The Neurology of Behçet's Syndrome - Jamie Cunliffe

(This article is unfinished and has remained so for well over 15 years. I cannot foresee any current prospect that I will find the time to update and finish it. So, if anyone finds ideas here that are worth pursuit, please feel free to take them on.)

IN 1937, A TURKISH DERMATOLOGIST, Hulusi Behçet, described a syndrome of aphthous ulceration, genital ulceration and iridocyclitis [..]. In so doing he immortalised his name, for it was his paper that finally focused the world's attention on this as a discrete disease entity. Nevertheless, there *are* earlier reports that appear to describe this disorder [..]: one author has even suggested that Hippocrates may have described it [..].

Other common components are recognised in addition to the Behçet's syndrome (**BS)** triad [..]. This emphasises the widespread inflammatory process that characterises this disorder. They include fevers, sweats, myalgia, malaise, adenopathy, a polymorphonuclear leucocytosis, a raised sedimentation rate, a reversed albumen/globulin ratio and a group of associated complications (NBSTabA) that include disorders of the nervous.system. The latter will be the focus of my attention in this paper.

The Behçet's syndrome components (NBSTabA)

Regular components

Arthralgia/arthritis
Epididymo-orchitis
Erythema nodosum
Inflammatory bowel disease
Meningitis
Pustular and destructive skin lesions:
- Acneiform lesions
- Boils
- Pustules
- Furuncles
- Ulcers
- Skin hyper-reactivity (pustulation after sterile needle prick)

Thrombophlebitis
Urethritis

Occasional components

Amyloidosis
Glomerulonephritis
Lung infiltration and hilar adenopathy
Myocarditis/pericarditis

Regular accompaniments

Fever, night sweats
Myalgia
Malaise, listlessness, insomnia
Minor gastrointestinal upsets
Psychiatric disturbances: neurosis, psychosis, depression

Frequency of the associated components in encephalo-myelitic BS (NBSTabA contd…)

Component	Males	Females	All
Retinitis/choroiditis/retinal vasculitis	35%	30%	34%
Mouth ulcers (BS definition)	100%	100%	100%
Genital ulcers	93%	88%	91%

Uveitis	66%	58%	63%
Skin pustules/ulcers	52%	30%	45%
Skin hyper-reactivity (recorded)	9.9%	15%	11%
Thrombosis	15.5%	24%	18.3%
Arthropathy	49%	39%	46%
Epididymo-orchitis	7%	------	------
Erythema nodosum	17%	52%	28%
Erythema multiforme	2.8%	6%	3.8%
Gastro-intestinal disturbances	15.5%	3%	11.5%

Many of the complications that occur in Behçet's syndrome (**BS**) can be regarded as ***component disorders***. These ***components*** are also encountered in other sero-negative arthritides [..] but in different patterns of association. All of them occur more commonly as isolated disorders (e.g., aphthous ulcers, urethritis, iritis, erythema nodosum). **BS** is characterised by the pattern in which its particular components are superimposed. An important conclusion of this review is that the meningo-encephalitis of **BS** also behaves in this component fashion - it has an equivalent, isolated component that is much more common than encephalomyelitic-**BS.**

BS remits and exacerbates. Relapses are accompanied by the simultaneous exacerbation of a number of component features. The pattern of relapse seems to be haphazard. For example, at one extreme fresh crops of ulcers may appear before the last crops have resolved while at the other, the disease may have remissions lasting for years. Occasional patients appear to have had single attacks that resolved and hadn't recurred before they were written up (a mono-phasic course). On average, relapses occur between every one and every six months. Even then, there may be random, prolonged remissions or relapses. In the first few years of the disease, there is total (apparent) resolution between exacerbations. However, cumulative scarring and direct tissue damage eventually disrupt function. This is particularly evident in the eye [..] and in the nervous system. Textbook accounts suggest that the disease burns itself out. In my view, objective evidence to confirm this is sparse. The statement probably originates from Mavioglu's review [..]. It is difficult to assess the true course of this disorder. Many of the published examples are written up within a decade of onset whilst few centres have large numbers under prolonged review.

The geographical prevalence of this disease varies widely. Japan reports the highest incidence (1 in 10,000 in one area [..]). More than half the world literature on **BS** stems from this country [..] and is difficult to access as most is in Japanese. The Mediterranean Basin, Europe and Britain follow in respective order [..]. One author has estimated the prevalence in Britain to be 1 in 100,000 [..]. The disorder is less common in North America. A problem in estimating incidence revolves around the definition of **BS**. In 1941 Tourraine pointed out that there are no clear clinical boundaries between minor aphthosis (aphthous ulcers alone) and *"la grande apthose",* that he reserved for **BS** [..]. Each level of the disease (mouth ulcers alone through to oro-genital ulceration and finally oro-genital ulceration with iritis) appears to be in clinical continuum with the next. The population prevalence of any level of aphthosis is inversely proportional to that level's severity (i.e., prevalence high/severity low: prevalence low/severity high). Some authors have accepted Curth's diagnostic features [..] as sufficient for the diagnosis of **BS** (coincident oral and genital ulceration). However, we know between 1 in 20 and 1 in 100 patients with mouth ulcers also have genital ulcers and that women more readily develop genital ulcers than men [..]. Women have a marginally higher prevalence of recurrent aphthous ulcers (**RAU**) than men but **BS** is more prevalent in men by a ratio of about 2:1 [..]. When Curth's less rigid diagnostic criteria are applied, the apparent prevalence of women sufferers rises [..]. Behçet's syndrome is probably not, therefore, a discrete disease but the most severe manifestation of *"les apthoses"*. Consequently, its diagnostic boundaries are arbitrarily set and the criteria for inclusion in the **BS** stable should encompass the essence that **BS** sits at the pinnacle of severity among *"les apthoses"*.

The neurological complications of **BS** have been reviewed in two previous papers. One analysed the non-Japanese world literature up to 1963 [..], and the other the Japanese literature up to 1967 [..]. In this review I have reanalysed these reports and included information from subsequent papers. It was beyond my resources to have the numerous Japanese papers translated. These are excluded from this review.

Lehner has shown that cell mediated immune (**CMI**) auto-aggression to oral mucosa increases during active aphthous ulceration [..]. (I shall subsequently refer to diseases with a dominant **CMI** auto-aggressive component as *"auto-rejective"*: the reason for this is clarified elsewhere.) This raises the probability that other components of the disease are associated with auto-rejection. The meningo-encephalitis is of particular interest: comparing the neuraxial disease of **BS** with that of multiple sclerosis (**MS**) may lead to a greater understanding of both. MS is considered by some to be the consequence of a predominantly **CMI** auto-aggressive disorder [..].

There are various estimates of the frequency of CNS involvement in **BS** (from 4 to 42%) [..]. Most authors who have reported personal experiences with groups of affected patients have estimated a frequency of between 10 and 25%. The apparent incidence will depend upon the criteria used to establish the diagnosis. As I have indicated elsewhere [..], the sero-negative arthritides and their component disorders are in continuum (see below). By definition, **BS** is at the pinnacle of aphthosis ("*la grande apthose*"). Relaxing the diagnostic criteria will inevitably appear to reduce the prevalence of CNS involvement.

THE SERO-ve ARTHRITIS/COMPONENT SPECTRUM

Single component		**Multiple component**
Milder	⟷	Severer
Isolated/discrete		Overlapping
Commoner		Rarer

The case histories I have included in the encephalitis group satisfy a minimum diagnostic criteria. For this I have used a modification of Mason and Barnes' criteria [..] (NBSTabB). In this modification, the component "uveitis" has been extended to include any part of a uveo-encephalo-myelitis. The justification for this is discussed later.

NBSTabB - International Study Group Criteria for Behçet's Disease (1990) recommendations

Major criteria (need 1)	Recurrent oral ulceration	Minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient that recurred at least three times over a 12-month period
Minor criteria (need 2)	Recurrent genital ulceration	Aphthous ulceration/scarring observed by physician or patient
	Eye lesions	Anterior or posterior uveitis or cells in vitreous on slit lamp examination; or retinal vasculitis observed by ophthalmologist
	Skin lesions	Erythema nodosum observed by physician or patient, pseudofolliculitis or papulopustular lesions; or acneiform nodules observed by the physician in a postadolescent patient who is not receiving corticosteroid treatment
	Positive pathergy test	As interpreted by physician at 24 to 48 hours

The criteria that I have used - and a suggested revision:

Major criteria (need 1)	Recurrent oral ulceration	Minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient that recurred at least three times over a 12-month period
Minor criteria (need 2)	Recurrent genital ulceration	Aphthous ulceration/scarring observed by physician or patient
	Eye & CNS lesions	Anterior or posterior uveitis or cells in vitreous on slit lamp examination; or retinal vasculitis observed by ophthalmologist; or any part of a uveo-meningo-encephalomyelitis - excepting an isolated meningitic presentation.
	Skin lesions	Erythema nodosum observed by physician or patient, pseudofolliculitis or papulopustular lesions; or acneiform nodules observed by the physician in a postadolescent patient who is not receiving corticosteroid treatment
	Positive pathergy test	As interpreted by physician at 24 to 48 hours

The logical argument for adopting this revised set is presented in the discussion section of my paper, "The Neurology of Behçet's Syndrome".

The complications that are of particular interest to neurologists include a variable combination of the following:-

(1) encephalo-myelitis (multifocal, perivascular).

(2) sterile meningitis.

(3) pseudo-tumour cerebri syndrome

(4) venous sinus thrombosis.

(5) peripheral nerve disorders and radiculopathies.

(6) sub-arachnoid haemorrhage.

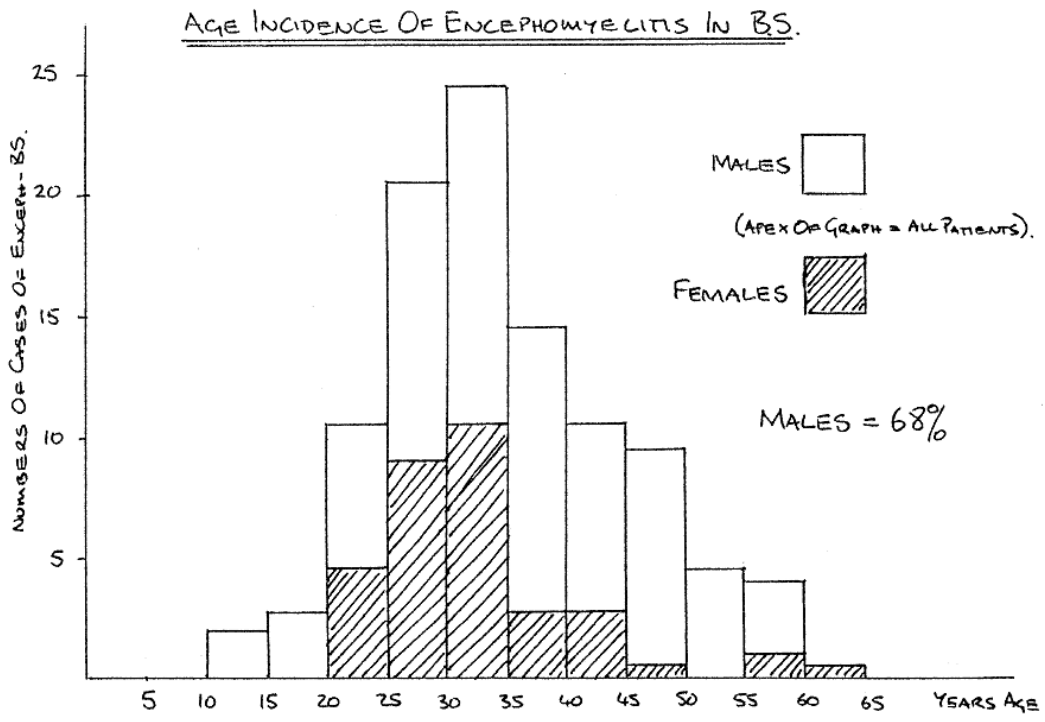
(7) muscle involvement.

(8) psychiatric disturbances.

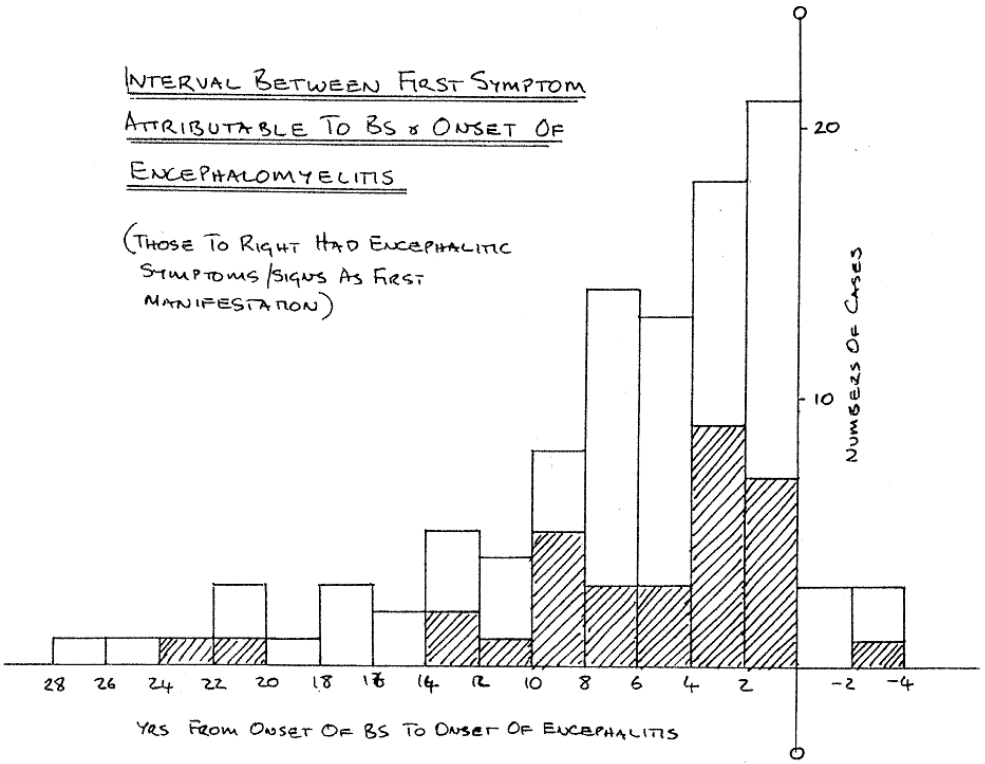
1) **ENCEPHALO-MYELITIS**:

(Shortened to encephalitis now for brevity). My search for articles that recorded case histories of patients with **BS** and a simultaneous encephalitis has located 106 adequately described case histories that met the specified diagnostic criteria.)

---**EPIDEMIOLOGY**: Plain **BS** is more prevalent in men than in women (2:1)[..]. The patients with encephalitis had a similar sex ratio. The age incidence distribution of the encephalitis tended to lag slightly behind that of plain **BS** (NBSFigA). Thus, encephalitis was the first manifestation of **BS** in only 5.8% of these 106 patients (NBSFigB)



NBSFigA



NBSFigB

.----**COURSE**: Exacerbations of the encephalitis are often accompanied by fresh aphthous ulcers and iritis. The course of the encephalitis is similar to **MS**. Relapses and remissions are common. In those reports in which the patient was followed up for a prolonged period, it was clear that males often suffered a stepwise or relentlessly progressive deterioration. This contrasted with the dramatic resolutions seen in other patients early in the course of their disease, especially young females (NBSTabC). In about a quarter of the 106 cases, the neurological signs that occurred during exacerbation were similar to earlier bouts (a *locus minoris resistentiae*). A course that was relentlessly progressive from the outset was noted in 18% and the mean age

of onset of the encephalitis in this subgroup was 40yrs. There were only four females with this progressive course: two of these were perimenopausal. A monophasic attack leading to clinical resolution and no relapses was noted in 3.2% of those patients whose reported follow up exceeded 2yrs (6, 8 and 13 yrs). The modes of onset of the encephalitis were the same in both sexes (NBSTabD). Catastrophic onsets were not reported but up to 30% appeared to have an onset that was fairly rapid and might have been confused with small infarctions.

NBSTabC

Disease course

Course	Males	Females
Multiple recurrence	72%	72%
Multiple recurrence giving way to a step or relentlessly progressive course	42% (Nb this is a sub population of the multiple recurrence course	20% (Ditto)
Step progression	6%	8%
Progressive course	19% (Average age 38 yrs)	16% (Average age 40 yrs)
Unipolar course	3%	4%

(Note eleven cases with a unipolar course are excluded for they were followed up for less than two years)

NBSTabD

Onset pattern

	Males	Females
Acute and abrupt	77%	73%
Subacute	16%	17%
Insidious	8%	10%

----**CLINICAL FEATURES**: Any area of the neuraxis may be involved in **BS**. NBSTabE lists the disturbances reported in this block of 106 patients. Like **MS**, the neurolological manifestations may be disseminated in both CNS location and time.

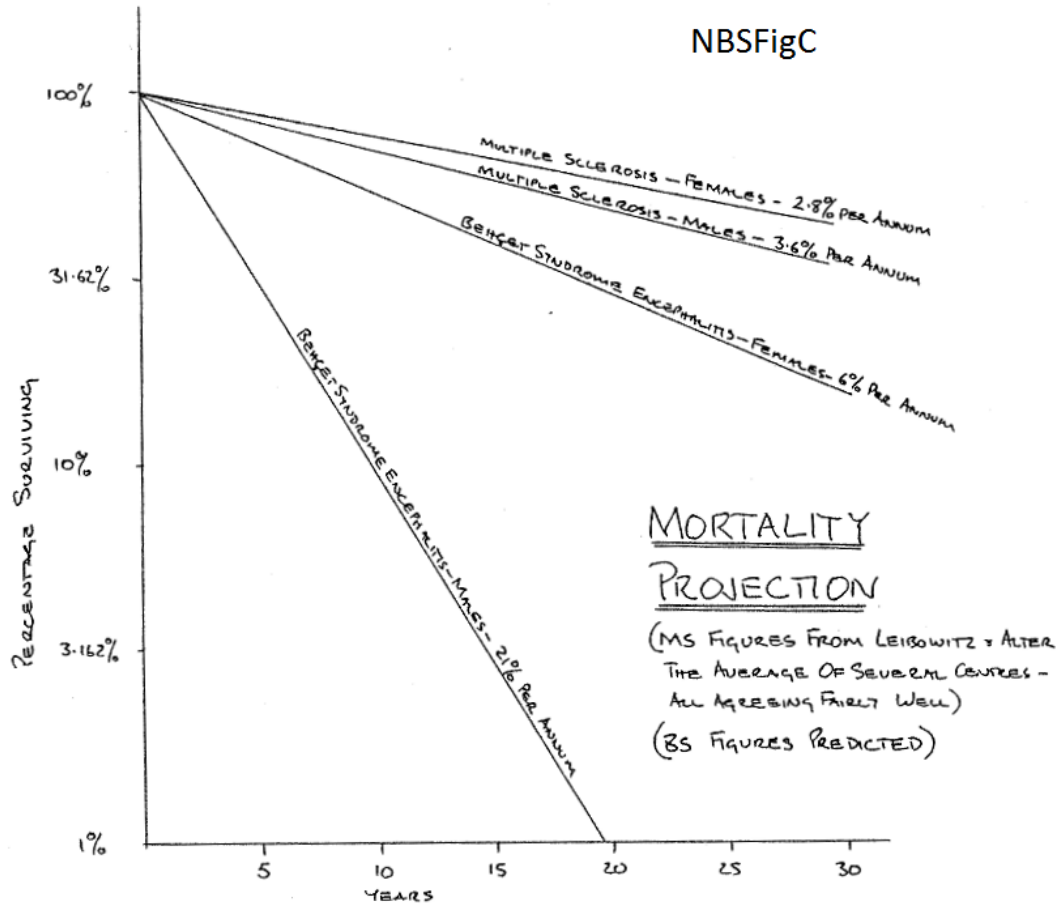
NBSTabE **Neurological** manifestation **in encephalitic Behçet's syndrome**

Headache		**56%**
Mental disorder	**(total)**	**67%**
Mild (anxiety, insomnia, malaise, aesthenia)		38%
Moderate		39%
Severe		23%
Emotional disturbance	**(total)**	**26%**
Lability		21%
Euphoria		12.50%
Cortical disturbances	**(total)**	**19%**
Fits		10%
Dysphasia		14%
Hemianopia		3.30%

Extrapyramidal	**(total)**	**14%**
Rigidity		3.30%
Bradykinesia		0.90%
Parkinsonism		1%
Loss of facial expression		5.70%
Choreo-athetosis		3.30%
Grimacing		2.90%
Pyramidal features		
Long tract signs (definite)		60%
Probable)		88%
(not clear)		11%
(absent)		1%
Paresis		
(total)		60%
(hemiparesis)		44%
(quadriparesis)		32%
(three limbs)		7%
(both arms or legs)		10%
(one limb)		7%
Cerebellar disturbance	**(total)**	**36%**
Dysmetria, dysdiadokokinesis		21%
Tremor		4.30%
Gait disturbance		26%
Scanning speech		7.10%
Brain stem involvement	**(total minimum)**	**54%**
- ditto -	**(total maximum)**	**79%**
Oculomotor		33%
Conjugate gaze and upward gaze palsies		9.60%
Fifth nerve involvement		11.40%
Seventh nerve involvement (upper and lower motor neurone)		35%
Eighth nerve involvement		3.30%
Dizziness	(total)	13.30%
Dizziness with true vertigo		5.70%
Nystagmus		26%
Dysarthria		34%
Bulbar signs		35%
Stupor		14.30%
Coma		14.30%
Total affected at some time with stupor or coma		25%
Positive sensory disturbances (e.g., dysaesthesiae)		9.60%
Negative sensory disturbances (that is loss)		27%
Negative and/or positive sensory disturbances		36%
Cortical disturbances		22%
Sphincter disturbances		20%
Lower motor neurone/root entry zone disturbances		8.60%

----**MORBIDITY AND MORTALITY**: The ultimate morbidity and mortality of encephalitic **BS** is hard to assess since more than half of these 106 cases were written up within 2yrs of the onset of their encephalitis and there is no further record of their course. There may also be a bias towards writing up (and also towards accepting for publication) the more interesting case histories, especially those with autopsy reports. Several authors have reported a series of first hand experiences with **BS**: their estimate of the seriousness of

encephalitic **BS** is well below that suggested in this series of 106 patients [..]. In this analysis, the mortality was high and especially so in males (NBSFigC). The male mortality remains remarkably constant in each year of follow up (about 21% each year). Extrapolated, this would produce a 95% mortality by the 11th year from the onset of the encephalitis, and a 5 year survival of 25%. The mortality rate in the pre-1963 cases [..] is higher than the post-1963 cases: this may reflect a response to those drugs that have become available since 1963 (steroids and immunosuppressives especially).



The causes of death are tabulated in NBSTabF. Deaths that were directly attributable to neurological disturbances were nearly all caused by an acute bulbar crisis. Neurological disease (dementia, fits, paraplegias and quadriplegias) led to death through pneumonia, pyelonephritis, bed sores, debility and cachexia. Deaths ***NOT*** due to neurological disease (primary or secondary) appeared to be more likely in the encephalitic group than in plain **BS** (4.5% - Mavioglu [..]). Thus, it seems that the addition of encephalitis to the classical **BS** triad brings an increase in mortality (severity?) that is not caused by or secondary to the neurological disturbance.

The assessment of morbidity in these 106 case histories was a subjective exercise for, in general, this aspect was not well detailed. I have called a disorder (paretic, cerebellar, psychiatric or demential) severely disabling if it either prevented unaided ambulation or seriously interfered with social integration (NBSTabG).

NBSTabF

Causes of death

	Males	Females	All
Overall mortality	64%	18%	48%
> 200 WCC in CSF	65%	12.5%	48%

Attributable causes of death

Directly neurological cause	Unequivocal + probable as well	7 cases 8 cases
Neuro-consequent cause	Unequivocal + probable as well	24 cases 26 cases
Either directly neuro or neuro-consequent cause	Unequivocal + probable as well	3 cases (same)
Non- neuro cause	Unequivocal + probable as well	6 cases 10 cases
Not stated		3 cases

(Note that of the female deaths, two thirds - ie, 4 cases - had non-neurological causes of death)

(Non-neurological causes of death includeed: cardiac failure -2 cases, hepatitis -1, Budd Chiari syndrome - 1, lung infiltrations with general deterioration - 1, peritonitis - 2, uncertain - 2)

NBSTabG

Morbidity in encephalitic-BS

Disability	Males	Females
Recovered	2.2%	8%
Mild	12%	28%
Moderate	18%	34%
Severe	68%	30%

(severity in males partially reflects the high mortality rate as all fatal cases with neurologically related causes of death were called severe)

----**NEURO-PATHOLOGY**: Thirty three of the 106 cases (xx%) had autopsy reports. There are other reports that also discuss the pathology of encephalitic **BS** [..]. The reported changes were not completely constant but generally conformed to the following. There is a mild diffuse encephalitis and a severer multifocal encephalitis. Both follow a perivascular distribution and favour the white matter. Fresh lesions, resolving lesions and healed (scarred) lesions are described reflecting the relapsing and remitting course of the disease. Autopsy material is hardly ideal for demonstrating the evolution of lesions so some interpretation is necessary and I have looked to MS and experimental allergic encephalitis (EAE) for help in interpreting this information. The following is partially my own synthesis.

(a) The **MILD DIFFUSE ENCEPHALITIS**: Many authors have remarked on this. Rubenstein and Urich [..] described it in detail. The initial change is a perivascular round cell infiltration that is both inconspicuous and diffuse. It consists of a single layer of round cells. This is most evident in the subependyma, in the basal ganglia and in the brain stem. There may be a thin rim of demyelination [..]. Healing is characterised by a mild diffuse perivascular gliosis. In general, neural structures are well preserved.

(b) The **SEVERE MULTIFOCAL ENCEPHALITIS**: Focal softenings are the hallmark of encephalitic **BS**. They range in size from 0.1mm to 10mm. The larger lesions tend to result from the confluent accumulation of several perivascular softenings around a central *"herald"* lesion. These foci are frequently observed encompassing a vessel (usually venules but sometimes arterioles) though they are not necessarily centred upon it. The histology varies according to the age of the lesion and the duration of the disease process. In the least destructive lesions there is an ill defined area of demyelination with relative or even complete sparing of axonal structures [..]. The commonest lesion is necrotic with destruction of axons and nerve cells (the latter in the grey matter). The earliest change is probably a fibrinous oedema surrounding a blood vessel [..]. Polymorphs are generally the first cells to arrive and are dominant in acute and severe lesions [..] reaching a peak of intensity when multiple micro-abscesses are formed [..]. A round cell infiltration quickly follows: this is the most common observation. In those cases where demyelination is prominent the cellular infiltration tends to be slight [..]. These round cells are variously described as lymphocytic or macro-monocytic. Other cell types are described (e.g., plasma cells and red corpuscles) but are of minor impact and inconstant. None of these cases had demyelinative plaques reminiscent of MS though two cases had demyelination that was descriptively reminiscent of acute disseminated encephalo-myelitis [..].

Haemorrhage occurs into some of the larger and more necrotic foci. This may be due to erythrocyte diapedesis (perhaps carried along with other inflammatory cells) or to rupture of necrotic vessel walls. Various degrees of endothelial pathology have been observed in **BS** ranging from simple endothelial proliferation, through a stage of intense medial infiltration of the vessel wall, to a disruptive or frankly necrotic inflammation of the vessel wall. Thrombi are often noted within the boundaries of severe lesions. Many authors have referred to these necroses as "ischaemic" but there is little to substantiate this presumption. Thrombi only occur in the most exuberant lesions and are often not so positioned that they could cause the lesion anyway. The vast majority of foci do not appear to have thrombi and, when they do occur, they are probably consequence rather than cause of the inflammatory process.

The organising phase of the **BS** focus consists of a perivascular accumulation of fat granule cells that begin to insinuate and congest the vessel wall as the fatty neural debris is cleared. There is often a slight astrocytic proliferation. Scarring is seen as glial nodules and focal gliosis. When there has been extensive necrosis, there is deposition of collagen and, in the most destructive lesions, collagen lined cysts may appear.

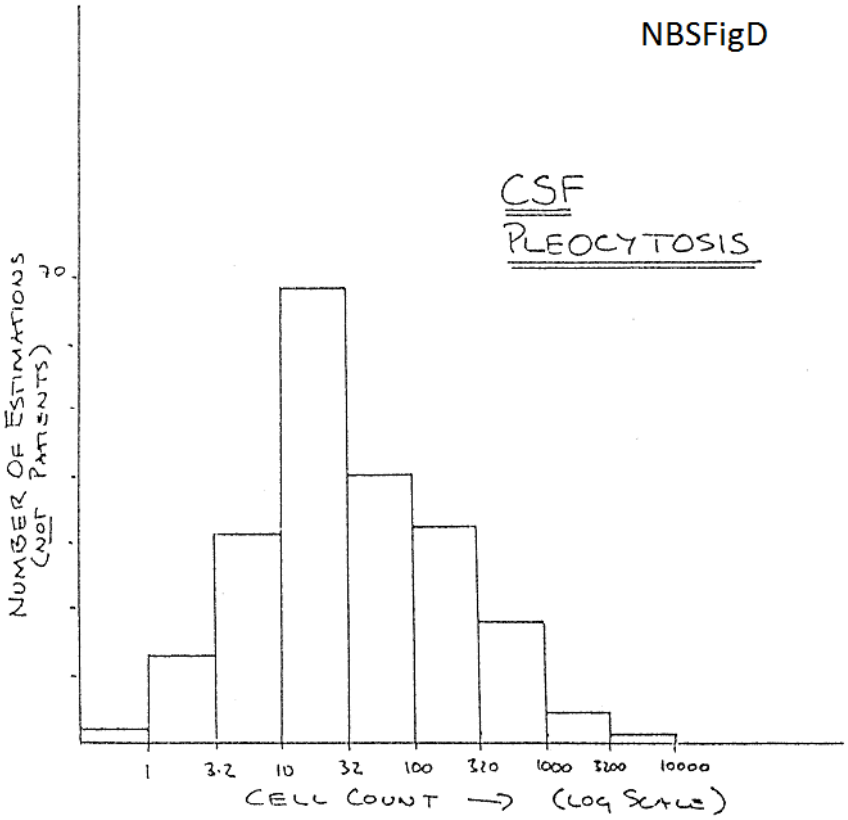
The foci of destruction can lead to Wallerian degeneration together with atrophy and distortion of the neuraxis. Mild ventricular dilatation and cerebral atrophy may occur [..] whilst distortions of the crurae, brain stem and spinal cord are common [..].

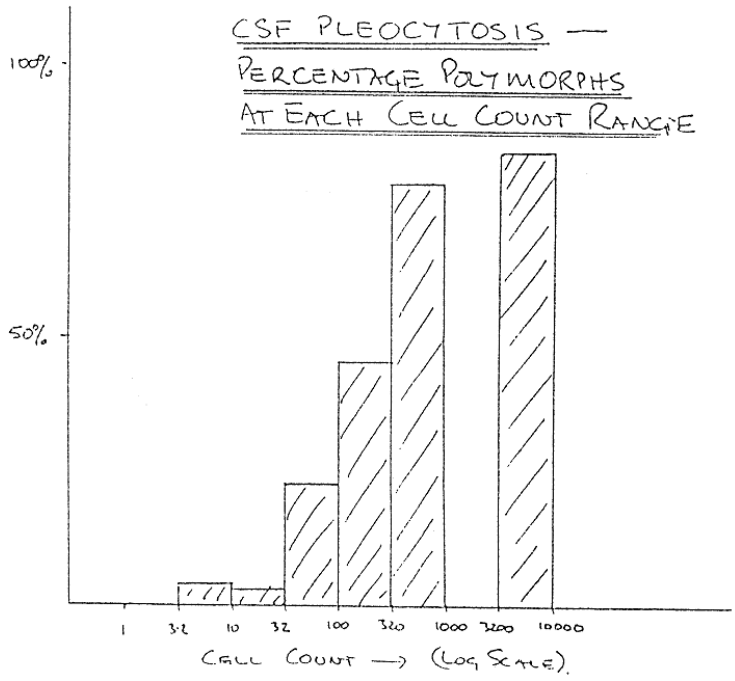
The foci are disseminated throughout the neuraxis. Certain predilections are noted. Cortical involvement is slight: when it occurs, there is a preference for the cortico-medullary junction [..]. Favoured sites include the internal and external capsules, the basal ganglia, the mid brain and the brain stem. The lesions in these areas are often large, haemorrhagic and in the process of cystic resolution. The cerebellum enjoys a relative immunity though there is frequent evidence of scarring. Only one of the cases had active cerebellar necrosis [..] though demyelinative foci [..], inflammatory cuffs [..], glial nodules [..] and gliosis [..] have been noted here. Periventricular and subependymal changes are frequently observed and may even resemble MS [..]. These changes include necrotic foci [..], softenings [..], demyelination [..], perivascular cuffing [..], glial nodules [..] and gliosis [..]. Hartemann noted that the sub-ependymal plexus of veins was the site of much focal inflammation: confluence of such inflammatory foci often led to the whole ependymal layer becoming involved in a dense purulent ependymitis [..].

Lepto-meningeal involvement is common. This is evidenced by thickening, opalescence and (histologically) a lympho-monocytic infiltration with subsequent lepto-meningeal fibrosis. The infiltrates are predominantly perivascular and follow the Virchow Robin spaces deep into the neuraxial tissues. These changes are particularly obvious at the base of the brain, over the vertex and deep within the sulci.

The optic nerve may also be involved. Necroses [..], demyelination [..], perivascular cuffing [..] and gliosis [..] are described and give rise to atrophy and distortion [..].

(2) **STERILE MENINGITIS**: Symptoms suggestive of meningitis occurred in 25% of the encephalo-myelitis group (out of a total of 106). Just over half of these patients (13/25) had a CSF pleocytosis of $200x10^6$/litre or more. Similarly, half the patients (from the 106) with 200+ cell counts (also 13/25) had definite symptoms of meningitis. The highest cell count recorded was $5,400x10^6$/litre. A few patients (apparently) without meningitis had a CSF pleocytosis exceeding a thousand [..]. A modest pleocytosis is common in encephalo-myelitic **BS**. Forty five per cent of the individual estimations made (not patients!) exceeded $32x10^6$/litre (NBSFigD). Polymorphonuclear forms progressively predominate over round cells as the pleocytosis increases (NBSFigE).





NBSFigE

When meningitis occurs in the course of **BS**, it is, perhaps, best to regard it as the involvement of a particular neuraxial site rather than as an expression of the overall severity and extent of neuraxial disease. If it were solely an expression of severity, the mortality in the meningitic group should be higher and there should also be fewer females in this subgroup than in the overall 106 patients. (Remember, not only is **BS** rarer in females but also - if it's accepted that mortality is a gauge of the pathological tempo of the CNS disease - the encephalitis they get is generally less severe.) A comparison of those patients who's cell counts are greater than $200x10^6$/l with those who's counts are less than this, reveals a uniform mortality and sex ratio (NBSTabH & NBSTabJ). The meningitis may well reflect the extent of (focal) sub-pial involvement. Five of the group with meningitis (i.e., 20%) seemed to have partial or complete myelitis. This figure is similar to the incidence of cord disease seen in all 106 patients (22%). Pallis and Fudge suggested that a meningo-encephalitic syndrome was a distinctly compartmentalised presentation of neuro-**BS**. This may well be illusory. In those patients who's cell counts were higher than $200x10^6$/l, there was no predilection for any area of the neuraxis other than (of course) the sub-pial region (NBSTabJ). The concurrence of meningitis and myelitis is probably attributable to multiple subpial foci. These are critically close to (and probably extend into) major pathways (that occupy large cross sections of the cord). There is further indication that the meningitis is due to foci being close to the neuraxial surface. There was a higher incidence of cortical disease (evidenced by symptoms like dysphasia), a lower incidence of non-localisable pyramidal tract involvement and extensive cord disease in the group of patients in whom cell counts were more than $200x10^6$/l.

NBSTabJ

Comparison of cases with and without a CSF pleocytosis of ≥ 200

Disease location	< 200 CSF WCC			≥ 200 CSF WCC		
	Males	Females	All	Males	Females	All
Spinal cord	36%	14%	24%	26%	37%	30%
Brain stem	55%	50%	53%	82%	62%	76%
Cerebellum	38%	40%	39%	47%	9%	38%
Cerebrum	69%	40%	59%	76%	56%	70%
Pyramidal	24%	28%	25%	0%	37%	12%
Meningitis (clinical)	38%	25%	34%	69%	56%	64%
Papill/oedema/itis/blurring	17%	24%	19%	18%	12%	16%
Pallor/optic atrophy	26%	20%	24%	18%	12%	16%

(Nb, meningitis refers to possible cases where severe headache was assigned an incidence score of 1/3, headache+nausea - 1/2 and headache+nausea+neck rigidity - 1. This, hopefully, will reflect a fairly true incidence of meningeal irritation).

There were 24% of males with a pleocytosis of ≥ 200 CSF WCC and, similarly, 24% of females – so meningitis acts more like a location than a severity characteristic.

(Nb, pyramidal disease refers to pyramidal tract signs that were not localisable to the cerebrum, capsules or brain stem on the evidence of co-incident signs from these sites.)

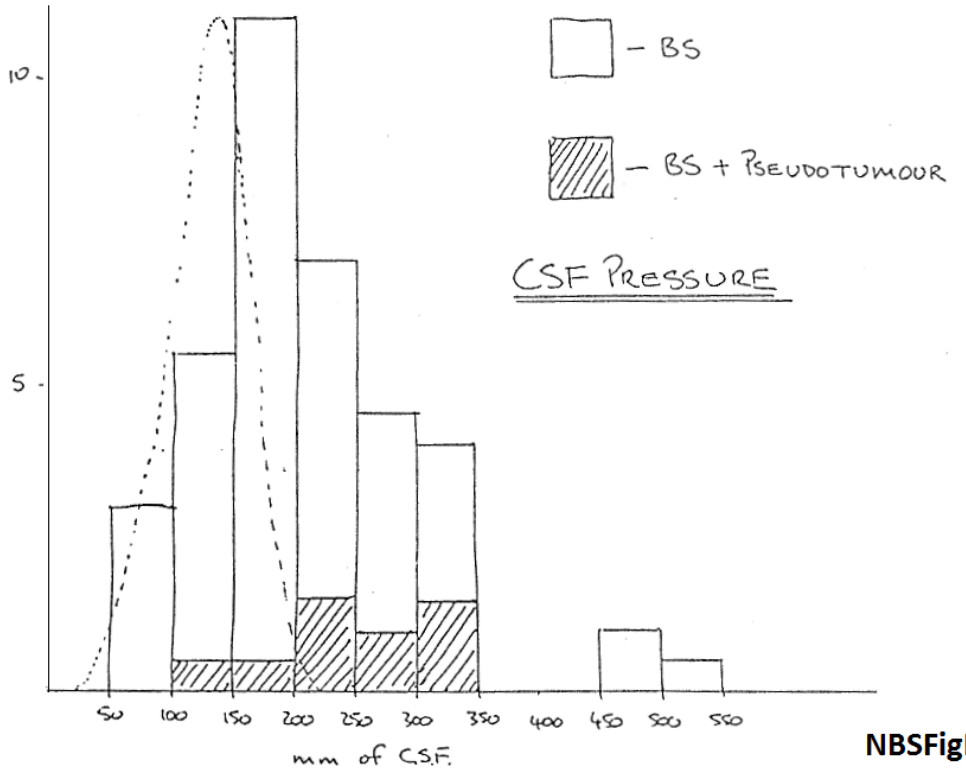
NBSTabJ

Location of encephalitis comparing > 200 white cell counts with < 200

	> 200 WCC in CSF	< 200 WCC in CSF
Coma	16%	14%
Dysphasia	20%	13%
Hemianopia	8%	1.3%
Bulbar crisis	12%	11%
Myelitis	20%	11%

(3) **PSEUDO-TUMOUR CEREBRI**: Calbian and Challis [..] were the first authors to emphasise this complication though earlier cases conform to the pattern: sixteen case histories satisfy the description. Four of these had oro-genital ulceration alone and two more had oro-genitial ulceration with one minor component. These six would have been disqualified from inclusion in the encephalitic group. Just one of the sixteen (subsequently) developed a bona fide encephalitis [..]. Eleven of these had a "full house" of headache, vomiting and papilloedema. Five of the remainder had either bilateral papilloedema (3/16), disc swelling or disc blurring; 4 of these 5 had a CSF column pressure exceeding 199mm (in lateral decubitus position); 4 of these 5 had headaches.

Of the whole group (16 patients), 8 had CSF pressures greater than 199mm, one pressure was said to be "raised" and two were said to be "normal": in two others the CSF pressure was not mentioned (NBSFigF). Neurological signs were minimal: those occurring included mild ocular palsies, mild facial pareses, nystagmus and long tract signs (hyperreflexia and upgoing plantars) without significant paresis. When carried out, contrast radiography was essentially normal: 10 had AEGs and/or ventriculograms; two had carotid arteriograms alone.



NBSFigF

Only one of these 16 patients died. This was due to "an exacerbation of her neurological illness" [..]. Thrombotic disease was relatively more frequent in this group (44%) than in a series reviewed by Chajek and Fainaru (24%) [..]. Venous (sinus) thrombosis should be considered as a possible cause of this complication. Ocular involvement was low in this group but that is, in part, directly due to the relaxation of diagnostic criteria (Curth's definition). Nevertheless, the age and sex distribution were similar to the encephalitis group (62% males).

(4) **VENOUS SINUS THROMBOSIS**: Indubitable VST occurred in only one case (an autopsy finding) [..]. Bienenstock and Marguiles [..] presented a case in which there was suggestive angiographic evidence of VST. Masheter believed the pseudo-tumour cerebri syndrome he described was due to VST: this was unsubstantiated [..].

(5) **PERIPHERAL NERVE DISORDERS AND RADICULOPATHIES:** Symmetrical peripheral

neuropathy has been described by Lobo-Antunes [..] and Houston and O'Duffy [..] though the latter's patient also had a "reticulo-endothelial tumour". One of these cases had prolonged latencies in terminal nerve conduction [..]. The other had an electrical "sensorimotor neuropathy" [..]. Fadli and Youssef also reported a case with prolonged terminal latencies [..]. A nerve biopsy was done on one patient [..] that "suggested an angiopathic neuropathy". Two Japanese reports [..] had biopsy evidence of "segmental demyelination" in the sural nerve and one of these papers reported prolongations of the sural nerve terminal latencies exceeding those of a control group.

RADICULOPATHY: Cauda equina syndromes simulating an acute disc prolapse have been reported [..]. In one of these, myelography had been normal and there was a rapid resolution with steroid therapy. A number of the encephalitis group had motor and reflex disturbances that were consistent with either root entry zone or anterior horn cell disease. Ardouin [..] described a patient who's only neurological disease was consistent with this neural complication (5).

6) **SUB-ARACHNOID HAEMORRHAGE**: Two reports described this complication and both patients died [..]. Arteritis may be responsible as both medial degeneration and arterial aneurysm formation have been reported at other sites within the body [..].

(7) **MUSCLE INVOLVEMENT**: Weakness due to "myopathy" has been reported [..]. Severe muscle pains may occur in **BS** and are most frequent in the lower limbs. The reported incidence of these pains varies between series. Mamo and Bagadasserian found that 10 of their series of 28 patients had this symptom [..]. Most reports mention only sporadic cases. Fadli and Youssef reported myopathic changes at electromyographic examination [..]. Garcin et al [..] found a tender nodule of electrical inactivity in their patient: they reported "myositic changes" in their biopsy specimen. Lobo-Antunes [..] noted perivenous round cell infiltrations in muscle biopsies.

(8) **PSYCHIATRIC MANIFESTATIONS**: I only carried out a systematic review of psychiatric symptoms in patients with encephalitic-**BS**. There was a high incidence in this group (NBSTabK). Neuraesthenia, anxiety neurosis, phobias, hypochondriasis, depression, schizophrenic and affective psychoses are all recorded. It is my impression that they are also common in **BS** unaccompanied by encephalitis.

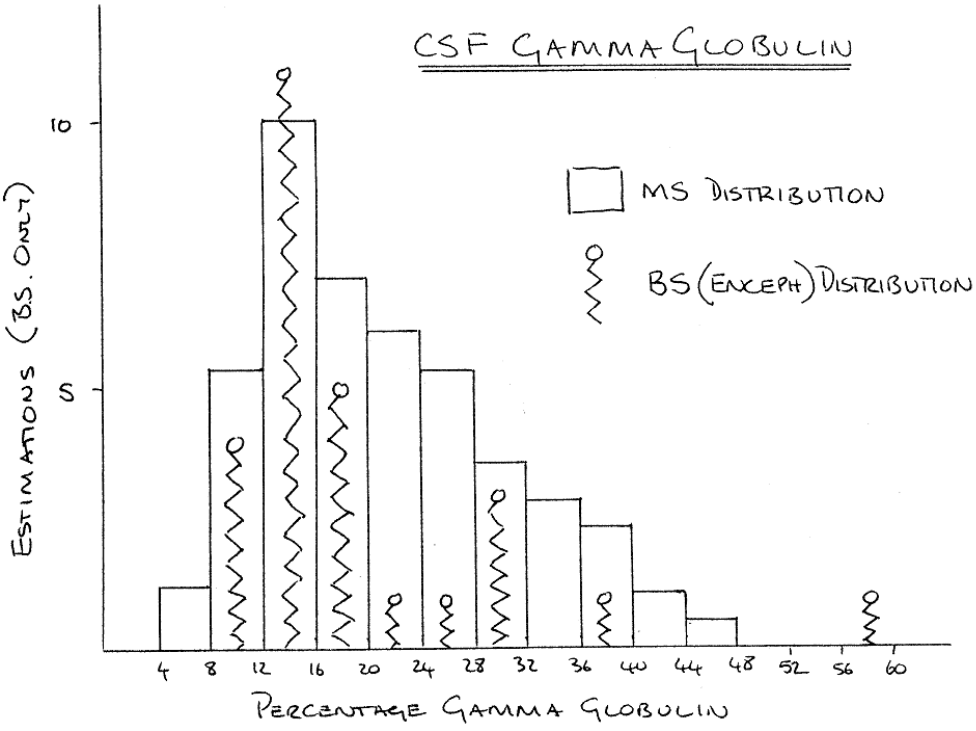
NBSTabK not completed yet

Epstein et al studied a number of patients with **BS** and noted that relapses of the illness were often precipitated by psychological stress. These patients also had a characteristic personality profile (similar to that reported in rheumatoid arthritis and ulcerative colitis). Dependency, submissiveness, indirect communication of hostility, a depressive self image, intermittent compulsiveness and a poor psycho-sexual adjustment were all prominent features. A similar array of psychological and psychiatric disturbances are observed in forms of aphthosis less virulent than **BS**. Precipitation by stress is reported in these also [..].

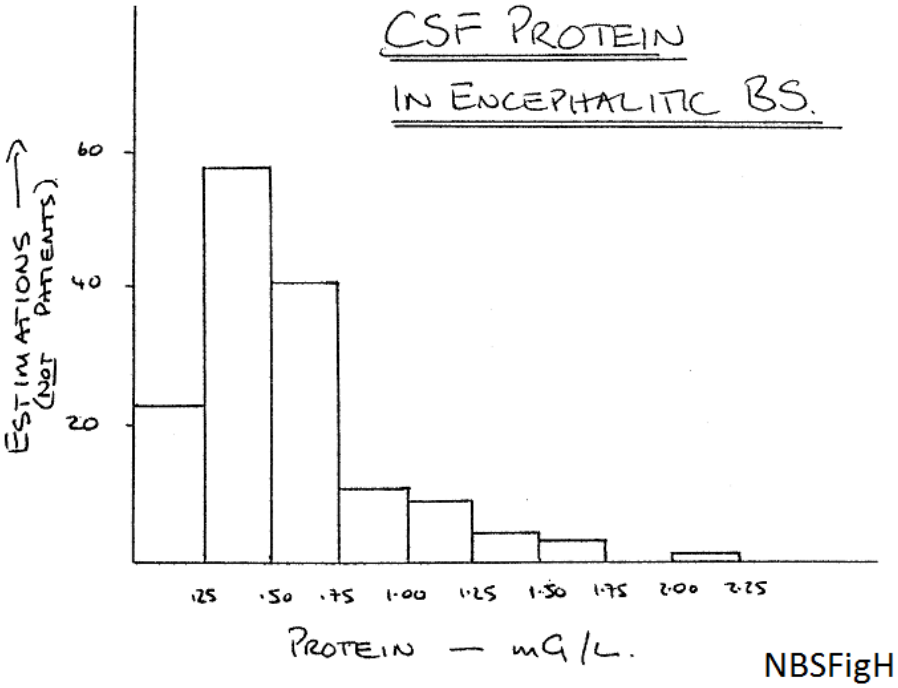
INVESTIGATIONS IN ENCEPHALITIC-BS: The laboratory findings are similar to those noted generally in **BS**. The sedimentation rate is usually raised: greater than 24mm/hr in 76% of those in whom it was recorded; greater than 49mm/hr in 46%; and greater than 99mm/hr in 13%. Mild anaemia is fairly common but rarely below 10G/dl. A polymorphonuclear leucocytosis was common: less than $5x10^9$/l in 5%; more than $10x10^9$/l in 44%. The serum proteins often show a reduced or reversed albumen/globulin ratio with a proportionally large increase in alpha-2- and gamma-globulins. The Rose Waaler or Rose Latex have been weekly positive in a few instances but there were no reports in which other routinely checked auto-antibodies were found. Anti-cytoplasmic antibodies have been demonstrated and there is an auto-antibody response directed against oral mucosa [..]. Fibrinogen levels frequently rise during exacerbations and there is simultaneous evidence of impaired fibrinolysis [..].

There are no abnormalities peculiar to encephalitic-**BS**. The EEG may show non-specific abnormalities including an excess of slow activity and occasional focal abnormalities. Carotid angiography has usually been normal though one case was reported to be "suggestive" of venous sinus thrombosis, and another demonstrated a basal ganglia mass that was further defined by computerised axial tomography. Air

encephalography has shown little other than occasional mild ventricular dilatation. Myelography has been normal except in one patient in whom there was a "spinal block and arachnoiditis" [..]. Arachnoiditis was suspected in one other patient because air failed to rise above the cervical cord during air encephalography [..]. There are two reports of computerised tomography in **BS** (though one patient did not fulfil the complete criteria): each of these demonstrated basal ganglia disease [..]. One of them [..] showed a remitting/relapsing space occupying lesion that distorted central neural structures. CSF gamma globulin levels are infrequently reported but, when they are, the proportion of gamma globulin in the CSF protein is usually increased (NBSFigG). A rise in the CSF protein is common (NBSFigH).



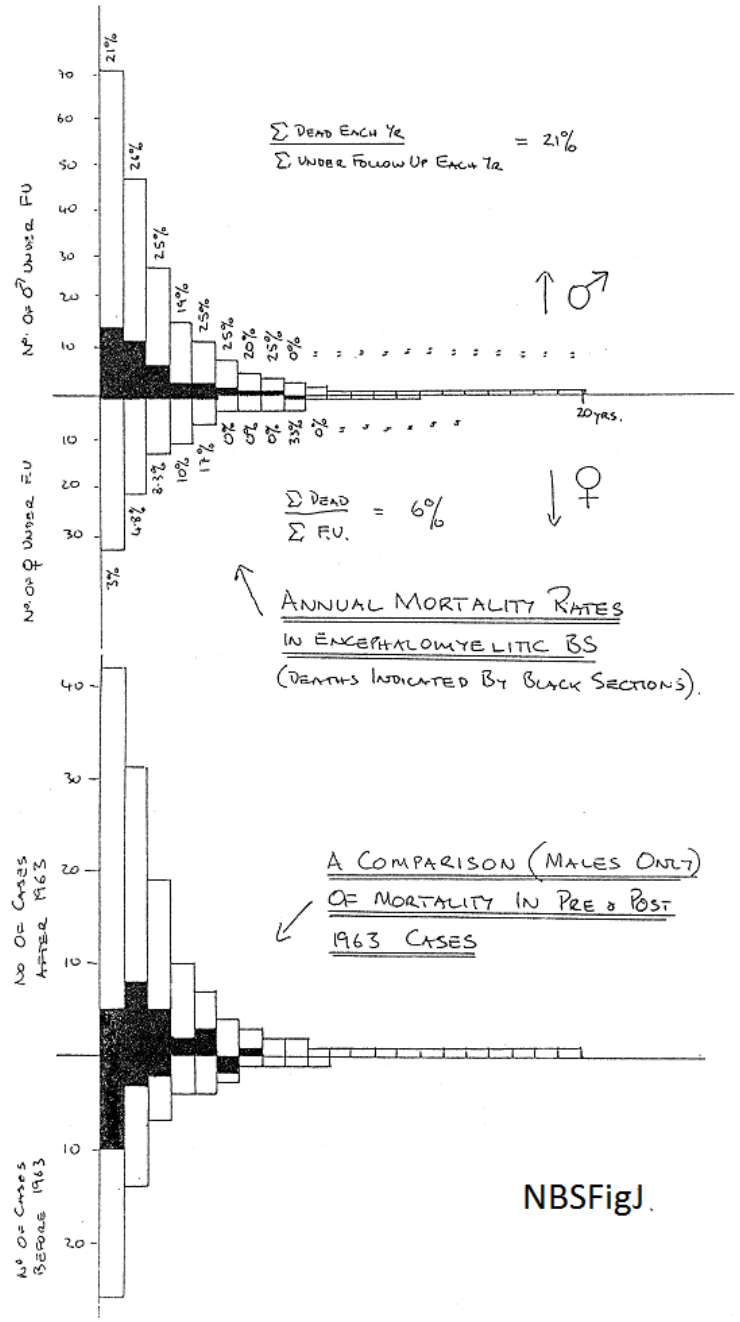
NBSFigG



NBSFigH

TREATMENT: Steroids, immunosuppressives, anticoagulants, fibrinolytic agents and the transfusion of certain blood fractions have all been advocated in **BS** [..]. However, because the disease is rare and it spontaneously exacerbates and remits, it is difficult, objectively, to assess the benefits of therapy. This is made more difficult by the relative paucity of reported cases that have had a prolonged follow up.

Steroids have become the mainstay of therapy. Doses equivalent to 40mg or more of prednisolone daily often lead to a dramatic improvement. In the encephalitic series, cessation of therapy has often been accompanied by a rapid recurrence of symptoms and signs . However, with progression of the disease, especially in the relentlessly progressive stages, steroids cease to produce discernable improvements. It is likely that steroids reduce the acute inflammatory reaction but that they fail to influence the insidious accumulation of tissue scars and the consequent disruption of function. There has only been a slight reduction in the mortality of the pre- and the post-1963 groups of male sufferers (chosen because they are large and uniform groups). The most obvious change is that the initial mortality is lower (NBSFigJ) and this is consistent with the initial benefit of steroids. Even if we exclude the patients said to be alive but who have had very short follow ups (since they might distort the actual first year mortality) the difference is still noticeable with a 42% mortality in the pre-1963 group during the first year and a 14.3% mortality in the post-1963 group.



NBSFigJ.

Cunliffe and Menon [..] introduced fibrinolytic therapy using phenformin and ethinyloestradiol. There are several reports that have claimed an improvement in all aspects of the disease using this therapy. Chajek and Fainaru [..] used streptokinase and streptodornase. They only found improvement in the thrombotic manifestations of the disease. Anticoagulant therapy was said to have stabilised Masheter's case [..] and helped two others [..]. Heparin helped according to one report [..].

There is considerable experience now with immunosuppressives. They are usually a useful adjunct to steroid therapy. Azothioprine, chlorambucil and cyclophosphamide have been used [..]. Two groups have used immunosuppressives in neuro-**BS** with some temporary benefit [..]: two reports found cyclophosphamide ineffective and one found methotrexate ineffective [..].

THE PATHOGENESIS OF BS : Previous papers have concentrated on three main hypotheses:

(a) an auto-immune aetiology.

(b) an infective aetiology.

(c) a vasculitic aetiology.

These will also be discussed here but there are a number of factors that are likely to shed some light on the aetiology of **BS**. These include:

(d) the relationship of **BS** to the other sero-negative arthritides.

(e) the relationship of encephalitic-**BS** to MS and EAE.

(f) the possibility that (a), (b) and (c) are all active in contributing to the pathophysiology.

There is considerable clinical overlap within the sero-negative arthritides (Moll [..]). Individual cases may be hard to assign to a particular disorder. Furthermore, the syndrome complexes overlap with the isolated components from which they are constituted. As observed earlier, there appears to be a clinical continuum of disease from mild aphthosis through to **BS**. A similar continuum is noted in other disorders (psoriasis through to psoriatic arthropathy: ankylosing spondylitis through to the sero-negative (spond)arthritides: NSU through to NSU+conjunctivitis through to RS: ulcerative colitis through to colitic arthropathy: and so on). Patients with isolated components are much more commonly seen than patients with multiple components. Sarcoidosis has a number of features in common with the sero-negative arthritides. The absence of a significant association with AS is no reason to exclude it from this group for **BS** is weakly, if at all, associated with AS [..]. Furthermore, **BS** is clinically close to Reiters Syndrome and colitic arthropathy, whilst Sarcoidosis can mimic the cutaneous distribution of psoriasis and the granulomatous pathology of Crohn's disease. This group of disorders are mimicked well by an experimentally induced animal arthritis called adjuvant arthritis [..].

ANIMAL MODELS: Pearson et al presented the first of a succession of articles on adjuvant arthritis in 1961 [..]. They noted how similar this experimentally produced arthritis was to the sero-negative arthritides (not then so named) and sarcoidosis (NBSTabL). The disease appeared to be caused either by a reaction to some component of the adjuvant material or by the induction of auto-aggression to self antigens. The authors favoured the tuberculous material (rather than self Ags) as the sensitising substance. It has been subsequently shown that the disease can be transmitted to naive animals by the transfer of white cells but not by the transfer of serum or filtered lymph. This suggests that CMI auto-aggression is an important factor in its pathogenesis.

NBSTabL

Adjuvant Arthritis

Joint lesions	polyarthritis spondylitis tendinitis & tenosynovitis
Nodules	erythema nodosum like
Muco-cutaneous	pustules acanthosis parakeratosis & hyperkeratosis
Urethritis	
Colon	non-specific diarrhoea inflammatory infiltration of the submucosa
Ocular	uveitis keratitis conjunctivitis
Heart	pericarditis myocarditis
Visceral	granulomata in liver and lungs
Neurological	focal encephalitis meningitis

One animal in Pearson's experiments developed CNS disease consistent with experimental allergic encephalitis (**EAE**) whilst four others developed a meningitis. If adjuvant arthritis does prove to be a legitimate animal model of the sero-negative arthritides the implication of this is that the encephalitis of **BS** may be similar to **EAE** and likewise a dominantly CMI auto-aggressive disorder. It further raises the possibility that encephalitic **BS** and **MS** have, at least, some areas of overlapping pathophysiology. The similarities, however, between the characteristic lesions of **BS** and **MS** are confined to their size, their distribution, their tendency to grow by accreting around a *"herald"* lesion and their dissemination in both both space and time. If there is any commonality in their pathophysiologies, then there is a factor that has conspired to bring about a distinct metamorphosis in the appearance of their respective lesions. I shall explore this possibility later in the article.

There seems to be a consensus that **EAE,** particularly chronic relapsing **EAE**, is a useful model of **MS** [..]. It mimics many of the clinical features of **MS** and suggests that the pathology of **MS** is dominated by a CMI auto-rejection of the nervous system. In simple **EAE** there is a relative paucity of demyelination [..]. The clear-cut diffused plaques of demyelination that characterise **MS** are not seen. In certain animals (usually particular strains) demyelination is absent or at least minimal and there are necrotic foci that affect all elements of the neuraxial tissue [..]. There is a moderately intense meningitis in **EAE** that produces a marked CSF pleocytosis: polymorphs predominate in the early leucocyte influx. **EAE** is a monophasic disorder with a significant mortality rate - far in excess of that associated with single relapses of **MS**.

The advent of chronic relapsing **EAE** has brought a model that mimics **MS** more closely [..]. Smaller lesions occur and these are seen to grow by a process of peripheral accretion around a *"herald"* focus. Scars are seen at the centre whilst acute, inflammatory lesions are being added to the outer parts of the focus. Plaques of demyelination are now more common and these appear to diffuse out from each focus. Lassman and Wiscnevski [..] have noted that one marked difference between chronic relapsing **EAE** and simple **EAE** is

the emphasis on perivascular inflammation and demyelination. In chronic relapsing **EAE**, demyelination is prominent and perivascular inflammation is slight whilst the opposite is true in simple **EAE**. A further variation of **EAE** (to which dogs and monkeys, in particular, are susceptible) is hyperacute **EAE**. This is dominated by a rapid and intense perivascular infiltration with polymorphonuclear cells. Perivascular accumulations of fibrinogen and fibrin produce foci of oedema. These are the earliest manifestation of disorder within the neuraxis. necrosis of all the neural elements within foci is common and haemorrhages may occur. The vessels within the lesions may be thrombosed with plugs of fibrin whilst the vessel wall may become heavily infiltrated with inflammatory cells. It may even become necrotic. In extreme examples, the neuraxis is studded with micro-abscesses. Demyelination (when it has chance to occur) is of minor impact and in sharp contrast to the extensive destruction of all neural elements within the foci of disease activity. Levine and Wenk [..] pointed out that *"the vasculonecrotic process seen in hyperacute **EAE** transcends, in apparent importance, other elements of the reaction"*. They hypothesised that these changes indicated a quantitative rather than a qualitative difference with the perceived visual changes being merely the consequence of tissue damage induced by an unusually intense immunological injury. Support for this comes from the observation that leucocyte transfers from animals with hyperacute **EAE** into naive recipients induce simple **EAE**.

It should by now be clear that the animal models used to mimic **MS** show that the perceived differences between the foci of **MS** and those of encephalitic-**BS** could be legitimately regarded as differences in their pathological tempo. Indeed, within the diagnostic stable of **MS**, necrotic variants are reported. Gerd Peters [..] quotes l'Hermitte: *"Le foyer de necrose ne represente nullement une anomalie qualitative des lesions mais seulement une variation quantitative, que est fonction de l'intensite et de la rapidite d'evolution du processus morbide"*. The tuberculin response (in the skin) studied in laboratory animals shows a similar swing towards necrosis with increasing severity of the reaction [..].

AUTO-IMMUNITY: The etymology of this popular term is a disaster. It was fashioned when all immune reactions were regarded as being aggressive. The name implies self-immunity but aggression to self is intended. *Immune auto-aggression* might have been more appropriate but *"auto-immunity"* is now too entrenched to oust. Passive transfer of immunoglobulins hardly ever seems to cause destructive disease whereas passive transfer of lymphocytes does and often does so in the absence of auto-antibodies. CMI auto-aggression appears to be a common sequel to any tissue damage and is so commonly demonstrated that its clinical relevance has often been questioned [..]. In an earlier article I have presented the concept of *"auto-rejective disorders"* and it is my opinion that encephalitic-**BS** belongs in this category [..].

Oshima et al were the first to report the presence of auto-antibodies to oral mucosa in **BS** [..]. Lehner [..] confirmed these findings and demonstrated similar though fractionally less constant auto-antibodies in patients with recurrent aphthous ulceration (**RAU**). He found no fluctuation in the quantities of these antibodies during exacerbations and remissions. There was, however, a direct relationship between the level of CMI auto-reactivity to oral mucosa and the ulcer crops (NBSFigJ) [..]. Dolby [..] demonstrated that auto-reactive lymphocytes readily lysed cultured oral epithelial cells but the corresponding auto-antibodies had no such effect. This demonstrated a temporal though not necessarily a causal relationship between CMI auto-aggression and clinical disease. It's possible that it represents no more than a final common event in the pathophysiology of the ulcers. Lehner has reported further histopathological observations that support the importance of coincident CMI auto-aggressive activity at the ulcer sites. Recent ultrastructural observations reinforce this [..]. The current status is reviewed in two later papers but these just confirm observations made in these earlier papers [..].

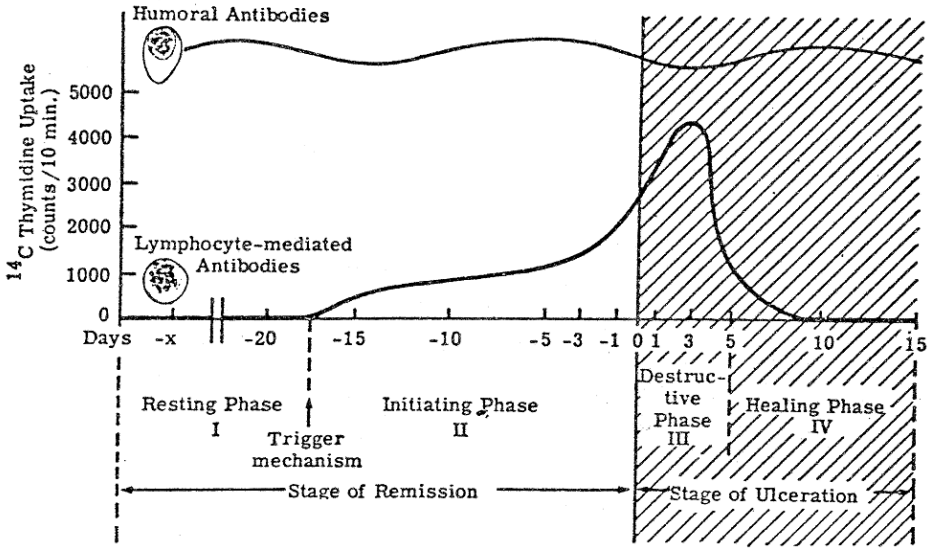
Lehner showed that the auto-antibodies reactive to oral mucosa reacted with a number of other epithelial cell types and also with collagen [..]. He demonstrated the similar though less extensive cross reactivity of auto-reactive lymphocytes with liver, skin and colon. This cross reactivity occurred in both RAU and **BS**. The tissues sharing cross reactivity are variably involved in the course of *"les grandes aphthoses"*. Many of the manifestations of **BS** may, therefore, be caused by CMI auto-reactivity or at least have this factor as a final common pathway in its pathophysiology.

It is pertinent, at this stage, to consider the role of cell mediated immunity in the process of graft rejection.

Circulating antibodies to grafts may be functionally damaging but they do not precipitate graft destruction in the absence of lymphocytes. Cell mediated immunity is both essential and dominant in graft destruction. For this reason, considerable insight may be gained by considering **BS** as a predominantly auto-rejective disorder: whatever the precipitating event, the final common factor seems to include a grossly exaggerated auto-rejection of self tissues. Pursuing this theme, it may be that the circulating auto-antibodies and immune complexes [..] found in **BS** are the result and not the cause of the disorder. They may add to the melee but they probably don't precipitate it. Other observations point towards a dominant immunological role in the aetiology of **BS**. There is skin reactivity to heat aggregated human gamma globulin [..], anticytoplasmic antibodies and a rise in serum mucoproteins [..]. Thymic hyperplasia [..] has been recorded and also various thymic abnormalities [..], a dramatic rise in the C9 component of complement [..] and Sjogren's syndrome [..].

Characterisation of mucosal antibodies in recurrent aphthous ulceration

Lymphocyte kinetics in recurrent aphthous ulceration



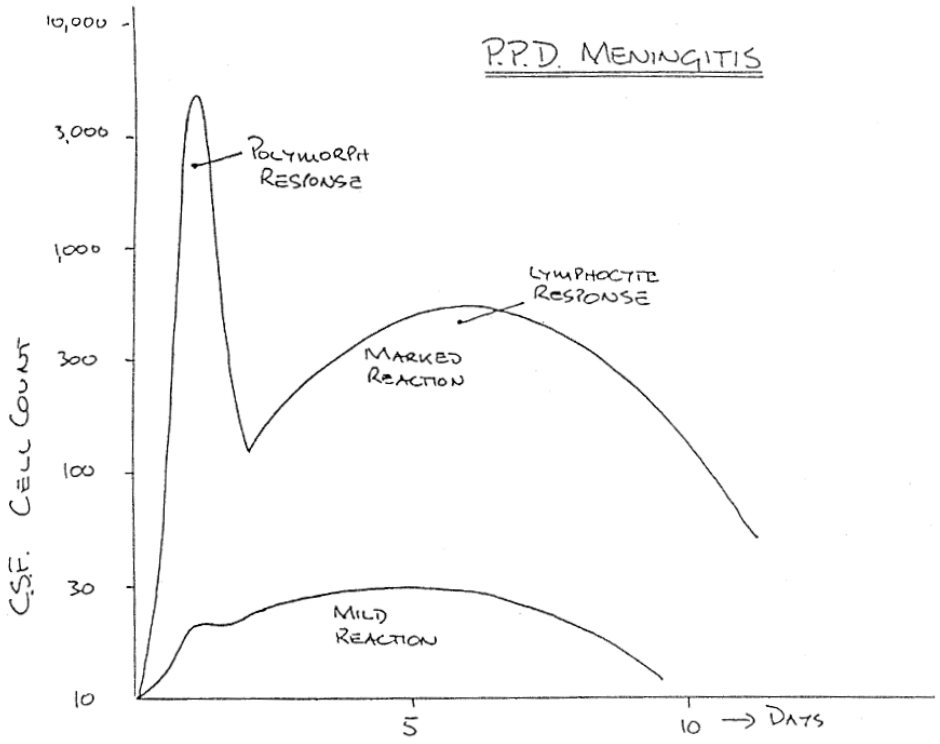
NBSFigJ Sequential determination of humoral and cell-bound antibodies in 1 patient.

The dominance of CMI auto-rejection in the aetio-pathology of **BS** is further supported by a similar dominance in the aetio-pathology of EAE and adjuvant arthritis. Both of these are transferrable by washed leucocytes but not by serum. Further clinical support for this dominance is seen in:-

(1) **OPHTHALMITIS**: **BS** is just one of a group of uveo-meningo-encephalitic syndromes (see below). MS may also be included within this category for it, too, demonstrates a minor meningitis [..] and a panopthalmitis [..]. In sympathetic ophthalmia occasional patients are noted to develop both meningitis and encephalitis [..]. Experimental allergic ophthalmitis (EAO) is the animal model of sympathetic ophthalmia. EAO is again a dominantly CMI auto-aggressive disorder [..]. Occasional animals with EAO develop an allergic encephalitis and the inverse applies to EAE [..]. In one series of experiments producing EAE in monkeys, there was a frequent retinal vasculitis [..]. CMI auto-aggression is probably also important in sympathetic ophthalmia: the development of a delayed type hypersensitivity (DTH) reaction to uveal Ag is an ominous event after eye injury whereas the appearance of uveal auto-antibodies is associated with a favourable prognosis [..].

(2) **MENINGITIS**: A number of observations point to the importance of CMI auto-aggression in the aetio-pathogenesis of the **BS** meningitis. Meningitic reactions occur in both EAO and EAE. In the latter there is an early polymorph dominance and a late lympho/monocytic cell dominance just as in **BS**. Further insight is gleaned from the experiments of Smith et al [..]. These authors studied the CSF response to intrathecal injections of PPD (tuberculin). Presumably, they were inducing the equivalent of a DTH skin reaction in the meninges. The DTH reaction is considered to be an archetypal CMI response. These injections rarely

produced a significant CSF pleocytosis in tuberculin negative animals. In sensitised animals, though, there was a typical response (illustrated in idealised form in NBSFigL): there was an early and dramatic polymorphonuclear cell invasion that then resolved as it was being replaced by a more indolent and less numerous wave of lympho/monocytic cells. Thus, the meningitis seen in **BS** is, at least, consistent with a DTH reaction (and by implication consistent with a CMI auto-rejective response).



NBSFigL

In a similar vein, Boughton and Spector [..] have studied the cutaneous DTH response to tuberculin and shown that there are a number of phases in the leucocyte chemotactic response. There was an initial polymorphonuclear cell invasion that was related to the intensity of the stimulus (i.e, the tuberculin strength). This was followed by a lympho-monocytic infiltration that increased as the initial invasion of polymorphs was rapidly dissipating. In milder reactions the polymorph response was feeble. It is recognised that phagocyte mobilisation from the marrow (polymorphs and monocytes) is stimulated by a common substance, Colony Stimulating Factor (CSF). High levels favour the pronounced egress of polymorphs from the marrow [..].

3) **ORCHITIS**: Like other experimental allergic diseases, EA orchitis has a dominant, though not exclusive, CMI auto-aggressive component. During the course of EA orchitis the occasional animal develops EAE. I have not found the reverse recorded.

(4) **CUTANEOUS HYPERREACTIVITY**: The phenomenon of cutaneous hyperreactivity seen in **BS** [..] reaches a peak of activity at about 48 hrs from the time of needle puncture. This is much like the time sequence in the DTH type reaction. The first manifestations of the response appear somewhat earlier than the typical DTH reaction: this has led several investigators to look for an early humoral antibody response but this has not been demonstrated. It has already been shown that the intense tuberculin response may have a marked polymorph ingress that occurs both earlier and at a greater intensity than the subsequent lympho-monocytic infiltration. Again, this may be an expression of severity rather than a fundamentally different pathology.

(5) **HISTOCOMPATIBILITY STUDIES**: Further evidence of immune system involvement is evident from histocompatibility studies. It is now clear that there is a strong association between **BS** and the HLA B5 antigen [..]. Ohno et al [..] have suggested that the association is stronger with a subcomponent of the B5

antigen, BW51 (controls 21% and **BS** 61%). In RAU, antigens HLA A2, B12 and AW29 were more prevalent though the statistical significance of these findings is not established [..]. Two of these antigens are also more frequent in **BS** [..]. The association of the B5 antigen with **BS** is a constant feature of Mediterranean **BS** but is not so prominent in the British series [..] and has not been found in the North American series [..]. However, Lehner has shown that the immuno-genetic susceptibility to **BS** depends upon the associated clinical features. It is the components rather than the syndrome that attract the histocompatibility Ag association. Thus, ocular **BS** is associated with B5; the relative risk that patients with the B5 antigen will develop **BS** is 7. The arthritic side of **BS** is weakly associated with HLA B27 and the muco-cutaneous form shows a slight association with HLA B12.

These findings are similar to the other sero-negative arthritides where the simultaneous possession of HLA B27 predisposes towards the arthritic forms of the illness. It remains to be seen whether the encephalitis of **BS** follows the same pattern. If so, it should be associated with the neuraxial antigens, A3, B7 and DW2 (BW22 in Asians).

(b) **INFECTIVE AETIOLOGY**: Behçet favoured a viral aetiology for his syndrome. This has remained a firm favourite for investigators but it is now clear that there is sparse reward to justify this enthusiasm [..] (NBSTabM). A number of reports have appeared that claim to have demonstrated a virus. These include the microsopic visualisation of viral particles [..], the presence of neutralising antibodies to a virus [..] and serial transmissions of a virus to egg membranes and laboratory animals [..]. The greater excess of reports, however, record that no virus could be isolated by any method. Dowling [..] and Nasemann [..] have critically reviewed the viral hypothesis and both authors consider it lacks definitive proof.

NBSTabM

The evidence for a viral cause

Specimen	Host	Observation	Reference
Hypopyon fluid and ulcers	None	Inclusion bodies	Behcet (1937)
CSF	Cisterna of intraocular route in rabbits	Retinitis, uveitis with hypopyon, meningoencephalitis passed through four generations	Alm and Oberg (1945)
Vitreous and subretinal fluid (3 cases)	CAM mice rabbits	Pocks; subcultured into mice inducing encephalitis and into rabbits inducing involvement. Filterable, CF & NT antibody in 12 patients' sera 0/14 controls	Seger (1953)
Blood	CAM	Pocks	Seger (1956)
Aqueous fluid and brain suspension	CAM	Pocks; filterable agent. NT antibody in 6/11 patients' sera, 0/14 controls	Evans, Pallis and Spillane (1957)
Eye material	CAM	Pocks; NT antibody in patients' sera	Nakagawa & Shingu (1958)
Blood, hypopyon, ulcerative tissue	CAM	Pocks and inclusion bodies	Mortada & Imam (1964)
CSF	Mice	Meningoencephalitis	Noyan, Gursey & Artin (1969)

Abbreviations: cerebral spinal fluid (CSF), chorioallantoic membrane of embryonating hen eggs (CAM), neutralising antibody (NA), complement fixation (CF).

Only one report has appeared since these two reviews that claims to have isolated a causative virus [..]. There is only one traced report of conjugal affliction with the disease [..]. In general, the lack of conjugal disease conflicts sharply with the slight familial predisposition (between 3 and 5% of cases are known to be related). This is similar to minor aphthosis [..] which, coincidentally, is frequently found in the immediate relatives of patients with **BS** [..]. Where familial affliction has occurred it has tended to show a temporal and spatial coincidence that does suggest an exogenous trigger [..]. In one of these instances, the clinical presentation of the affected sisters was so similar that it raises the possibility that the genetic susceptibility might influence finer points in the presentation than just the classical triad. Familial aggregation like this, without evidence of increased conjugal affliction, is a characteristic feature of other sero-negative arthritides [..] and sarcoidosis [..].

A comparison with other sero-negative arthritides and rheumatic fever show how infection might trigger **BS**. In Reiter's syndrome a variety of infections are known to trigger the illness: these include URTIs, gonorrhoea, chlamydial infections, salmonella, shigella, Yersinia and amoebiasis. In Whipple's disease it has been suggested that the cause is an unusual susceptibility to an intracellular infection with a streptococcus [..]: the familial nature of the disease and the absence of conjugal affliction suggest that this is a highly idiosyncratic susceptibility. The same is true of rheumatic fever. Here the disease is precipitated in the wake of streptococcal infections, helped on by an inherited susceptibility Thus, the evidence to date suggests that infection may play a part in the patho-physiology of **BS** but only by inducing an idiosyncratic response to (common?) pathogens. It is unlikely that patients with **BS** would play a significant role in the natural history or contribute significantly to the infective reservoir of this putative pathogen. The only exception to this would be if the same agent was also the cause of the minor aphthoses. Whatever, it is the individuals *RESPONSE* to the infection and not the direct damage caused by the pathogen that is the most significant factor in the pathogenesis of the disorder.

A few reports have shown that there may be serological and CMI abnormalities in responses to common infective agents in **BS** [..]. Somewhat raised antibody levels to chlamydia [..], candida species and mycoplasma hominis [..] have been recorded. One of the cases I dealt with had a raised mycoplasma pneumoniae titre. Elevated antibody levels to a variety of agents is also noted in systemic lupus erythematosis and MS [..], in sarcoidosis [..] and in the Guillain Barre syndrome [..]. In the last case the authors suggested two possible mechanisms: the first that the infection was the direct trigger and the second (and preferred explanation) was that there was a change in the host's immune status favouring a minor recrudescence of latent viral (or micro-organism) activity that was consequent upon and not the cause of the underlying immunological disruption.

The interpretation of those reports that claim to have transmitted the **BS** virus to laboratory animals must remain guarded. First, the resultant animal disease bore little resemblance to **BS** in anything other than its neuraxial expression. Second, this neuraxial disease was sufficiently reminiscent of EAE to require the exclusion of this as a possible cause.

The age of *"specific aetiologies"* led, fortunately, to the discovery of many infective agents that were shown to be the cause of particular diseases. We are still largely conditioned to expect discrete agents to be the cause of all diseases [..]. However, it looks increasingly likely that pathogens pervert various facets of the immune response to their own advantage in order to usurp an otherwise insurmountable defence. The host itself causes the largest part of the consequent tissue damage and this is an inevitable response to the pathogen's continuing presence within the body tissues. In the sero-negative arthritides (and **BS** in particular) the way the host attacks its own tissues may be the result of a violent over reaction to a minor and indolent infection. This principle is well illustrated by lympho-chorio-meningitis (in the mouse). Young mice are barely compromised by the infection whereas adult mice, meeting the virus for the first time, set about destroying their own neuraxis. The lethality of this infection is dramatically reduced by immuno-suppression [..]. One salient feature worth noting here is that most viruses known to cause CNS disease have a monophasic course. They begin, worsen and then either resolve or kill the animal. The exceptions are the slow viruses that cause a progressive degeneration of the neuraxis. I know of no clear precedent in which a virus produces a chronically relapsing/remitting neuraxial illness such as is seen in MS and **BS**. The nearest

example is herpes simplex that recurs in epithelia.

(c) **VASCULITIS**: Some authors have favoured the concept that **BS** is due to a *"vasculitis"*. Many observers have recorded vessel changes such as thrombosis, intimal hyperplasia and medial or adventitial infiltration with inflammatory cells. There is perivascular round cell infiltration in most affected tissues. Fentom and Easom [..] noted that the primary ocular event was an obliterative vasculitis whilst O'Duffy et al [..] and Chajek et al [..] suggested that **BS** resulted from a necrotising vasculitis. However, the vessel walls are markedly inflamed or degenerate only in a small proportion of cases whilst in most patients the salient feature is an intense perivascular inflammation accompanied by florid leucocyte diapedesis. In milder lesions it is reminiscent of the lympho/monocytic response that is seen in the tuberculin response. It has already been observed that as the intensity of a DTH response rises, so the polymorphonuclear invasion, the prominence of thrombosis and the so called *vasculitic* features also escalate in intensity. In particular there is a shift from an almost exclusively perivenous infiltration to a periarteriolar infiltration as well. In TB this leads to intimal hyperplasia and endarteritis obliterans. In syphilitic lesions, that have many features similar to tubercular lesions, there is a frequent shift towards primary vasculitis with medial degeneration and aneurysm formation (all of which are also noted in occasional **BS** patients). Vessel necrosis is a prominent feature of hyperacute graft rejection and is not seen in immuno-suppressed animals (e.g., the nude mouse). In this accelerated form of rejection there is a shift from the more usual perivenous lympho-monocytic cell infiltrations to an arterial vasculitis with many polymorphs, medial infiltration, thrombosis, intimal hyperplasia and medial necrosis. By regarding **BS** as an auto-rejective disorder, the vasculitic features can be viewed in a fresh perspective.

The frequency of thrombotic disease in **BS** has further encouraged the proponents of the *"vasculitic"* aetiology. Note, however, that similar veno-occlusive complications are seen in Reiter's syndrome [..] and inflammatory bowel disease [..]. The clotting mechanism is not only intimately involved with CMI reactions, it has also evolved hand in glove with them. Clotting, inflammation and encapsulation are intimate cooperators even in invertebrate species [..]. Intense immune activity, especially of the CMI variety is bound to mobilise the coagulation cascade. Indeed, large amounts of anticoagulant can even inhibit the CMI response [..].

DISCUSSION:

Earlier reviewers, when discussing the neurological manifestations of **BS**, have suggested that there are several distinct variations in the way that encephalo-myelitic-**BS** presents . Pallis and Fudge [..] suggested that there were three main categories: a brain stem syndrome, a meningo-myelitic syndrome and an organic confusional syndrome. Later, Alema and Bignami [..] categorised it into a pseudo-bulbar form, a multiple sclerosis like form and a general paresis like form. Many authors have been struck by the occasional close resemblance to MS. McMenemy concluded, however, that "the resemblance to MS is little more than superficial". This opinion has persisted until recently when several Japanese papers have suggested that the clear-cut histological differences may mask an important pathophysiological relationship [..]. Indeed, the discrimination of encephalitic-**BS** from MS is less clear if we accept that the transitional scleroses are severer variants of MS. The visible differences in the foci of MS and of encephalitic-**BS** has led many to conclude they have fundamentally different pathophysiologies. I have summarised a number of articles that show that the encephalitis of MS may simply be a milder form of neuraxial auto-rejection than encephalitic-**BS**. This would be consistent with the view that MS represents the component form of the meningo-encephalitis that is associated with **BS**.

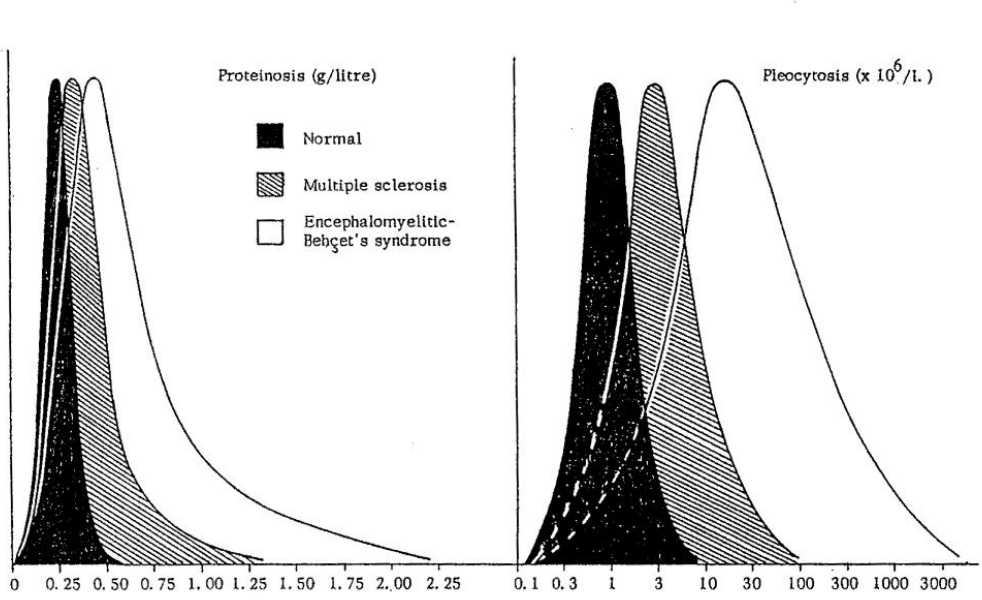
Behçet's syndrome occupies a broad swathe of the sero-negative arthritis spectrum. The borders that distinguish **BS** from its close relatives are not, in practice, precisely delineable: **BS** must, therefore, be carefully defined if its compartmentalisation is to be meaningful. There are several borders to consider: on the one hand **BS** overlaps RS [..] and on the other it overlaps Crohn's disease and ulcerative colitis [..]. The "severity border" is also imprecise: minor aphthosis needs to be distinguished from major aphthosis and the transitional scleroses need to be distinguished from the encephalitis of **BS** (this is more clear-cut). Mason and Barnes helped to define **BS** within the spectrum of the sero-negative arthritides [..]. They also placed it (partly inadvertently, I think) at the pinnacle of severity amongst the aphthoses. The adoption of Curth's

criteria would smudge this severity border. *Formes frustes* of **BS** undoubtedly occur: these are particularly noted amongst the aphthoses [..] and encephalitides [..].

So, the diagnosis of **BS** is made whilst scrutinizing the four directions from which confusion might arise. First, there is the distinction from the other sero-negative arthritides, sarcoidosis and systemic lupus erythematosis (note the latter's association with mouth ulcers): this is not always clear-cut, particularly when RS is associated with meningo-encephalitis [..]. Second, there is the distinction from the minor aphthoses and the transitional encephalitides [..]. Third, there is the distinction from syphilis: this mimics many facets of **BS** but can be excluded by serology. Fourth, there is the distinction from other uveo-meningo-encephalo-myelitides. The latter include syphilis, sarcoidosis, RS, sympathetic ophthalmia, Vogt-Koyanagi Harada syndrome, Devic's and Eale's disease. RS is the only one of these disorders that regularly presents with aphthous ulceration. For this reason, I believe it is sensible to modify Mason's and Barnes' criteria so that the major criterion "iritis" is expanded to include any part of a "uveo-encephalo-myelitis".

A number of features of the encephalitis of **BS** have close parallels with MS. For instance the age incidences of the two are essentially identical. The demyelinating diseases that occur in Japan and other oriental countries demonstrate a spontaneous drift towards neuraxial necrosis (*tendence necrotique*) and the transitional scleroses are more common here [..]. There are more reports describing uveo-meningo-encephalo-myelitic disorders originating from the orient than other areas [..]. As in MS, environmental factors appear to affect the prevalence of **BS**. One survey searched for **BS** in the Japanese population of Hawaii. No cases were found. A search through an equivalent ethnic cohort living in Japan should have found 15 cases [..]. Around 3-5% of the **BS** patients reported in the world literature had a relative who also had **BS** [..]. Overall, 4.8% of the encephalitis group had a family member with **BS**. In just two of these (2%) each sibling had an encephalitis [..]. MS, also, is more prevalent in the families of (MS) affected individuals than in the general population. Familial MS is reported in about xx% [..]. (We might, therefore, expect to find a similarly raised incidence of MS in the families of patients with encephalitic-**BS** much as RAU is commoner in the families of patients with **BS**. I'm not aware that this has been reported: the prevalence could be about 1 in 100. The inverse, that is **BS** in an MS patient's family, would not apply!)

MS does have a meningitic component but, because it is slight, it is usually overlooked. It is readily apparent at autopsy [..]. The meningeal surfaces most affected are similar to those in encephalitic-**BS** but substantially less severe. This is reflected by the mild though constant pleocytosis that occurs in MS (idealised in NBSFigM).



NBSFigM

The clinical courses of the two disorders share many similarities. The onset, the distribution between progressive and relapsing/remitting forms, the relative rarity of the progressive form (from the outset) in pre-menopausal women and its predilection for being progressive (from the outset) in older patients (their average age was just under 40) are features common to the two disorders. The incidence of monophasic disease (3%) and the marked tendency towards a *"locus minoris resistentiae"* are also typical of both. Whilst MS is commoner in women the outlook tends to be more bleak in men (NBSFigN). This reflects the higher mortality among males with encephalitic-**BS**. Note that, like the slight female preponderance in MS, minor aphthosis is slightly more common in women than in men [..]. Once again we see that the apparent difference of encephalitic-**BS** from MS may be explained on the basis of severity and reflects the greater susceptibility of males to the severer forms of disease.

NBSFigN not yet completed

The clinical pattern of their respective neurological disturbances is also similar. The major distinctions are: a higher incidence of onset with paresis in **BS** (a characteristic of poor prognosis MS!); a moderate incidence of extrapyramidal features in **BS** (signs of this are uncommon in MS though basal ganglia foci -plaques- are relatively common); a higher incidence of epilepsy; a higher incidence of coma and stupor (reflecting the severity of brain stem disease in **BS)**; and a low incidence of positive sensory phenomena (e.g., dysaesthesiae and only one report of l'Hermitte's sign [..]). Other differences, that can probably be regarded as expressions of either disease severity or of disease duration, include paretic asymmetry, severe dementia and a lower incidence of cord disease. Note that headache is a common symptom of MS [..], as is mild dementia [..] and focal cortical disease [..]. The lower incidence of positive dysaesthesiae in **BS** may be due to the greater tendency to neuraxial destruction in **BS**(the lesions of MS being irritative rather than destructive). Psychiatric disturbances similar to those noted in **BS** are also reported in MS [..]. These may relate to the mild diffuse component of the neuraxial inflammation seen in **BS** [..] and, probably, also in MS [..].

About a third of patients who develop optic neuritis will at some time also develop MS. A tortuous calculation suggests that the situation may be similar in **BS**. Here is the argument. Mavioglu reported the incidence of optic neuritis in all cases of **BS** to be about 15%. In encephalo-myelitic-**BS** the incidence of optic neuritis is about 20%. So, if up to 25% of all patients with **BS** develop an encephalitis, 20% of these will have coincident encephalitis and optic neuritis (i.e., 5% of all patients with **BS**). Thus, one third of all **BS** patients who develop optic neuritis will also develop an encephalitis (i.e., 5% divided by 15%). There are assumptions and pitfalls in this argument but the comparison is interesting nonetheless.

Periphlebitis retinae (about 10% incidence) and iritis (about 4% incidence) are both associated with MS [..]. The same features occur in **BS** though the pathological tempo is much greater than in MS. These ocular disturbances occurring in MS, together with its very mild meningitis, warrant inclusion of MS within the uveo-meningo-encephalo-myelitides. Transitional forms in the putative MS/encephalitic-**BS** spectrum may be represented by Eale's disease [..], Devic's syndrome [..] and other transitional scleroses [..]. Singal and Dastur reported a series of 11 patients with Eale's disease and neurological involvement [..]. They proposed that the CNS disturbance was a demyelinating disorder. The CSF changes were intermediate to those noted in MS and encephalitic-**BS** (NBSFigM). This is also true for Devic's syndrome: there is one report of a patient with a CSF pleocytosis of $3000x10^6$/l and this patient showed a dominance of polymorphonuclear forms [..]. A rise in CSF gamma globulin is common to all these disorders. There are a number of reports of an encephalitis that is histologically similar to **BS** but in that there were no symptoms to warrant the diagnostic label of **BS** other than ocular and neuraxial involvement [..]. Similarly, there are case histories of patients with apparent MS who have uveitis and meningitis [..]. In general, the rarity of reports of these intermediate forms probably reflects their diagnostic anonymity, since, in the instances where these intermediate forms are reported [..], they are based upon personal series of patients. These numbers greatly exceed the expected number of personal cases of encephalitic-**BS** that are likely to have been observed by one centre.

Superficial visual resemblances between the foci of MS (plaques) and those of encephalitic-**BS** are notably lacking. However, a deeper inspection reveals considerable continuity. Adams [..] reviewed the pathological

changes during the onset and progression of MS lesions. As in encephalitic-**BS** the dominant changes are perivascular and multifocal. There is a widespread perivenous infiltration with round cells that is followed, in some areas, by perivenous demyelination. Some of the perivascular infiltrates become focally severe and develop by a process of local demyelination, confluent accumulation of foci and subsequent diffusion of the globulin plaque to produce the definitive lesion of MS. Maturation of this lesion is accompanied by glial scarring. Axis cylinder preservation within the plaque is almost invariable and it is only in the severer variants of MS (the transitional scleroses) that actual tissue necrosis occurs. In these disorders necrosis often leads on to cavitation. The evolution of foci in encephalitic-**BS** is similar though the trend within them is now towards almost complete tissue destruction (necrosis). This is not, however, invariable. Indeed , the metamorphosis from an MS like lesion to that of **BS** is illustrated in several reports [..]. There is one reported case of **BS** in which there were lesions typical of **BS** in the hemispheres and lesions typical of MS in the cord [..].

The distribution of the focal lesions in MS and encephalitic-**BS** show many similarities. In **BS** there are both new lesions (necroses) and old ones (glial scars or nodules). In **BS** fresh lesions are rarely observed in the cerebellum (one case only [..]) but this is also true of early MS [..] (remember, most autopsy cases of encephalitic-**BS** die early in the course of their disease). In **BS** old cerebellar lesions are more common. In MS the older lesions are visually dramatic due to the plaque of demyelination diffusing outwards from the focus. Not only is the severity of focal lesions (necroses) more severe in **BS** but the rate of relapse also appears to be higher. In encephalitic-**BS** there were just under 2 per year whilst in MS they average 0.3 per year.

The clinical manifestations of MS, except for secondary complications like UTIs, are largely confined to the neuraxis. Several observers have, however, suggested that MS might be part of a wider systemic disorder. Abb and Schaltenbrand (ref quoted from Kurtzke [..]) described pseudo-rheumatic complaints in 28% of patients presenting with MS. Lumsden noted an increased incidence of infective skin conditions in patients who had recently developed MS [..]. This is faintly reminiscent of the pustular complications of **BS** The serum proteins in MS are usually normal but computer analysis of multiple results shows a characteristic increase in alpha-2- and gamma-globulins. This is similar to, though less intense than, the changes seen in **BS** and other systemic disorders (e.g., SLE).

A miscellany of other observations are of interest. Fibrinogen levels have been reported to be elevated in exacerbations of MS [..] and anticoagulants have enjoyed a transient vogue in the treatment of MS [..]. Recent reports have suggested that there may be subtotal villous atrophy in both MS and in RAU [..]. MS and ankylosing spondylitis are believed to be significantly associated conditions [..]. Relapses of **BS** are sometimes recorded at menstruation [..] and there are several reports that suggest it may improve during pregnancy [..]. This pattern is fairly typical of inflammatory bowel disease [..], RAU [..] and probably also MS [..]. In these conditions, menstrual exacerbation, second and third trimester remission and puerperal relapse are commonly noted. Pregnancy has no overall adverse effect on the progression of the disease: exacerbations are stretched over one stage (the second and third trimester) only to be squeezed into the next (the puerperium). Peripheral nerve abnormalities have been described in MS though these are relatively mild and always symptomless [..].

One of the cases I was personally involved with had an apparent anterior spinal artery syndrome. Suchenwirth described an arterially distributed spinal disturbance in his patient [..]. The pathophysiology of this sort of presentation is of interest for it does not conform to the pattern of small sporadic foci of necrosis. Two explanations are possible. The obvious one is that it is simply due to thrombosis. Thrombosis is certainly observed within other tissues in **BS** [..]. The second is more tortuous. The sero-negative arthritides have a variety of phenomena that can be considered as *"loci minoris resistentiae"* (places of lesser resistance). These are often precipitated by some unrelated damaging process that initiates a focal inflammation. What follows is a runaway inflammation that has features typical of the underlying disorder. The Koebner phenomenon, the hypersensitivity reaction in **BS**, the appearance of erythema nodosum at areas of trauma and the focal precipitation of skin nodules in adjuvant arthritis [..] are all examples. It may be that minor ischaemia precipitates a runaway inflammation of accreting foci within the distribution of the compromised blood vessel.

The cause of the pseudotumour cerebri syndrome associated with **BS** is not obvious. It is likely that normal pinocytotic resorption of CSF is impaired rather than that there is an increased secretion. The higher incidence of thrombosis in this group tentatively suggest a veno-occlusive cause.

CONCLUSION:

The neurological complications associated with **BS** have been reviewed. The most significant associations are pseudo-tumour cerebri and meningo-encephalo-myelitis. The latter is a multifocal perivascular encephalitis (usually perivenous) that shares many similarities with the severer forms of experimental allergic encephalitis. It is argued that a continuum of disease exists, from the pathologically more indolent encephalitis of **MS** through to the destructive encephalitis seen in **BS**. In this sense, **MS** represents the isolated component form of an auto-rejective disorder that, when it occurs in the course of **BS**, is pathologically more intense. **MS** probably bears the same relationship to the encephalitis of **BS** that common recurrent aphthous ulceration bears to the aphthous ulceration seen in the course of **BS**.

TABLES A-L FIGURES A-O 11,104 words on 17/1/86