Post-infectious disease syndrome

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Summary: Many post-infectious syndromes have been recognized in the last 50 years, some following viral infections and others closely related to bacterial disease. The occurrence of prolonged fatigue following an apparent viral illness of varying severity is also well documented. The lack of a recognizable precipitating cause and the tendency for epidemic fatigue to occur among hospital staff led many to believe that the illness may be psychogenic in origin. However, there is serological evidence that some cases may follow enterovirus infections or occasionally delayed convalescence from infectious mononucleosis.

Much interesting work is currently in progress relating fatigue to persisting immunological abnormalities, and the development of molecular immunology makes this a most exciting field of research.

This paper reviews the evidence for and against a definitive post-viral fatigue syndrome and examines the results of research carried out in the last 50 years.

Introduction

Most patients who have had an acute infection expect to pass through a variable period of convalescence before they regain their usual health. An unlucky minority recover from the symptoms of acute disease only to be assailed by a new illness; a post-infectious syndrome. Many post-infectious syndromes have characteristic clinical features and can be traced to their causative organism both on epidemiological evidence and by laboratory testing. By no means all post-infectious syndromes are viral in aetiology, a fact that is well illustrated by two of the best-established syndromes: rheumatic fever, first shown to follow Streptococcus pyogenes infection by Coburn in 1931, and post-streptococcal glomerulonephritis, first defined by Ellis in 1942 as his type I glomerulonephritis. An indication of the range of post-infectious disorders and their causative agents is given in Table I, together with some original and review references.

Fatigue syndromes

A post-infectious complaint which is not found in this well-accepted list of syndromes is the syndrome of fatigue, muscle weakness and variable neurological abnormalities which has been described from various parts of the world. This syndrome has been described both as sporadic illness and in outbreaks. Some of the more noteworthy outbreaks are listed in Table II.

The main symptoms of these fatigue syndromes are described as muscular and neurological. The muscular symptoms are predominantly of weakness with or without pain. In many cases the weakness is described as following muscular effort, and persisting for several hours or even a number of days afterwards. The leg muscles are those most often affected, but the upper arms and the back are also frequently involved.

The neurological symptoms are very variable. Mental exhaustion and poor concentration are almost universally present, but other complaints include paraesthesiae in the limbs or face, local weaknesses of a wrist or ankle, or the face, diplopia, blurred vision and headaches. Many patients also describe periods of excessive sweating, and severe coldness of the limbs. Other symptoms described by the patients, and elicited by some investigators include altered hearing, frequency of micturition or retention of urine, emotional lability and vivid dreams.

In spite of the number of symptoms described by sufferers, the physical signs elicited are often subtle and few. Fever is not a major sign, though many patients have a temperature of 37 to 37.5°C throughout the day, described by many as a low-grade fever.

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Scott and the Royal Free physicians reported lymphadenopathy as common in their series of patients. The physicians of the Royal Free Hospital reported facial weakness or paralysis in one-fifth of their cases, almost always unilateral in distribution. Many of the patients in different reports were said to have mild nystagmus. They also had small areas of hypoaesthesia on the limbs, and marked muscle tenderness which was often extremely localized. Transiently upgoing plantar responses on one or both sides were described by almost all of the authors of reports, but did not affect all of the patients in any outbreak; the Royal Free physicians described it in 20 per cent of their cases. They and other groups reported the frequency of muscle fasciculation but all were agreed on the complete absence of muscle wasting.

The most striking feature of these outbreaks is that the illness often lasted several months, and in some cases never fully resolved. In the Durban outbreak more than 10 per cent of the patients were still unwell after three years. In the Cumbria outbreak, 20 per cent of patients had persistent or recurring symptoms for a number of years. In Iceland only 44 per cent of patients who were originally severely ill had fully recovered seven years after the outbreak and in Los Angeles over half of affected staff took six months or more to return to full duties. Some individual cases are described as having marked foot-drop or ankle weakness persisting years later, in particular a young (male) doctor in the Cumbria outbreak, a nurse from the Middlesex Hospital in one of the London outbreaks and a nurse in the 1955 outbreak in Durban.

<table>
<thead>
<tr>
<th>Table I</th>
<th>Some well-described post-infectious disorders and their causative agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aplastic anaemia</td>
<td>Non-A, Non-B hepatitis</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Shigella, salmonella, yersinia, campylobacter, meningococcus, rubella, mumps</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>Measles, varicella, influenza, rubella, vaccinia (smallpox vaccination), rabbit brain or duck embryo rabies vaccines</td>
</tr>
<tr>
<td>Erythemas</td>
<td>Tuberculosis, leprosy, yersinia, herpes simplex, hepatitis B</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>Streptococcus pyogenes, hepatitis B, mumps</td>
</tr>
<tr>
<td>Guillain–Barre syndrome</td>
<td>Cytomegalovirus, Epstein–Barr virus, hepatitis A, hepatitis B</td>
</tr>
<tr>
<td>Auto-immune haemolysis and cytopenias</td>
<td>Syphilis, Mycoplasma pneumoniae</td>
</tr>
<tr>
<td>Haemolytic uraemic syndrome</td>
<td>Many common viral infections</td>
</tr>
<tr>
<td>Reiter's syndrome</td>
<td>Escherichia coli 0157</td>
</tr>
<tr>
<td>Rheumatic fever</td>
<td>Non-specific genital infection</td>
</tr>
<tr>
<td>Serositis</td>
<td>Streptococcus pyogenes</td>
</tr>
<tr>
<td></td>
<td>Meningococcus</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Table II</th>
<th>Some major outbreaks of fatigue syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outbreak</td>
<td>Population affected</td>
</tr>
<tr>
<td>Los Angeles, 1934</td>
<td>Hospital staff</td>
</tr>
<tr>
<td>Switzerland, 1937 and 1939</td>
<td>Soldiers in a garrison</td>
</tr>
<tr>
<td>Iceland, 1948–94</td>
<td>Akureyi district residents</td>
</tr>
<tr>
<td>Adelaide, Aus., 1949–51</td>
<td>Town residents</td>
</tr>
<tr>
<td>New York State, 1950</td>
<td>Local residents</td>
</tr>
<tr>
<td>London, 1952</td>
<td>Hospital staff</td>
</tr>
<tr>
<td>Coventry, 1953</td>
<td>Hospital staff</td>
</tr>
<tr>
<td>London, 1955</td>
<td>Hospital staff</td>
</tr>
<tr>
<td>London, 1955–58</td>
<td>Suburban residents</td>
</tr>
<tr>
<td>Cumbria, 1955</td>
<td>Rural adults and children</td>
</tr>
<tr>
<td>Durban, SA, 1955</td>
<td>Hospital staff</td>
</tr>
<tr>
<td>London, 1964–65</td>
<td>Suburban residents</td>
</tr>
<tr>
<td>London, 1970–71</td>
<td>Hospital staff</td>
</tr>
<tr>
<td>Lake Tahoe, USA, 1984–85</td>
<td>District residents</td>
</tr>
</tbody>
</table>
Controversy over the existence of true post-viral fatigue syndromes

Up until the 1960s, reports of these fatigue syndromes had apparently been received with little comment. At the end of the 1960s, a group in psychological medicine had been interested in episodes of 'illness' in groups of schoolgirls, which were attributable to hyperventilation or indeed to 'mass hysteria'. They investigated retrospectively the outbreaks of fatiguing illness reported from both their own hospital, the Middlesex Hospital and from the Royal Free Hospital as well as a review of several other outbreaks. In their subsequent publications they concluded that there was a strong element of hysteria in many of the outbreaks, and that the Royal Free Hospital outbreak was probably a pseudo-epidemic in which patients with varieties of vague symptoms were collected together and labelled as having an unusual disease, which then attracted other patients with vague complaints. They did feel, however, that not all outbreaks could be considered purely hysterical.

In spite of public retorts from several people who reported the outbreaks, the 'mass hysteria' theory of the disease became the majority view and up to the present day there can be few illnesses which provoke such heated discussions between doctors, and such vehement responses to those complaining of these fatigue syndromes.

It has to be pointed out that several of the reported outbreaks coincided with outbreaks of poliomyelitis, a much-feared disease, and that these were often among hospital staff, who might be thought to have a particularly institutional view of the situation. On the other hand, although low-grade fever, muscle pains and weakness are very common early features of poliomyelitis, it was almost immediately obvious to both patients and doctors that there was no rapid progression to paralysis and wasting as would be usual in polio. In many other outbreaks, there was no association with polio, and the patients were members of the community. In the community outbreaks, the sex ratio of affected patients was usually near 1:1 and young children were quite often affected, features not so characteristic of 'functional' illness.

The result of this controversy was that fatigue syndromes became rather disreputable. The various names by which they had become known: Iceland disease, Royal Free disease, epidemic neuromyasthenia, benign myalgic encephalomyelitis and others, were mentioned only disparagingly. Many doctors did not know what to think, others were plainly disbelieving and a few pointed to small numbers of cases in which they had recorded distinct physical signs and abnormal laboratory findings. Meanwhile, a very large number of people continued to present with complaints of prolonged fatigue on a sporadic basis. A recent review article in a national newspaper was said to have provoked enquiries from 11,000 individuals. Our own unit received 20 to 50 enquiries per week requesting information or consultation, and colleagues from other infectious diseases units handled a similar number of enquiries. Many people who suffered from long-term fatigue subscribed to a support group, the ME (myalgic encephalomyelitis) Association.

Thus far the pendulum swung away from general acceptance of fatigue syndromes as an entity. But then the very scientific necessity for objective data, which made acceptance of ill-defined syndromes so difficult, began to produce some interesting possibilities for further investigation. The suggestion that an outbreak of fatigue in Lake Tahoe, USA might be related to chronic active Epstein–Barr virus infection awakened fresh interest in the problem. Interestingly, also, American sufferers formed a CEBV (chronic Epstein–Barr virus) Association. In the meantime, new techniques had been used to investigate some cases in the United Kingdom. The pendulum began to edge back.

Positive aspects of fatigue syndromes: clues to aetiology and pathogenesis

Evidence of a lesion, possibly in the brain, certainly in skeletal muscle

The large variety of rather subtle central nervous system complaints is extremely difficult to investigate. Early investigators were led to study the electroencephalogram (EEG) in a selection of their patients, often those with drowsiness or disorientation. A total of 23 cases were examined in the Cumbrian outbreak of 1955, of whom 15 had various non-specific abnormalities. A similarly abnormal picture was found in a total of 43 patients from the London outbreaks of the 1950s.

The most consistent complaints are those of muscle pain, tenderness, weakness and extremely prolonged muscle fatigue after exertion. Except for a number of patients with evidence of fasciculation, suggesting damage to motor units at anterior horn cell level, classical electromyographic studies have produced normal results in most cases. Biochemical evidence of muscle involvement has been found, however, even in early case reports when the range of available tests was limited.

Poskanzer and his colleagues demonstrated excessive creatinuria, with an increased
creatinine, suggesting damage or disuse of muscle. This returned to normal when the patient recovered. Ramsay and Rundle reported a detailed biochemical examination of ten patients. They found increased serum myoglobin levels in eight with falling levels during recovery from the initial weakness. These patients’ fasting blood pyruvate levels were depressed. Creatine phosphokinase, lactate and ATP levels were normal, as were most transaminase levels and transpeptidase levels. This suggested the presence of muscle damage associated with a disorder of oxidative metabolism. In a few patients this has been dramatically confirmed by 31P nuclear magnetic resonance (NMR) spectroscopy. Unlike NMR imaging this does not depend on the presence of hydrogen atoms and does not produce a picture of the anatomy of the tissues. It produces a spectrum with peaks which represent phosphorus atoms in different molecular situations. Different peaks are produced by inorganic phosphate, creatine phosphate and the phosphates in ADP and ATP. Furthermore these spectral peaks are predictably displaced by changes in pH in the tissue being examined. 31P NMR spectroscopy can demonstrate the transfer of phosphate to creatine phosphate, and the fall in pH as lactic acid is produced. In some patients, muscle fatigue and pain coincides with the failure to maintain adequate levels of creatine phosphate in the muscle cell, associated with a grossly excessive fall in pH. This suggests that oxidative phosphorylation (proton transfer along a redox gradient) is not able to keep up with muscle energy requirements. Normal pH and creatine phosphate levels may take many hours to restore during rest, suggesting a severe defect in this metabolic pathway which depends on normal mitochondrial function. Unfortunately, although early studies were very promising, only a minority of patients tested have shown evidence of ‘mitochondrial myopathy’.

More fortunately another abnormality has been demonstrated using the technique of single-fibre electromyography. This allows the study of a phenomenon called ‘jitter’ in muscle fibres. The characteristics of jitter in normal fibres depend on normal neuromuscular conduction of nerve potentials. Jamal and Hansen found significant abnormalities of these characteristics in 30 of 40 patients with fatigue syndromes. The same abnormalities had already been described in patients with acute viral infections, so they can only be regarded as non-specific evidence that ‘something is wrong’ in the fatigued patients. The nature of the abnormalities suggested that the neuromuscular junction was intact, for there was increased jitter without impulse blocking. The authors concluded that conduction within the muscle fibre was abnormal. Subtle abnormalities of muscle structure may accompany these physiological abnormalities. As part of a larger study Behan et al. carried out muscle biopsies on 20 fatigued patients. All of the patients had excess numbers of moderately enlarged type II fibres, containing more mitochondria than normal as well as some tubular inclusion bodies. Fifteen of the 20 had necrosis of single fibres, without any inflammatory reaction, scattered throughout their biopsy. Similar changes within muscle fibres have been described in two patients with neuropathy and inflammatory myopathy, and two with myalgia following acute, ill-defined illnesses. Again, the findings are possibly not specific, but in one study they were associated with evidence of reduced respiratory function of the mitochondria.

It seems undeniable that many, if not most, patients with fatigue syndromes will have a demonstrable abnormality of muscle physiology using the very discriminating tests now available. Such tests are not available to all patients, however, and not all patients would willingly undergo muscle biopsy even using modern, small-bore needle biopsy techniques. The importance of the findings is that they suggest a true pathological basis for the muscular fatigue that these patients describe.

The search for a causative agent

Almost all patients with fatigue syndromes relate the beginning of their illness to a definite but mild viral-type illness. Not surprisingly, as microbiological science, particularly virology, has diversified so has the search for a causative agent.

Some initially promising findings have been disappointingly unrepeatable in subsequent cases. One report of recovery of ECHO 9 virus or of rising titres of neutralising antibody may have been just a local outbreak of mild viral meningitis. Innes in 1970 investigated four cases with symptoms of fatigue. The cerebrospinal fluid of two produced viruses in cell culture, one Coxsackie B2, and one ECHO 3. The other two cases had high titres of serum neutralizing antibodies to Coxsackie B2, and B5.

Serological evidence suggesting exposure to coxsackie B viruses has been found in some recent outbreaks of fatigue syndromes. In an outbreak in Ayrshire, 18 of 22 patients studied had high titres of neutralizing antibodies to Coxsackie B. Twelve patients had titres of 1:512 or more; this compared with only four per cent of the general population having similarly high titres. In a further outbreak, 20 patients were compared with 100 normal controls and again had higher titres of neutralizing antibody. Another uncontrolled study in West
Kilbride showed very similar results.\textsuperscript{50} Similarly raised titres of neutralizing antibody were found in the study of Behan et al.\textsuperscript{44} and six of their patients had IgM antibodies to Coxsackie B.

These are interesting findings, even though only one of the studies used concurrently tested controls. There is no evidence, however, of rising or falling titres of neutralizing antibody to Coxsackie B; all of the titres that were repeated showed static levels of antibody. Perhaps this is not so surprising: the initiating illness is seldom so severe that the patient seeks medical advice, and it is often several weeks before persisting fatigue drives him or her to the doctor’s rooms. In these circumstances, the time for detecting changes in antibody titres has usually passed, as indeed has the chance of isolating virus. Coxsackie virus would be a likely candidate for causing a disease affecting both the nervous system and the muscles. It is known to cause meningitis, meningocencephalitis, pericarditis, cardiomyopathy and Bornholm disease. Coxsackie B RNA sequences have been detected in cardiac muscle biopsies from patients with cardiomyopathies.\textsuperscript{51}

Rather indirect support suggesting that the aetiological agent could be related to the enteroviruses (ECHO, Coxsackie and polio) comes from the findings of Sigurdsson et al.\textsuperscript{52} that previous exposure to an outbreak of fatigue syndrome in Iceland modified the response to subsequent polio immunization.

Coxsackie, or possibly related enteroviruses are not the only candidates for the causative agent of fatigue syndromes. The Epstein–Barr virus (EBV) has also enjoyed supporting evidence in recent years. It has long been known that infectious mononucleosis may be followed by a prolonged period of malaise and fatigue, and in 1982 Tobi and others\textsuperscript{53} described evidence suggesting that excess levels of IgM antibodies against EBV capsid antigen (CA) persisted in their patients. In most patients the first serological response to EBV infection is the appearance of antibodies to a small range of early antigens (EA), followed by an IgM anti-EVCA. During convalescence the IgM anti-EVCA is replaced by IgG anti-EVCA and finally anti-EV nuclear antigen (EBNA) appears to join IgG anti-EVCA. Two papers in 1985\textsuperscript{33,34} described fatigued patients with IgG anti-EVCA and anti-EBNA and without IgM anti-EVCA but who nevertheless had persisting EA antibodies. This was taken to be firm evidence of an abnormal persistence of EBV activity in these patients. An analysis of cases and controls from the outbreak involved was undertaken by local epidemiologists in association with CDC Atlanta.\textsuperscript{54} They studied the serology of 15 cases compared with age-, sex- and race-matched controls. They found that, although the cases were more likely to have increased anti-EA and IgG anti-VCA titres, they were equally more likely to have raised IgG antibody levels to cytomegalovirus and herpes simplex virus. Moreover, on repeated testing, fourfold differences in titres were obtained from the same serum sample on nearly 18 per cent of occasions. This further highlights the pitfalls of diagnosing persisting infections by testing single, uncontrolled serum samples.\textsuperscript{55} These caveats must apply equally to the measurement of other viral antibodies, and lymphokines such as interferon, to immune complexes and to T-cell subsets. It even seems likely that storage of the various samples may be followed by particular changes in titres.\textsuperscript{54}

Coxsackie B and EBV are of course not the only contenders for the dubious honour of causing post-viral fatigue syndromes. Fatigue is known to follow hepatitis A (whose virus is very like an enterovirus), cytomegalovirus infection and a variety of severe viral illnesses. The patient with the severe defect of muscle oxidative pathways\textsuperscript{49} was well until he had chickenpox. In addition to this, influenza viruses, measles and other paramyxoviruses\textsuperscript{56,57} are known to infect human peripheral blood lymphocytes, altering some of their specialist functions. Some novel viruses may also fit into this disease pattern. The proposed SMON virus\textsuperscript{58} might be considered, and the new HBLV\textsuperscript{61} is 'looking' for an acute primary 'disease' to explain its presence in human lymphocytes.

The likely truth is that more than one aetiological agent can be associated with post-viral fatigue. It is even possible that the close association in time of two related infections could modulate the patient’s long-term response. Dengue haemorrhagic fever is the effect of consecutive exposures to different dengue virus types; could the experience with polio immunization in Iceland\textsuperscript{52} represent a similar behaviour of enteroviruses? The question of aetiology must therefore remain open for the time being, while the natural variation of human responses to viral infections is further studied and elucidated.

Possible pathogenetic mechanisms for post-viral fatigue

The pathogenesis of post-infectious conditions is a complex and entrancing subject on which whole books could be written, and indeed have been, even about individual illnesses. The subject is very wide, and some good, up-to-date reviews are available.\textsuperscript{59} The main categories of immune mechanisms discussed in this context are molecular mimicry and autoimmunity, immune complex disorders, lymphocyte function and dysfunction, the role of
allergy and the role of host susceptibility. Methods and facilities for studying these factors routinely have to date been limited but they are now diversifying in both number and sophistication. Their relevance to post-viral fatigue syndromes and the emerging results of their application will be discussed briefly.

Molecular mimicry is an attractive means of explaining selective tissue damage after infection. Antibodies with an affinity for cardiac muscle may play a part in the pathogenesis of rheumatic fever, the appearance of anti-I cold haemagglutinins after Mycoplasma pneumoniae infections, and the cross-reactivity of the HLA B27 epitope with antigens of certain bowel bacteria may be considered in this context. A variety of autoantibodies can be demonstrated in patients with fatigue syndromes, but can also be found in patients with other infections, and with acquired immunodeficiency syndrome (AIDS). Of particular interest is recent work by Walker and Jeffrey showing that the enzymes histidyl tRNA synthetase and analyl tRNA synthetase, from E.coli, both contain long amino acid sequences homologous with sequences from the tropomyosin of skeletal muscle and with human keratin. They were also homologous with sequences from influenza virus, EBV and adenovirus. This is strong encouragement to keep an open mind about the aetiology of fatigue syndromes.

Lymphocyte functions are many and various in the response to infection. The total lymphocyte count may alter, the proportions of lymphocyte subsets may change, lymphocyte activation may be demonstrable, as may the presence and effect of various lymphokines.

Immune complexes can be detected in the blood of many patients with post-infectious disorders. If they are confined to the circulation their significance may be dubious. However, if they are deposited in vascular endothelium or glomerular membranes they are often associated with inflammation. Behan et al. found inconsistent results in their assays for circulating immune complexes in 50 patients. From 18 to 30 per cent were positive, depending on the method used. There was no consistently abnormal finding on assay of a number of individual complement components. Absolute levels of IgM, IgA and IgG were normal.

The absolute lymphocyte count has not been found consistently abnormal in any report so far. Most physicians have failed according to their unpublished opinion to find more than the occasional abnormal T4:T8 ratio. However, by segregating their 40 patients into a group of 11 who had not been ill for more than six months, and 29 who had been ill for one to 20 years, Behan et al. showed some differences. Compared with healthy controls, the 11 'acute' cases had significantly reduced T8 counts while the 29 'chronic' cases had reduced T4 counts. The 'chronic' group had significantly lowered T4:T8 ratios. Hamblin et al. studied 17 patients who had been fatigue for between one and 10 years following infectious mononucleosis. They showed a reduced T4:T8 ratio in cases compared with healthy controls, which returned to normal in the ten patients who recovered. They attributed the reduced T4:T8 ratio to an increase in suppressor cells, and confirmed this in 11 patients by assay of suppressor activity. These two sets of results, not identical, from two different investigations leave the door wide open for further studies in other patient groups, to see whether the results are reproducible and comparable. Possibly, the effects of regular exercise, or of stress on the T4:T8 ratio should also be taken into account. It is known that physical training and stress increase the ratio; does an enforced sedentary life reduce it?

Behan et al. showed that lymphocytes from 35 of their 50 patients had reduced protein synthesis activity compared with controls. This is of interest because the clinical picture of fatigue and weakness is similar to the effects of interferon, either produced during acute viral infection or administered therapeutically. Interferon levels are difficult to measure in serum, but increased levels of 2,5 oligoadenylate synthetase, an interferon-induced enzyme, have been found in patients complaining of fatigue after EB virus infection. Other lymphokines, such as tumour necrosis factor (TNF) are even harder to detect in the clinical setting, but may well affect muscular function.

Allergy has been a popular hypothesis put forward to explain prolonged malaise of several types. Allergy to Candida albicans or to yeasts in general has been suggested as an aetiological factor in fatigue syndromes. Some patients have taken anti-Candida medication and others a diet designed to exclude yeasts (this is quite a rigorous undertaking if much fresh food is usually eaten). The results of controlled trials in this field are awaited.

Host susceptibility probably plays a large, as yet poorly understood part in infectious, immunological and allergic disease. Family outbreaks of fatigue syndromes have not been remarked upon in the literature, though individual physicians often know of one or two such instances. The determination of HLA types in sufferers has not been carried out in sufficiently large series to draw any firm conclusions. The question of host susceptibility has therefore not yet been addressed, and might best be approached in the setting of a large epidemic.
Future developments in the treatment of fatigue syndromes

It has been suggested that patients suffering from fatigue after EBV infection have not developed enough antibody to abolish virus activity. Dubois reported reduced antibody dependent cytotoxic cell activity (ADCC) in 20 of 22 patients studied, and followed up this finding with a controlled double-blind trial of intramuscular gamma globulin (which produced normal results in ADCC assays). The exact method for the trial is difficult to understand, as patients had successive injections which were randomly either gamma globulin or placebo, and then commented upon the effect of each injection. Of the 73 gamma globulin injections 39 were followed by improvement, while only 19 of 60 placebo injections caused improvement. Other trials of immunoglobulin are currently in progress in different groups of patients and the results are awaited. Attempts to treat individuals or small groups of people with acyclovir or the immune stimulant drug inosine pranobex have not been discussed in publications. The results are in any case difficult to interpret because of the unpredictable tendency of many patients to recover, even after more than two years of disability.

It can be seen from this discussion that fatigue syndromes are beginning to become established as bona-fide illnesses and that persistent research into their nature and cause is gradually being rewarded. The development of knowledge, like the course of disease, is slow and unpredictable so that for the investigator as well as the patient the game is only now getting under way, and all has yet to be played for.

References


Post-infectious disease syndrome.

B. A. Bannister

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