distributions of symptoms at the first examination were very similar for the two groups.

The results for the patients who reported on each of the three days are shown in Table II. On each day the proportion recovering was slightly smaller in the treated than in the control series, but none of the differences is statistically significant.

TABLE II.—*Results for Patients who Reported on Each of Days 1, 2, and 7*

	Day 1		Day 2		Day 7	
	Treated	Controls	Treated	Controls	Treated	Controls
Cured ..	6	9	56	68	168	163
Improved ..	208	215	213	203	121	120
No effect ..	165	142	110	95	90	83
Total ..	379	366	379	366	379	366
% cured:						
Treated ..	1·6		14·8		44·3	
Controls ..	2·5		18·6		44·5	
Difference ..	−0·9		−3·8 ± 2·7		−0·2 ± 3·6	
% cured and improved:						
Treated ..	56·5		71·0		76·3	
Controls ..	61·2		74·0		77·3	
Difference ..	−4·7 ± 3·6		−3·0 ± 3·3		−1·0 ± 3·1	

The experience of the patients with incomplete records is shown in Table III. In this group the controls also showed a statistically insignificant advantage over the treated.

TABLE III.—*Results for Patients with Incomplete Records*

	Day 1		Day 2	
	Treated	Controls	Treated	Controls
Cured	8	9	31	39
Improved	169	191	127	142
No effect	141	144	87	68
Total ..	318	344	245	249
% cured:				
Treated	2·5		12·7	
Controls	2·6		15·7	
Difference	−0·1		−3·0 ± 3·1	
% cured and improved:				
Treated	55·7		64·5	
Controls	58·1		72·7	
Difference	−2·4 ± 3·9		−8·2 ± 4·2	

No direct or indirect questions were asked concerning possible side-effects. The number of patients who had conditions which they attributed to the treatment was too small for detailed analysis, for only 14 in the treated group and 13 in the control group complained that the tablets had any adverse effects. Most of the symptoms described could in fact have been symptoms of the cold.

Conclusion

A large-scale trial of antistin failed to show that this drug had any effect on the course of the common cold.

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EARLY CLINICAL MANIFESTATIONS OF DISSEMINATED SCLEROSIS

BY

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The object of this investigation was to determine which clinical features of disseminated sclerosis are of most diagnostic value, with special reference to the paramount importance of early recognition. The report is based on an analysis of 389 cases of disseminated sclerosis, 79 of which were investigated in a medical ward in the Western Infirmary, Glasgow.

Although not directly concerned in this report with the aetiology of disseminated sclerosis, we would suggest, as does McAlpine (1946), that the evidence in favour of the infective nature of the disease is increasing. Such a contention is strengthened by the recent work of Steiner (1941) and of Margulis and his associates (1946). Campbell and his colleagues (1947) and Campbell (1947) re-emphasize the possible relationship between disseminated sclerosis and agricultural exposure, previously referred to by Morawitz (1904), Steiner (1918), Dreyfus (1921), Adams (1923, 1927), and Wilson (1927).

The diagnosis of disseminated sclerosis at an early stage is important from the point of view of treatment. If therapeutic measures are to be of benefit they must be employed before irreparable damage has been inflicted on the central nervous system. This will be equally true if and when the causal agent is known and specific treatment is available for its eradication. As stressed by one of us in 1923, the ideal hope for the future lies in prevention of infection of the individual by detecting the mode of transmission. Ferraro (1944) has suggested that, once the initial aetiological basis is established, additional factors, such as the development of antigens from the white or grey matter, may play a part in the progress of the disease or in its exacerbations. Bailey and Gardner (1940) have shown that antigenic substances can be derived from myelin sheaths. If such an allergic reaction should indeed occur the importance of early diagnosis and treatment is obvious. The most satisfactory standard of diagnosis will entail recognition of the disease at a monosymptomatic stage.

This standard cannot be achieved, however, until disseminated sclerosis is made known to the general public. It is surprising how infrequently the patient communicates the first symptom to a doctor. Unless the lay public are taught to appreciate the potential significance of such symptoms as temporary weakness in a limb, transient dimness of vision, and diplopia the latter part of Buzzard's (1897) criticism, "the full-grown disease is frequently not recognized, the infant disease practically never," must remain justified.

Early diagnosis depends on proper appreciation of the disease process. We would like to stress the concept that in its early stages disseminated sclerosis is a functional nervous disorder. It was emphasized by Head (1920) that "all disease of the nervous system manifests itself

in loss of function." "Functional" is not the antithesis of "organic," and is not a euphemism for "hysterical." Experience has shown that certain signs depend, commonly, on the destruction of particular parts of the nervous system. It must be appreciated, however, that these are, *per se*, signs of deranged function. In the early stages of disseminated sclerosis they may not be proof of irreversible changes in the central nervous system. Since it is perhaps only at this stage that complete cure can be hoped for, the disastrous policy of waiting for multiple signs and symptoms to become apparent is at once obvious. This paper is mainly concerned with emphasizing those symptoms and signs which appeared first in our series, with a view to the earliest possible recognition of the disease.

Diathesis of the Patient

An important aspect of the clinical recognition of disseminated sclerosis is an appreciation of the type of individual most often attacked by the disease. In the past there has been a tendency to study disseminated sclerosis from the point of view of the "seed" to the exclusion of the "soil." The causal agent of what is almost certainly an infective process may be extensively distributed in nature. The occurrence of the disease in a clinically recognizable form would then be conditioned by personal susceptibility, predisposing factors, or exposure to an overwhelming infection. Such a hypothesis presupposes the existence of subclinical forms of disseminated sclerosis. This possibility has been referred to by Schaltenbrand, and quoted by McAlpine (1946). As in neurosyphilis, there can be little doubt that disseminated sclerosis may exist in an asymptomatic form.

In one case in our experience a paretic curve to colloidal gold was noted in a pensioner suffering from hysteria and showing no clinical evidence suggestive of an organic basis. Four years later loss of the abdominal reflexes was noted. Six years after the colloidal-gold observation had been recorded the patient was admitted to hospital suffering from unmistakable disseminated sclerosis.

With regard to personal susceptibility, disseminated sclerosis occurs most commonly in the sympatheticotonic type of individual. This view has been expressed by Adams, Blacklock, Dunlop, and Scott (1924) and by Adams and Sutherland (1948). As pointed out by Purves-Stewart (1945) in another connexion, sympatheticotonia may be localized. McAlpine (1946) suggests that sympathetic stimulation, by causing a vascular disturbance in the central nervous system, may in some instances be responsible for the appearance of clinical signs. It is not unreasonable to suppose that the effects of such stimulation will be most marked in sympatheticotonic individuals. The occurrence of the disease in patients with a frankly vagotonic diathesis is rare in our experience.

In this series the occurrence of the disease in more than one member of a family has been exceptional. This was also the experience of Risien Russell (1910), Bramwell (1917), Adams (1923), and Wilson (1940). On the other hand, Curtius (1933) found more than one case of disseminated sclerosis in 6 out of 56 families investigated. McAlpine (1946) found a familial incidence in 5% of 143 cases, and Brain (1947) considers that some 5–10% of cases of disseminated sclerosis have a near relative similarly affected. In one case in our series, from a mixed farm in Ayrshire, the patient's father and uncle had died from disseminated sclerosis, whilst his cousin living on an adjacent farm was probably similarly affected. This series of four cases shows common familial and occupational factors.

Predisposing Factors

In 127 cases (32.6%) one or other of four factors preceded the first symptoms of disseminated sclerosis by a short period of time. In no instance did this exceed six months. By so doing, they might reasonably be regarded as predisposing to the illness. These factors were febrile illness (14.4%), trauma (10.5%), pregnancy (4.5%), and emotional upset (2.8%). The association of one of them together with a symptom such as weakness in a limb or diplopia should suggest the possibility of disseminated sclerosis.

Infection

A relationship between disseminated sclerosis and infection has been noted by many workers. Head (1920) observed that disseminated sclerosis not unusually begins with short attacks of what is called "influenza." Bramwell (1917) found this relationship in 28 of his 200 cases (14%). Wilson (1940) and McAlpine (1946) suggest 5% as the possible figure. As a transitory febrile illness may be readily forgotten by the patient, the value of statistical evidence on this point is difficult to assess. Brain (1947) grants that such an illness may be reasonably regarded as a predisposing factor, but considers the cause of the pyrexial reaction to be unknown. Collier and Adie (1933) emphasized the possibility that in some cases this reaction may be a febrile phase of disseminated sclerosis itself.

By analogy with syphilis it was thought that a febrile onset might be associated with a long latency of infection subsequent to the initial manifestation. Thus, Mattauschek and Pilcz (1913) and Browning and Mackenzie (1924) have observed that the course of syphilitic infection may be modified by an intercurrent infection. This possibility was investigated by relating the mode of onset to the duration of the period before the patient presented for treatment. The results obtained suggest that a febrile onset does not materially influence the subsequent course of the disease with regard to latency of infection or progression of the disease process. Of the 56 cases which gave a history of febrile onset, 13 (23.2%) presented for treatment within one year of the first recognizable manifestation of the disease, and 35 (62.5%) within five years. In the 293 cases in which no history of febrile illness was obtained the corresponding figures were 56 (19.1%) and 173 (59%).

Trauma

In 41 (10.5%) of the 389 cases there was a history of either accidental or surgical trauma occurring shortly before the first manifestation of disseminated sclerosis. In a further considerable number of cases a history of trauma preceding an exacerbation was obtained.

This relationship is noted, amongst others, by Marie (1895) and by Adams, Blacklock, Dunlop, and Scott (1924). It appears to exist in 5–10% of cases of disseminated sclerosis (Brain, 1930, 1947). Thus Bramwell (1917) noted the influence of trauma in 17 (8.5%) of 200 cases, von Hoesslin (1934) in 59 (11.4%) of 516 cases, and McAlpine (1946) in 8 (5.6%) of 142 cases.

The mode of action of peripheral trauma as a predisposing factor is not known and the various theories will not be discussed. It is worthy of mention, however, that Browning and Mackenzie (1924), observing that the existence of latent periods in disease is not peculiar to syphilis, consider that trauma may give rise to disturbed relations between the patient and organisms which have already been present for some time without causing an active lesion. In disseminated sclerosis it is possible that trauma may act by adversely influencing the antigen–antibody balance

mechanism in the central nervous system. Klauder (1947), investigating the relationship of trauma and herpes zoster, has afforded some evidence that trauma may light up a latent virus infection.

Pregnancy

The first symptoms of disseminated sclerosis occurred after childbirth in 19 (8.8%) of the 216 female cases. Many authors have referred to the deleterious effect pregnancy and parturition have on this illness. Mention of this is made by Gowers (1893). Risien Russell (1910) observed that pregnancy or parturition may be responsible for relapses or more rapid progress of the disease, and stated that the first symptoms of the malady are not infrequently observed in these instances.

The National Multiple Sclerosis Society (1947) considers that the onset of the disease or a relapse is precipitated in about 40% of female patients who become pregnant. Walshe (1947) refers to the possible ill effects of pregnancy on disseminated sclerosis, but considers that it is not uniformly deleterious, while Wilson (1940) emphasizes the difficulty of establishing a causal nexus between the two. We would suggest that pregnancy in disseminated sclerosis should be regarded as avoidable trauma, and that the occurrence after parturition of a symptom referable to dysfunction of the central nervous system calls for the closest clinical examination.

Emotional Upset

An emotional upset such as grief, worry, or fright preceded the onset of disseminated sclerosis by a short period in 11 cases (2.8%). This relationship has been referred to by Risien Russell (1911), Bramwell (1917), McAlpine (1946), the National Multiple Sclerosis Society (1947), and Adams and Sutherland (1948). Emotional upset may act by "accentuating or evoking phenomena previously existing" (Risien Russell, 1910) or by "reducing resistance" (Wilson, 1940). Emotional reaction may produce stimulation of the sympathetic nervous system, resulting in localized vascular phenomena. It is important to note that in this series patients were not questioned specifically about the occurrence of an emotional upset. The 11 cases concerned volunteered the information, and a note to this effect was made in the case record.

Age and Sex Incidence

Only the age incidence can be regarded as being of diagnostic significance. As will be seen from Table I, 271 (69.7%) cases were in the third and fourth decades of life. It is relatively infrequent for the first symptom of disseminated sclerosis to occur in a patient under 20 or over 45 years of age.

TABLE I.—*Age Incidence at Onset of Disease in 389 Cases of Disseminated Sclerosis*

Age at Onset in Years	Private Series		Hospital Series		All Cases	
	No.	%	No.	%	No.	%
Under 20	22	7·1	5	6·3	27	6·9
20–24	48	15·5	10	12·6	58	14·9
25–29	56	18·0	19	24·1	75	19·3
30–34	61	19·7	19	24·1	80	20·6
35–39	46	14·8	12	15·2	58	14·9
40–44	33	10·7	11	13·9	44	11·3
45–49	14	4·6	1	1·3	15	3·9
50	11	3·5	2	2·5	13	3·3
Not stated	19	6·1	—	—	19	4·9
Total	310	100	79	100	389	100

In this country female cases slightly predominate. Our figures of 216 (55.5%) female cases and 173 (44.5%) male cases are in accordance with results previously reported by Bramwell (1917), Adie (1937), Wilson (1940), and Brain (1947). Neither the age nor the sex of the patient was found to influence materially the initial symptomatology, with the exception that retrobulbar neuritis predominated in the younger age groups and motor weakness in the older. Thus in the 20–29 years age group of 133 patients, 28 (21%) suffered from transient loss or dimness of vision as a first symptom. In comparison, the 40–49 age group of 59 cases had four cases (6.8%) so affected. Similarly, paresis of one or more limbs was the initial manifestation of the disease in 61 (45.9%) cases in the 20–29 years age group, and in 37 cases (62.7%) of the 40–49 years age group.

Symptomatology

As emphasized by Adie (1932), the onset of disseminated sclerosis is sudden, if by "onset" the appearance of the earliest symptom is referred to. The first symptom is generally attributable to a single lesion in the white matter of the central nervous system. In most cases the initial symptom, after persisting for a variable time, disappears. This is followed by a more or less complete remission, during which time the patient feels in normal health.

An appreciation of those symptoms which suggest the onset of disseminated sclerosis is of fundamental importance. The earliest manifestations in 389 cases are recorded in Table II. It is apparent that the common early symptoms are weakness in one or more limbs (51.4%), visual upset (26.8%), paraesthesiae (8.7%), vertigo (3.8%), and upset of micturition (2.8%). One or other of these symptoms was the earliest manifestation of disseminated sclerosis in 93.5% of cases. The figures obtained differ in no significant manner from those previously recorded by Wilson (1940), who reviewed the initial symptomatology in 539 cases from four series.

TABLE II.—*Initial Symptoms in 389 Cases of Disseminated Sclerosis*

Symptoms	No.	%
Weakness in one lower limb	90	23·1
Weakness in both lower limbs	73	18·8
Temporary dimness or loss of vision in one eye	54	13·9
Diplopia	50	12·9
Paraesthesiae	34	8·7
Weakness in one upper limb	19	4·9
Weakness in one lower and one upper limb	16	4·1
Vertigo	15	3·8
Upset of micturition	11	2·8
General debility; exhaustion; weakness	4	1·0
Mental confusion; inability to concentrate	3	0·8
Pain in leg(s)	3	0·8
Pain in back	3	0·8
Weakness in all four limbs	2	0·5
Epileptiform attacks	2	0·5
Dysarthria	2	0·5
Unilateral facial paralysis	2	0·5
Loss of sensation over side of face; weakness of mastication	2	0·5
Staggering gait	2	0·5
Vomiting	1	0·3
Nervousness	1	0·3

We should like to make further reference to the occurrence of acute retrobulbar neuritis in disseminated sclerosis. Owing to the long remission which may follow transient dimness or loss of vision in one eye, the accuracy of statistical evidence on the subsequent development of disseminated sclerosis after retrobulbar neuritis is difficult to assess. Gunn (1904) found that of 233 cases of primary retrobulbar neuritis 51 (21.9%) were due to disseminated sclerosis. Marburg (1920) reported that 14 (58.3%) out of 24 cases of retrobulbar neuritis subsequently developed disseminated sclerosis. Weill (1923) investigated 22 cases of retrobulbar neuritis; 12 were found to be suffering from disseminated sclerosis, and a further five subsequently developed the disease.

Adie (1932) examined 70 cases of retrobulbar neuritis within one or two weeks of onset. He found 31.3% of

these cases to be suffering from disseminated sclerosis, and in a further 41.8% the diagnosis was probably disseminated sclerosis. Thus in only some 26.8% was there no other suspicious symptom and no definite sign of organic nervous disease. Adie (1929) emphasized that "there is only one known, proved, common cause of this condition, and that is disseminated sclerosis." This fact was previously stressed by Adams (1927). We would suggest that as the primary chancre or secondary rash of syphilis need not portend neurosyphilis, so retrobulbar neuritis need not progress to widespread involvement of the central nervous system. It is nevertheless probable that almost every case of otherwise idiopathic retrobulbar neuritis is due to the causal agent of disseminated sclerosis.

Emphasis has rightly been placed on those initial symptoms which occur most commonly, and, by so doing, to some extent suggest the diagnosis. We would stress, however, that in some 5% of cases the first symptom may not in itself be suggestive of the onset of disseminated sclerosis. Thus we have encountered, as the first manifestation of the disease, mental confusion, pain in the back, pain in legs (each three cases, 0.8%), epileptiform attacks, facial paralysis, loss of sensation over side of face, dysarthria, and staggering gait (each two cases, 0.5%).

Potential Relationship Between Occupation and Initial Symptoms.—This aspect was investigated, but with the exception of brain workers difficulty was experienced in classifying the occupation of the 389 patients into clear-cut divisions. It is interesting, however, that the clearly defined group of brain workers showed the highest incidence of retrobulbar neuritis. It is known that in tabes dorsalis occupational overstrain of the eyes predisposes to optic atrophy.

Potential Relationship Between Initial Symptoms and Latency of the Disease.—Adie (1932) observed that very long remissions "up to 20 years or more" are not uncommon where retrobulbar neuritis is the first symptom. He considers, however, that similar remissions are not common after other modes of onset. This question was investigated by relating initial manifestations to the duration of the period before the patient reported for treatment. In some instances this period will refer to the rate of progress of the disease rather than to absolute latency of infection. Despite this, it seemed to constitute a reasonable basis for investigation.

A latent period of 15 years or more followed the initial symptoms in 31 cases (7.9%). The only initial symptoms to be followed by a latent period of such duration were dimness or loss of vision in one eye in 8 cases (14.8%), paresis in 19 (9.5%), and diplopia in 1 (2%). It would therefore be reasonable to suppose that, since these symptoms may be followed by such a long latent period in some instances, they may be the sole manifestation of disseminated sclerosis in a lifetime. As Adie (1929) suggested in connexion with retrobulbar neuritis, "If a remission should last for 24 years, why not 54?" It should therefore be stressed that a prolonged remission following the initial symptom does not in any way invalidate the diagnosis of disseminated sclerosis. A further manifestation may occur at any time, or the remission may last for a lifetime.

Later Symptomatology.—Table III lists the main symptoms in 389 cases on presenting for treatment. Most of these patients were suffering from multiple symptoms; in a few instances the disease was fully established. A noticeable feature is the frequency with which upset of micturition occurs in the later stages of the disease. As an initial symptom bladder control was defective in only 11 cases (2.8%). In comparison, on presenting for treatment 173 patients (44.5%) complained of some defect of micturition. In view of the nature of this paper further discussion on late symptomatology is unnecessary.

TABLE III.—*Main Symptoms in 389 Cases of Disseminated Sclerosis on Presenting for Treatment*

Symptoms	Patients Affected No.	%
Paresis of limb(s)	368	94·6
Upsets of micturition	173	44·5
Paraesthesiae	135	34·7
Diplopia	84	21·6
Dimness or loss of vision	57	14·7
Vertigo	32	8·2
Facial paralysis	12	3·1
Pain in legs	11	2·8
Pain in back	10	2·6
General debility	10	2·6
Headache	8	2·1
Disorder of speech	6	1·5
Loss of sensation over one side of face	4	1·0
Vomiting	3	0·8
Deafness	3	0·8
Epileptiform attacks	2	0·5
Difficulty in swallowing	2	0·5
Mental confusion	1	0·3

Examination of the Patient

It would be reasonable to suppose that, in the early phases of disseminated sclerosis, signs which by custom we speak of as being "organic" are minimal. As previously emphasized, however, these signs are in reality evidence of disturbed function and not of structural change. Thus even in the earliest stages of disseminated sclerosis signs occur which are of fundamental importance in differentiating the disease from hysteria. This difficulty in distinguishing early disseminated sclerosis from hysteria was stressed by Buzzard (1897) in the following words: "In its infancy . . . the name given to disseminated sclerosis is hysteria.' Further, it must be remembered that in all the phases of disseminated sclerosis hysterical manifestations complicate the clinical picture. Brain (1930) has observed that hysterical symptoms occur more often with disseminated sclerosis than with other organic diseases of the nervous system.

The physical findings which will be referred to are largely based on the result of examination of cases in the hospital series. The majority of these patients were in the oligosymptomatic stage of disseminated sclerosis. We are of the opinion that these signs occur and are of equal significance in the earlier phase of the disease.

1. Mental State of the Patient

The frequent hysterical overlay in cases of disseminated sclerosis has already been mentioned. Cottrell and Wilson (1926) stressed as being of diagnostic importance the triad of change in prevailing emotional disposition, change in emotional expression and control, and change in sense of physical well-being. Since available records were inadequate, no statistical analysis of this aspect was undertaken. Our impressions, however, are in accordance with the conclusions of these authors.

2. Neurovascular Phenomena

Vasomotor symptoms are common in patients with disseminated sclerosis. Thus cold hands and feet, acroparaesthesiae, and chilblains are often encountered. Erythromelalgia occurred in one case. Purves-Stewart (1945) observes that this condition may be one of the earliest signs of organic spinal cord disease such as disseminated sclerosis.

We have been impressed by the fact that weakness in a limb is often associated with a lowered skin temperature in that limb. It is possible that cutaneous angioneurosis may be an expression of "the soil" which predisposed to the development of disseminated sclerosis. Vasomotor instability of the extremities in disseminated sclerosis has also been referred to by Langworthy (1948).

3. The Eyes

We have found that three ocular signs have an important diagnostic value in disseminated sclerosis. This triad consists of imbalance of the ocular muscles, mydriasis, and hippus.

The ocular imbalance does not amount to strabismus, which in our experience is infrequent; it rather suggests a somewhat dissociated action of the extrinsic muscles of the eyes.

The pupils are generally larger than the average. In only five cases (6.3%) of the hospital series were the pupils myotic. Associated with this is the fact that the pupils are unduly mobile. The reaction to light is generally brisk. In only two cases (2.5%) was the light reflex absent. Similarly, the reaction of the pupil to near vision was found to be brisk in 74 cases (93.7%). The occasional occurrence of paralysis of accommodation has been referred to by Kinnier Wilson (1940), and was observed in three cases (3.8%) of the hospital series. In no instance were the requirements of the Argyll Robertson pupil fulfilled.

In a considerable number of cases the phenomenon of hippus was observed. Lagrange and Marquezy (1924) have referred to the occurrence of hippus in disseminated sclerosis, but it is felt that its presence is not accorded enough importance in textbooks or in teaching.

Gowers emphasized the difficulty in distinguishing between cases of disseminated sclerosis and neurosyphilis. We would suggest that the association of ocular imbalance, mydriasis, and hippus in disseminated sclerosis is of considerable importance in the differential diagnosis of these two conditions. With regard to other ocular manifestations, the pupils are not infrequently unequal and sometimes irregular. Nystagmus occurred alone or in combination with other components of Charcot's triad in 38 (47.9%) of the 79 hospital cases. The "characteristic" ophthalmoscopic picture is that of pathological pallor of the temporal half of the optic-nerve head. Such was found in only 13 (16.5%) of the hospital series. This figure is very low compared with that of "over 50%" suggested by Brain (1947). It closely approximates, however, to the incidence of symptoms referable to retrobulbar neuritis which occurred in 13.9% of the total series as a first symptom. Further, it is our experience, as it was of Adie (1932), that retrobulbar neuritis occurs relatively infrequently after the disease is established. In our series pathological temporal pallor of the optic disk was not present in a high proportion of cases; the absence of this feature should in no way cast doubt on this diagnosis.

4. Knee-jerks

Of the various tendon reflexes, particular diagnostic importance attaches to the knee-jerks. These were regarded as normal in only 7 (8.9%) of the 79 hospital cases. The knee-jerks were unequal in 36 patients (45.5%). In no patient in this series were these reflexes abolished.

5. Abdominal Skin Reflexes

In the diagnosis of disseminated sclerosis the importance of the abdominal skin reflexes is evident from the fact that they were abnormal in 77 patients (97.4%) in the hospital series. They were present normally in only two instances. In 69 cases (87.3%) there was bilateral loss of the reflex; in three (3.8%) unilateral loss was reported, and in five (6.3%) the abdominal reflexes were regarded as being readily exhausted.

The importance of the absent abdominal reflex was noted by Risien Russell (1910). Strümpell is quoted by him as finding them absent in 67% of 24 cases of disseminated sclerosis, compared with 13.5% in 185 persons with normal nervous systems. In Probst's series, quoted by Russell, the abdominal reflex was absent in 73% of cases. "The almost constant absence" of this reflex was emphasized by Adams (1921). Kinnier Wilson (1940) considered that suspicion of disseminated sclerosis should be attached to a case in which the abdominal reflex can be tired. Similarly, Purves-Stewart (1945) stresses the significance of absence or diminution of the reflex on one or both sides. Further, we would suggest that disseminated sclerosis should be suspected in a young patient whose abdominal reflexes do not share in the overactivity of the knee-jerks, should this latter abnormality be present.

Böhmig (1922), analysing 155 cases, considered that the addition of any single nervous physical sign to the combination of spastic phenomena in the lower limbs and the loss of the abdominal reflexes justifies the diagnosis of disseminated sclerosis, syphilis being excluded. This view is undoubtedly correct. It is emphasized, however, that spastic phenomena in the legs are not essential to the diagnosis. In a young adult the presence of a sign or symptom referable to a lesion in the white matter, associated with any of the abnormalities of the abdominal skin reflex mentioned above, should arouse suspicion of disseminated sclerosis. Wartenberg (1944) considers that the abdominal muscle reflex was of value in detecting a pyramidal-tract lesion "much earlier, better, and more surely" than the loss of the abdominal skin reflex. Such a view may be acceptable if significance be restricted to the loss of the skin reflex. If, however, the importance of the other abnormalities of the skin reflex be appreciated, it is felt that in disseminated sclerosis, at any rate, this reflex is at least of equal value in the early recognition of disturbed pyramidal-tract function.

The abdominal skin reflex was abnormal in several instances in which the plantar response was either equivocal or flexor. On the other hand, in no instance was an extensor plantar response associated with normal abdominal skin reflexes. An extensor plantar response (Babinski phenomenon) occurred in 66 cases (83.5%), in 8 (10.1%) it was equivocal, and in 5 (6.3%) it was flexor. In several instances Chaddock's sign has furnished evidence of pyramidal-tract dysfunction at a stage in which the plantar response was flexor or equivocal.

6. Adductor Spasm

We have found hypertonus of the adductor muscles of the legs to be the earliest manifestation of spastic phenomena in the lower limbs. As such, by constituting one of Böhmig's criteria, it is of value in the diagnosis of disseminated sclerosis.

7. Sensory Phenomena

The presence of signs referable to dysfunction of the posterior columns occurred in 37 cases (46.8%) of the hospital series. In this connexion, impairment of vibration sensibility was found to be the earliest manifestation of dorsal cord involvement. Loss of spinothalamic-tract function was unusual, and was found in only three patients (3.8%).

Summary

The symptoms and signs of 389 cases of disseminated sclerosis are discussed.

Weakness in one or more limbs was the first symptom in more than half the cases examined, while visual upset was the earliest manifestation in a further 26% of the patients.

The onset of the disease was found generally to occur in the age group 20–45 years, and when disseminated sclerosis is suspected in patients outside these limits other aetiological factors should be carefully considered.

For the development of disseminated sclerosis personal susceptibility is of importance, and in our experience the incidence of the disease is greatest in those with a sympatheticotonic diathesis.

Reference is made to those clinical signs which are of importance in distinguishing disseminated sclerosis from the manifestations of hysteria. In this connexion significance should be attached to the association of overactive knee-jerks and sluggish or readily exhausted abdominal skin reflexes. Other signs of diagnostic value are the mental state of the patient, the presence of neurovascular phenomena, and the triad of ocular imbalance, mydriasis, and hippus.

Stress is laid on the need for recognition of the disease before permanent damage has been inflicted on the central nervous system. Whatever advances in treatment the future may hold, the degree of recovery will depend on the stage at which a diagnosis is first established.

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AFTER-HISTORY OF SUCCESSFULLY TREATED CASES OF SUBACUTE BACTERIAL ENDOCARDITIS

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The outstanding achievement of penicillin in overcoming infection in subacute bacterial endocarditis and in procuring a 65% cure (Christie, 1948) has presented new problems in prognosis. The immediate prognosis has received much attention, and an evaluation of the facts on which it may be based has often been presented (Jones *et al.*, 1947 ; Christie, 1946, 1948, 1949). The long-term influence of the infective process on the heart has naturally not received equal attention owing to the relatively short time since successful treatment of the infection was initiated. As penicillin has now been available for the treatment of subacute bacterial endocarditis since 1944 in America and since 1945 in this country, sufficient cases have been followed over a period of years for a tentative expression of remote prognosis to be offered.

Prognosis in rheumatic heart disease itself is always difficult owing to the tendency to additional damage due to relapse or reinfection, *ouvert* or subclinical. When it is appreciated, as Matthew and Gilchrist (1949) and MacIlwaine (1947) have shown, that the bacterial infection is frequently engrafted on a heart the seat of concomitant active rheumatic carditis, the difficulties of the assessment of the prognosis in subacute bacterial endocarditis will be seen to be further increased. Therefore prognostication of the after-effects of a bacterial infection engrafted on such a background cannot be easy, nor is it likely to be accurate. Deterioration will be difficult to ascribe either to the natural trend of the original rheumatic infection (DeGraff and Lingg, 1935) or the occurrence of rheumatic relapse, or to the after-effects of successful penicillin therapy for the superimposed bacterial infection. Despite such difficulties, it is important to know the fate of survivors from a disease which up to six years ago carried a 96% mortality (Lichtman, 1943).

Of a total of over 40 patients treated for subacute bacterial endocarditis, 20 have been cured for 27 months or longer. These 20 unselected patients provide the information on which assessment of remote prognosis is based. These patients have been closely followed up for periods varying from $2\frac{1}{4}$ to $5\frac{1}{4}$ years. Since discharge from hospital no survivor has relapsed or become reinfected, although at least one has had a further attack of rheumatic fever. The absence of relapse or reinfection is noteworthy, as Christie (1949) has indicated that the incidence of delayed relapse is of the order of 2% per annum.

A severe infection of the endocardium and myocardium, often of six months' duration before being arrested, is likely to lead to further cardiac damage. Apportioning of the degree of damage by the bacterial infection, in a heart already the seat of rheumatic or congenital pathology, is difficult for the reasons already advanced. Deterioration, if noted, cannot invariably be ascribed to the healing of the bacterial infection, as the relentless progress of the underlying rheumatic lesion will, especially in the elderly patient, contribute to a greater or less extent.

The cardiac efficiency of successfully treated cases can best be assessed by a study of three factors: (1) a comparison of the patient's capacity for effort before infection and after recovery ; (2) changes in the heart size as noted