10</td>
<td>32 y/M</td>
<td>+</td>
<td>Fatigue, fever, pharyngitis</td>
<td>320</td>
<td>20</td>
</tr>
<tr>
<td>11</td>
<td>20 y/F</td>
<td>-</td>
<td>Fatigue, fever</td>
<td>80</td>
<td>&lt;5</td>
</tr>
<tr>
<td>12</td>
<td>15 y/M</td>
<td>+</td>
<td>Fever, myalgias, pharyngitis</td>
<td>160</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

NOTE. Data are from Miller et al. [13], with permission.

* AIM = onset of illness was (+) or was not (-) associated with acute infectious mononucleosis.

† Reciprocal titer of antibodies to EBV antigens.
The Chronic Fatigue Syndrome

As a rule, we are unable to identify a cause for the fatigue and other complaints that plague such patients (table 3). In the 1860s, Beard [15] termed the syndrome neurasthenia and recognized, as we do today, that the majority of its victims are young women. In the 1940s, the diagnosis of chronic brucellosis became fashionable for these patients, to be followed more recently by diagnoses of hypoglycemia, total allergy syndrome, fibrositis, and chronic candidiasis [16-19].

My introduction to this disorder was a referral, in 1979, of a patient who remained severely fatigued for over a year after having acute mononucleosis. His antibody titers to EBV antigens were noted to be high. At the time, normal individuals were not believed to display substantial levels of antibodies to EAs for more than a few months after acute infection [20]. Comparable observations with a few other patients, and the report of seven similar patients in Israel, prompted us to accelerate our analysis of this disorder [21]. By late 1984 we were prepared to publish studies of our first 23 patients, in whom we noted higher geometric mean titers of antibodies to VCA and EA, the occasional lack of antibodies to EBNA, and a variety of other tantalizing but subtle immunologic abnormalities [2].

As part of our efforts to further address the hypothesis that EBV may underlie many of the features of the chronic fatigue syndrome, we initiated a controlled therapeutic trial of intravenous and oral acyclovir in 1984. Although demonstrating no therapeutic benefit of acyclovir, the study taught us an enormous amount about the natural history of the syndrome [22]. In particular, we observed frequent temporary, spontaneous improvements, and in several instances the clinical improvement persisted long beyond the conclusion of the trial.

One important observation of the study was the lack of a correlation between EBV antibody titers and clinical status. Furthermore, recent seroepidemiological studies have revealed that antibody titers to EAs persist in a substantial proportion of healthy individuals for two to four years after acute infection [23]. These observations have substantially reduced the value in our minds of EBV serologies as an aid in assessing the syndrome.

Epidemic Neuromyasthenia

In 1985, physicians in one medical practice serving Incline Village near Lake Tahoe, Nevada, noted a sharp increase in number of patients presenting with an acute infectious-type illness that was followed in many, by chronic fatigue, myalgias, headache; feverishness, and cognitive problems [3, 4]. Although the majority of patients had no contact with others having similar complaints, small clusters of the syndrome were noted in surrounding communities. Media coverage of the problem stimulated additional fatigued patients to seek evaluation. By 1987 >200 patients had been seen. Much of what is known of the “outbreak” derives from unpublished communications with physicians from that community, as well as with scientists from the Centers for Disease Control, the National Cancer Institute, and Harvard University, who also evaluated some of the patients.

The features of this outbreak are most reminiscent of >30 similar ones described since 1934, each involving a few to nearly a thousand individuals [24-27]. Most of the patients had been young to middle aged and highly educated; 70%-90% were female. As in Lake Tahoe, the majority recovered completely within a few weeks to months, but some had persistent fatigability that was said to be exacerbated by physical or emotional stress.

The onset of the illness in some of the Tahoe patients was associated with a modest atypical lymphocytosis, partial hypogammaglobulinemia, or a high ratio of helper to suppressor lymphocytes (P. Cheney, D. Peterson, A. Komaroff, personal com-
In a highly selected subset of the patients, investigators from the Centers for Disease Control confirmed histories of an acute infectious-type onset, splenomegaly, and higher antibody titers to EBV antigens than in matched controls from the community. Antibodies to cytomegalovirus, measles virus, and herpes simplex viruses were also significantly elevated, however, an observation suggesting a nonspecific immune activation rather than an EBV infection [4].

One still perplexing feature of some patients in the Tahoe outbreak is the report that magnetic resonance imaging demonstrated small foci of increased signal in the brain (P. Cheney, D. Peterson, A. Komaroff, personal communications). These unidentified bright foci are similar to ones associated with multiple sclerosis, but the patients possessed none of the other physical or laboratory stigmata of that disease, including its tendency to progress. We have been unable to detect such foci by magnetic resonance imaging in the vast majority of patients with chronic fatigue from other parts of the country or in most of the patients we have studied from the Lake Tahoe area. Because bright foci are commonly found in healthy individuals of middle age or older, their detection in younger patients with chronic fatigue is of uncertain physiological importance.

Neuropsychological Features

An early hypothesis regarding the etiology of the chronic fatigue syndrome is that its manifestations represent somatic expressions of psychoneurosis. It is impossible to completely dispel the notion that the chronic fatigue syndrome represents a psychoneurotic condition. On the contrary, there are observations that support the hypothesis.

Reassessment of some outbreaks of epidemic neuromyasthenia indicated a very high prevalence of neurosis in affected individuals. In one of the most famous such epidemics, occurring among staff of the Royal Free Hospital in London, England in 1955, the progression of the outbreak was argued plausibly to resemble mass hysteria [27, 28].

In the 1950s, careful studies were undertaken to assess the validity of Evans’s hypothesis [16] that brucellosis could precipitate a syndrome of chronic fatigue. Patients were evaluated after being confirmed as having acute brucellosis. In some the initial illnesses gradually transformed into a syndrome with debilitating fatigue, but with few other objec-

tive features of active Brucella infection [29]. Imboden et al. [30] noted the psychological profiles of individuals with “chronic brucellosis” to differ from those of individuals who recovered in a timely fashion from acute brucellosis. The differences involved a higher incidence of emotional disturbance, particularly depression, among patients with persisting fatigue. Those retrospective studies could not discern whether the depression was a consequence of lingering symptoms of the disease. It was argued that they were not just reactive problems, because equivalent emotional disturbances persisted among patients who recovered from post-brucellosis fatigue.

In more compelling studies, conducted before and during the Asian influenza epidemic of 1957, it was demonstrated that the time to convalescence from influenza correlated with preexisting psychoneurotic aberrations [31]. Specifically, individuals who before influenza exhibited a “propensity to become depressed” recovered more slowly than individuals lacking this premorbid psychological trait. It was concluded that certain psychological factors render one vulnerable to postinfectious chronic fatigue. In such individuals, it was argued, somatic complaints of psychological origin become established during

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**Table 4. Immunologic findings in patients with the chronic fatigue syndrome.**

<table>
<thead>
<tr>
<th>Finding</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humoral immune responses</td>
<td></td>
</tr>
<tr>
<td>Elevated antibodies to viral proteins</td>
<td>1, 2, 4, 21</td>
</tr>
<tr>
<td>Low or absent antibodies to EBNA or EBNA-1</td>
<td>2, 13</td>
</tr>
<tr>
<td>Partial hypogammaglobulinemia</td>
<td>2</td>
</tr>
<tr>
<td>Elevated circulating immune complexes</td>
<td>2</td>
</tr>
<tr>
<td>Decreased immunoglobulin release in vitro from mitogen-stimulated lymphocytes</td>
<td>35</td>
</tr>
<tr>
<td>Lymphokine and interleukin responses</td>
<td></td>
</tr>
<tr>
<td>Increased leukocyte 2',5'-oligoadenylate synthetase</td>
<td>2</td>
</tr>
<tr>
<td>Decreased interleukin-2 synthesis in vitro by mitogen-stimulated lymphocytes</td>
<td>36</td>
</tr>
<tr>
<td>Decreased immune (gamma) (Y) interferon synthesis in vitro by mitogen-stimulated lymphocytes</td>
<td>36</td>
</tr>
<tr>
<td>Lymphocyte number and function</td>
<td></td>
</tr>
<tr>
<td>Increased helper to suppressor ratios</td>
<td>2</td>
</tr>
<tr>
<td>Increased suppression of immunoglobulin synthesis in vitro</td>
<td>34</td>
</tr>
<tr>
<td>Decreased natural killer cell activity</td>
<td>36, 37</td>
</tr>
<tr>
<td>Decreased EBV-specific cytotoxic T cell activity</td>
<td>35</td>
</tr>
</tbody>
</table>
recovery from acute infection and merge imperceptibly with those of the resolving physical illness. Greenfield et al. [32] arrived at similar conclusions in their study of psychological attributes that correlate with the length of recovery from infectious mononucleosis.

Psychiatric evaluations performed at the National Institutes of Health in collaboration with Dr. Markus Kruesi indeed reveal that a very high proportion of patients with the chronic fatigue syndrome possess histories of depression, phobias, or anxiety disorders, histories that frequently predated the onset of their chronic fatigue by several years (unpublished observations). More-recent studies performed with Dr. Jordan Grafman indicate that over half of our patients score as being significantly depressed by the Beck's Depression Scale (unpublished observations).

The cumulative findings lead to the inescapable conclusion that psychoneurosis contributes to the chronic fatigue syndrome, but it is not yet certain whether psychoneurosis can fully explain some of the physical and immunologic aberrations noted in such patients.

Immunologic Features

The notion that the manifestations of the chronic fatigue syndrome are solely psychoneurotic ones is at odds with the data from a number of studies revealing immunologic abnormalities in such patients (table 4). In addition to unusual serological profiles to EBV and other herpesvirus antigens, there appears to be an uncommon prevalence of partial hypogammaglobulinemia, particularly involving mild IgA deficiencies [1, 2]. One-fourth to one-third of patients possess elevated levels of circulating immune complexes, ones that still remain below those typically associated with immune complex-mediated disorders [2].

Cellular immune abnormalities are noted as well. A higher-than-normal ratio of helper to suppressor lymphocytes among patients from the Lake Tahoe area apparently reflects a diminution in suppressor cells rather than an absolute increase in the number of helper cells. This is in contrast to the findings of Hamblin et al. [33], who, by using a different assay, reported a diminution in T helper cells and an increase in T suppressor cells in young patients who remained chronically fatigued following acute infectious mononucleosis. Functional evidence of increased suppressor cell activity was reported by Tosato et al. [34], who noted that purified T cells from patients with the chronic fatigue syndrome suppressed in vitro immunoglobulin synthesis by cultured B cells.

In their study of four individuals with symptoms that persisted for more than two years after documented acute mononucleosis, Borysiewicz et al. [35] observed a rather different spectrum of immunologic abnormalities. These patients had normal immunoglobulin levels, T and B cell numbers, T cell proliferative responses, and natural killer cell activity. Their cells, however, did exhibit reduced in vitro immunoglobulin synthesis and reduced EBV-specific cytotoxic T cell activity. Kibler et al. [36] identified significant reductions in in vitro synthesis of interleukin-2 and immune interferon by cultured lymphocytes from 13 patients with the chronic fatigue syndrome. In their studies, natural killer cell activity was similarly deficient, a finding that has been confirmed independently by two other groups (R. Herberman, personal communication) [37].

We found patients with the chronic fatigue syndrome to possess normal (low or undetectable) levels of circulating interferon but, paradoxically, to show a modest but statistically significant increase in levels of leukocyte 2',5'-oligoadenylate synthetase activity [2]. This enzyme is induced during acute viral infections, including acute mononucleosis [38].

The combined literature regarding immunologic responses of patients with the chronic fatigue syndrome is an unsatisfying one in its lack of consistent and reproducible findings. The magnitude and types of abnormalities do not appear to correlate with the severity of symptoms. While already yielding a tantalizing series of observations, future immunologic studies of patients with chronic fatigue need to be undertaken in a more orderly fashion, and patients who are physically deconditioned or clinically depressed should be included as additional control subjects.

Human Herpesvirus Type 6

In October 1986, scientists at the National Cancer Institute reported the discovery of a new human herpesvirus released from mitogen-stimulated peripheral blood mononuclear cells [39]. The initial study indicated that the virus replicated efficiently in cord blood B lymphocytes; hence, they named this virus human B lymphotropic herpesvirus. Subsequently, it became clear from their work, and from that of
Lopez and his colleagues at the Centers for Disease Control, that the virus replicates well in T cells and other cell lines (C. Lopez, personal communication) [40]. This broader tropism led to the proposal that the virus be renamed human herpesvirus type 6 (HHV6).

The patients from whom the virus has been recovered thus far are generally ones with lymphoproliferative disorders. The virus, however, can also be recovered from the peripheral blood mononuclear cells of some patients with the chronic fatigue syndrome. The first such patients tested were from the Lake Tahoe area, a finding that fueled the speculation that HHV6 is associated with outbreaks of chronic fatigue syndrome. Subsequently, the virus was recovered from the blood of other individuals with the chronic fatigue syndrome.

What is known of this virus and in what way might it relate to the chronic fatigue syndrome? The physical and molecular features of HHV6 are those of a typical herpesvirus. It is a large, enveloped particle whose inner core contains a double-stranded DNA genome of ≈165 000 kilobase pairs in length. The viral DNA and proteins exhibit little homology to those of other human and animal herpesviruses. Unlike EBV, HHV6 apparently lyases, but does not transform, B lymphocytes. This property makes it difficult to explain the detection by Southern hybridization of HHV6 DNA in the tissue of a few patients with B cell lymphomas (H. Streicher, personal communication).

The early seroepidemiological studies indicate HHV6 to be a fairly ubiquitous agent. With use of indirect immunofluorescence assays that appear to be specific but not highly sensitive, antibodies to HHV6 are found in the serum of between 10% and 40% of normal American adults. The seroprevalence ranges from 60% to 80% among patients with AIDS, B cell lymphomas, sarcoidosis, and the chronic fatigue syndrome (H. Streicher, S. Straus, Z. Salahuddin, R. Gallo, unpublished observations).

The higher seroprevalence in patients with the chronic fatigue syndrome could indicate an association between this syndrome and HHV6 infection. It is more likely, however, an epiphenomenon of the subtle immunologic abnormalities that characterize the syndrome. Either the syndrome permits more frequent reactivation of latent HHV6 that, in turn, stimulates antibody responses or a nonspecific polyclonal activation augments the titers of antibodies to many viruses. Because antibody titers to other viruses are also elevated in the chronic fatigue syndrome, the latter scenario is the most appealing [4]. Whatever the cause for elevated HHV6 antibody titers, patients with such titers are more likely to be scored as seropositive by using the current, relatively insensitive, serological methods.

HHV6 remains an orphan virus in search of a disease with which it can be associated. Thus far, there are no clinical syndromes that are attributable to primary or reactivation infection with this virus. As a lymphotrophic herpesvirus, its clinical spectrum might be similar to that of EBV. There is little to link the chronic fatigue syndrome and HHV6, but it is reasonable to presume that infection with this virus could precede the onset of chronic fatigue in the same manner that the syndrome follows infections with other viral and nonviral pathogens [41].

A Unifying Hypothesis?

In that the population of patients with the chronic fatigue syndrome is highly heterogeneous, it is impossible to attribute this syndrome to a single etiology [42]. Over the past decades we have seen the successive demise of chronic brucellosis, hypoglycemia, chronic candidiasis, and allergy as adequately explaining the chronic fatigue syndrome. EBV, because of its ability to establish lifelong infection, is an appealing agent to consider as causing the syndrome; however, it is likely to realize the same fate as these other hypothetical causes of chronic fatigue. As indicated earlier, EBV can incite severe, chronic infections, as do Brucella and Candida spp. Although there are no compelling data to suggest that the chronic fatigue syndrome commonly results from chronic infection with any one of these agents, it is tempting to consider that a subset of patients possesses mild, chronic EBV infection, primarily patients in whom the illness clearly began with a primary EBV infection or those in whom antibodies to EBNA proteins are deficient. It is even more appropriate and satisfying, however, to speculate that the syndrome represents a general response to a variety of psychological or physical irritants.

If the chronic fatigue syndrome is not a pure expression of psychopathology, then there must be common processes that cause fatigue and the other physical symptoms of this syndrome. To postulate these mechanisms is trivial, considering the prevalence of such symptoms in our lives. All of us experience fatigue and other constitutional symptoms.
of this syndrome in the setting of acute infections. Influenza, for example, a localized infection, leads to malaise, myalgias, feverishness, and general prostration. These symptoms reflect the systemic and nonspecific consequences of the host response to infection, which includes the release of potent lymphokines and mediators of inflammation. Certain symptoms that both acute viral infections and the chronic fatigue syndrome share are reproduced by therapy with interferons [43].

The resolution of acute infection should be accompanied by a relaxation of the immune defenses and a clearing of immunologically agonists. It is possible, however, that sustained immunologic activation perpetuates the fatigue, malaise, and depression. Many agents could trigger responses that are initially appropriate but that become pathological when they remain unbridled. There is no necessity in this model for presuming the inciting agent to be active in order for the features of the syndrome to persist.

Ultimately, any hypothesis regarding the cause of the chronic fatigue syndrome must incorporate the psychopathology that accompanies and, in some cases, precedes it. The link between the psyche and the immune system could be relevant to this problem [44, 45]. Unfortunately, the present generation of scientists is ill equipped to explore this aspect of the hypothesis.

References


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