AETIOLOGICAL ASPECTS OF MULTIPLE SCLEROSIS

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PART II†

The essential clue to the causation of multiple sclerosis may be lacking amongst the observations outlined in Part I, and may await some apparently unconnected advance in another field of medicine, just as subacute combined degeneration and kernicterus were clarified by new haematological knowledge, or Wilson's disease by studies of copper metabolism. It is also possible that more convincing evidence than hitherto may be forthcoming to link the occurrence of the disease with *tuberculosis* (Ahringmann, 1949-50), high *dietary fat* intake (Swank, 1953), or the geographical distribution of *heavy metals* or *trace elements* (Campbell *et al.*, 1947, 1950); that the roles of *microthrombosis* (Putnam and Alexander, 1939), *vasospasm* (Brickner, 1950), or *red-cell sludging* (Roizin *et al.*, 1953) may prove to be more than incidental; or that the recent experimental production of demyelination by such agents as *potassium cyanide*, *sodium azide*, or *anoxia* may be more relevant to the human disease than appears at first sight.

Present Position

In general, however—and with the reservation that our ideas and discussions are relevant only within the framework of contemporary conceptions, and doubtless reflect current preoccupations every bit as dated as Cruveilhier's "insensible perspiration"—it would appear that the main controversy rests between two concepts. The first is that the disease is caused by a specific infective agent, most probably a virus; the second is that it represents one clinical form of a characteristic pathological response in the nervous system, variable in localization and tempo, and in some way related to a disturbance in the balance of immunity and allergy.

In our view the clinical features, natural history, and epidemiology of multiple sclerosis do not specially favour a direct origin in infection by a specific virus, but the possibility certainly cannot be excluded and clearly merits the continued application of new virological techniques.

The unitary allergic hypothesis of Pette and of Ferraro relates to pathogenesis rather than to aetiology, and indeed the two concepts of the disease are not necessarily exclusive. The allergic view is based on the similarities that exist between multiple sclerosis, acute disseminated encephalomyelitis, and experimental allergic encephalomyelitis. The analogous nature of the

last two syndromes is widely accepted. The gist of the problem concerns the relationship between acute disseminated encephalomyelitis and the uniquely human chronic disease multiple sclerosis.

To discuss such a relationship demands some definition of terms. The reluctance of most writers on the subject to define multiple sclerosis, and the studied vagueness of such definitions as have been attempted, immediately arouse an uneasy suspicion that some of the argument in the literature may be about words rather than things.

If we were to synthesize a brief clinical definition of multiple sclerosis from current textbooks it would depict a chronic relapsing disease of the nervous system, of unknown aetiology, chiefly affecting young adults, initially intermittent but subsequently characterized by progressive disability, and terminating after a period of years in severe incapacity and death. An acute encephalomyelitic illness, on the other hand, is generally regarded as an isolated self-limited episode, usually following a frank infection, more sudden and catastrophic in onset than the chronic disorder, and either immediately fatal or more often leading to rapid and lasting recovery.

Such definitions and the orthodox formulation which they present are implicit in most of the current literature. How far do they correspond with the facts? The senior author of the present paper is one of many who have in the past attempted to explore and define the differences between these two symptoms, but it must be admitted that this traditional position has been rendered more insecure by the clinical and pathological evidence of the last few years, and in particular by the definitive description of encephalomyelitis following inoculation against rabies to which attention has already been directed. Virchow's aphorism that system and authority are the greatest enemies of medical advance is not entirely inappropriate in this context, and increased understanding of these diseases may depend less on the acquisition of new facts than on the rearrangement into new patterns of facts already familiar.

Informed appraisal of the histopathological issues already briefly outlined is beyond our competence; the remainder of this discussion is devoted to clinical considerations relevant to this relationship. Histopathological appearances are often regarded as the final court of appeal in issues of this kind, but in the present instance such limitation does not involve great sacrifice. The contribution of histopathology in human cases relates only to terminal findings; it is often uncertain how far atypical appearances in encephalomyelitis indicate different reactions or merely different stages in a single process; and, in any case, only the clinical history will indicate the *development* of the lesion and reveal possible aetiological factors. The clinical aspects discussed are limited to three headings—symptomatology, natural history and prognosis, and aetiological background.

Symptomatology

With regard to symptomatology, McAlpine's (1931) classical observations on the differentiation of these two groups of cases are constantly employed as guides to the difficult matter of prognosis in individual cases, and they remain generally valid: the more explosive the onset of symptoms in an equivocal acute neurological

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illness of this type, the greater would appear to be the chance of its rapid and lasting resolution. In fact, however, the symptomatic outlines of both these syndromes are blurred. There is no single clinical feature encountered in cases diagnosed as multiple sclerosis which cannot be duplicated in encephalomyelitis, and vice versa. The literature bears ample witness to the fallibility of expert diagnosis in this field, and our personal experience of more than a thousand patients with multiple sclerosis and of close on a hundred cases diagnosed as acute disseminated encephalomyelitis confirms the aphorism of the American neurologist who said that the only typical feature of multiple sclerosis was that it was always atypical.

Amongst particular symptoms generally regarded as of diagnostic value one example will suffice. *Clouding of consciousness* is a sign of encephalitic illness so classical that a semantic difficulty arises: almost any neurological illness characterized by stupor tends to be so labelled at some stage. In acute disseminated encephalitis as in other cerebral illnesses the degree of impairment of consciousness is closely related to prognosis, and is an index both of the severity of the lesion and of its generalized nature. In contrast, mental clouding more rarely results from the less acute and focal lesions of multiple sclerosis. In fact, however, a frankly encephalitic syndrome not only may initiate multiple sclerosis, but may recur during its course.

Case 138.—A previously healthy woman of 23, two months pregnant, was admitted to hospital in April, 1956, as a case of undiagnosed fever of six days' duration, characterized by intense headache, vomiting, marked drowsiness, photophobia, and neck stiffness. An equivocal left plantar response was the only focal sign and the spinal fluid was normal. Within seven days the temperature fell from 102.5° F. (39.2° C.) to normal, revealing gross ataxia as the only abnormal finding. The paucity of objective neurological signs was such that one experienced observer suggested that the fever might have been simulated. She was discharged undiagnosed a week later, with very slight unsteadiness of gait as the only sign. After a further month, insidious weakness of the left leg developed, with a definite extensor plantar response. Euphoria became evident, followed within six weeks by an acute right retrobulbar neuritis. Almost complete recovery once more ensued; but nine months later, in April, 1957, she developed a further acute neurological illness characterized by stupor, disorientation (she could not recognize her husband), and gross cerebellar ataxia. Rapid recovery over the course of 14 days left some euphoria, ataxia of gait, a left extensor plantar response, and pallor of the right optic disk, as the only abnormal findings.

If a further symptomatological illustration is required it is furnished by Devic's syndrome of *neuromyelitis optica*, dependent on simultaneous or successive demyelinating lesions in the optic nerves and spinal cord. Brain (1951) has reported this condition as a sequel of measles. Scott (1952) has drawn attention to partial syndromes of this nature and to their generally favourable prognosis, while Miller and Evans (1953) have reported a benign recurrent form. Finally its occurrence as a manifestation of typical multiple sclerosis is now well authenticated. It is true that neither an identical localization of signs nor a similar basis in demyelination necessarily implies aetiological unity. Nor, on the other hand, does the variable prognosis of neuromyelitis optica constitute in itself a valid basis for postulating differences in the essential pathology of this relatively stereotyped syndrome.

Natural History and Prognosis

Critical consideration of the natural history in patients diagnosed as suffering from multiple sclerosis and from acute disseminated encephalomyelitis yields similarly equivocal results. The course of classical multiple sclerosis is initially remittent, advancing to a later stage of progressive deterioration. However, remission may be classical, but it is by no means invariable: more than 10% of cases diagnosed as multiple sclerosis deteriorate progressively without any interval of arrest or improvement. At the other extreme is an appreciable proportion of patients, well recognized since the time of Marie and familiar to every neurologist, in whom the disease runs an essentially benign course. Deterioration may be barely perceptible over decades, while in some cases disability and signs become quite static.

Such illnesses tend to run true to type, and a favourable prognosis is especially common where the onset has been mild or monosymptomatic: the majority of Hyllested's (1950) series of patients affected by acute retrobulbar neuritis either remained well or were only trivially disabled by minor evidence of multiple sclerosis nine to twenty-five years later. Nor are relapse and recurrence unknown among cases recorded as instances of acute disseminated encephalomyelitis, especially where the initial episode has followed the type of non-specific upper respiratory infection which results in less lasting immunity than in the case of an exanthem. Furthermore, a single encephalomyelitic episode may on occasion give rise to a non-progressive syndrome of residual disability with signs quite indistinguishable from those of established multiple sclerosis (Miller and Evans, 1953).

Aetiological Background

A convincing history of infective illness immediately preceding the onset of multiple sclerosis is less common than in the case of perivenous encephalomyelitis, but this may be partly due to the fact that the chronic disease so often develops insidiously that it may be difficult accurately to identify its beginning. However, such aetiological factors as can be defined in the natural history of multiple sclerosis seem to be of much the same kind as in acute disseminated encephalomyelitis. McAlpine and his colleagues (1955, Case 137) have indeed recorded one case in which an illness that subsequently declared itself as typical multiple sclerosis either followed or was initiated by neurological symptoms which developed after an attack of scarlet fever at the age of 10 years, and recurred in association with varicella at 17. The same authors have also reported the onset of the disease after various forms of vaccination. In this last connexion our experience parallels that of McAlpine.

Case 189.—Five years after an uneventful primary vaccination a previously healthy 23-year-old woman was revaccinated against smallpox. Within 48 hours she developed dragging of the left leg, clumsiness of the left hand, and dysuria. These symptoms cleared up in the course of a few months, but 12 months later, in 1946, she developed a left retrobulbar neuritis. In 1949 the right eye was similarly affected, and in 1953 the left. In 1956 she had an episode of precipitancy of micturition. Examination in July, 1957, revealed bilateral optic atrophy, some peripheral blunting of sensation in the lower limbs, absent abdominal reflexes, and a right extensor plantar response. Disability was minimal.

Case 313.—In 1942 a 22-year-old airman, who had received primary vaccination against smallpox and T.A.B./

T.T. inoculation six weeks previously without ill effect, was inoculated against yellow fever. This was followed within a matter of hours by progressive failure of vision in the left eye, in which he became almost blind within 72 hours; vision on the right was blurred. As he was on an overseas draft he was suspected of hysteria, and was admitted to hospital under police escort, where a severe left retrobulbar neuritis was discovered. There was no unequivocal evidence of involvement of the right eye. A year later, immediately after marriage and in relation to a period of fatigue and late hours, he developed a brief episode of right retrobulbar neuritis. Between 1944 and 1951 he had about a dozen recurrent episodes of more central involvement, with numbness on either side of the body (sometimes including the face), hemiparesis, and emotionalism. From 1951 until examination in November, 1957, there had been remission, with no acute exacerbations and little if any deterioration. At this time slight ataxia of gait, left optic atrophy, left intention tremor, absence of the abdominal responses, and some euphoria were the only positive findings, and disability was slight.

Case 77.—In June, 1955, at the age of 45, 26 years after a right facial palsy and 18 years after a transient diplopia, a reserve airman was secondarily vaccinated against smallpox and received a combined T.A.B./T.T. inoculation. Between 1941 and 1945 he had been inoculated with similar material on six occasions without ill effect. Within 12 hours of the injection in June, 1955, fever, rigors, blurred vision, and diplopia developed, and persisted for 48 hours. Two weeks later a second T.A.B./T.T. inoculation was followed by a similar but rather less severe disturbance. In February, 1956, he developed weakness of the right leg which cleared up in six weeks, and in June clumsiness of the right hand of sudden onset persisted for two weeks. In August, at the time of the Suez crisis, fever, blurring of vision, and difficulty in focusing on near objects followed a further T.A.B./T.T. inoculation. In November he was affected by a severe episode of vertigo. Examination in December revealed dysarthria, nystagmus to the left, right facial weakness, intention tremor of the left hand, and an absent right lower abdominal reflex. Disability was minimal.

Comment on Cases

We believe that there can be no reasonable doubt about the diagnosis of multiple sclerosis in these three cases, and that they are of considerable theoretical importance as indicating that the chronic disease can not only be exacerbated (Case 77) but also be initiated (Cases 189 and 313) by a variety of inoculations in which the incrimination of a common specific infective agent is highly improbable. This is especially so in Case 77, which recalls the exacerbation of pre-existing multiple sclerosis by successive injections of autogenous vaccine seen in Case 202 of McAlpine *et al.* (1955). It is of interest also in connexion with the cases of Bannwarth (1948) from the Germany Army, in which recurrent but self-limited neurological illnesses followed repeated inoculations of T.A.B. So far as Bannwarth's follow-up of these cases went, no relation to multiple sclerosis was suggested, the critical difference being the absence of any neurological recurrences independent of further inoculation.

Case 189 complements a previous paper (Miller, 1953) in which the usually excellent prognosis in patients surviving neurological complications of Jennerian vaccination was stressed. Twenty-seven cases were described, including eight in which involvement of the spinal cord occurred, either alone or as part of an encephalomyelitic picture. These cases were followed for periods varying from two to twelve years (the average follow-up being six and a half years), and in none had

neurological symptoms recurred. The post-vaccinal case (No. 189) is drawn from the same service material, but in view of the fact that the condition would not be officially classified as an example of "neurological sequelae of vaccination" it may well be amongst a number of such instances lost sight of by a change of diagnosis to multiple sclerosis.

In Cases 189 and 313 there would appear to be no more reason to deny a genuine aetiological relationship between the inoculation and the subsequent development of multiple sclerosis than in the case of the acute self-limited neurological lesions following inoculation described by Miller and Stanton (1954). What gives these cases of multiple sclerosis their special character is a tendency to the subsequent occurrence of similar neurological episodes arising independently of any repetition of the original aetiological insult, and it is in this tendency to apparently spontaneous recrudescence that any special nature of the chronic disease would appear to consist.

It is noteworthy also that in each of the above three cases the multiple sclerosis was of a very mild type. It might be speculated either that the pathogenetic mechanism of the disease in these individuals was of a less active nature, or, conversely, that they possessed some power of resistance to the intensity and spread of the lesion such as has frequently been postulated in similarly benign cases. Whichever mechanism be involved, it seems conceivable that had they not encountered this particular exogenous insult to the nervous system they might have avoided the initiation of the pathological process which ended in the development of multiple sclerosis.

Conclusions

The practical usefulness of current classification as a rule-of-thumb guide to prognosis is beyond question; not even the most ardent monist would impugn the pragmatic value of clinical differentiation between most cases of post-measles encephalitis and most cases of multiple sclerosis. It is when we come to consider the nature of these disorders that the clinical evidence outlined in the previous sections of this paper lead us to question its ultimate validity. Neither clinical nor pathological considerations permit finality, but the unitary hypothesis of Pette and of Ferraro appears to us to do less violence to the facts than do the arbitrary and confident subdivisions which have gradually taken shape over the years from the gradual accretion of fragmentary clinical observations.

The unitary hypothesis visualizes a spectrum of demyelinating disease ranging from the most acute cases of frankly post-infective or post-vaccinal encephalitis or myelitis at one end of the scale to the insidious and remorselessly progressive chronic spinal form of multiple sclerosis with which we are familiar in middle-aged patients at the other. There are good reasons to include in such a spectrum also a number of other syndromes such as *acute haemorrhagic leuco-encephalitis* (almost certainly a manifestation of hypersensitivity) and *Schilder's disease* (now widely regarded as an analogue of multiple sclerosis), but such considerations are outside the scope of the present study.

The hypothesis postulates a common origin for this type of pathological reaction in some kind of hypersensitive disturbance, and on this reckoning the relation

between acute disseminated encephalomyelitis and multiple sclerosis might be compared with that between the acute disseminated exudative reaction of miliary tuberculosis and chronic remittent recrudescing fibroid phthisis—strikingly dissimilar syndromes of identical aetiology that owe their differences entirely to the subsequent interplay of the forces of immunity and allergy. Possibly the obscure condition of Boeck's sarcoidosis—where if there ever was a tubercle bacillus it has disappeared without trace, leaving only the ravages of its disintegration—provides an even more suggestive hint of the mechanisms which might operate in neuro-allergy.

In this view the whole concept of classical multiple sclerosis represents in essence an extrapolation made by applying certain arbitrary nosological criteria to a group of clinical phenomena not so subdivided in nature. In this way a semantic artifact has developed, growing both larger and vaguer over the years, but endowed with a spurious precision which fades on critical examination. It can hardly be denied that much of the confusion in this situation is a matter of terminology. A good deal of the argument—for example, on whether in some instances disseminated encephalomyelitis *turns into* multiple sclerosis, or whether the two acute illnesses are *different but indistinguishable*—is almost meaningless, and endows the idea of a disease-entity with a reality and an immutability strikingly at variance with Lord Cohen of Birkenhead's apt description of it as a "convenient conceptual label."

As we see it, what may be broadly termed the allergic hypothesis may be briefly developed in the following terms. The initial lesion in multiple sclerosis appears to be focal disseminated microscopic perivenous exudation and oedema. This is accompanied or followed by an inflammatory reaction of variable intensity at the same site, which is in turn succeeded there by the well-defined demyelination and glial proliferation typical of the established disease. The active margin of this characteristic lesion subsequently extends, either massively or by confluence, either insidiously or episodically, in a manner which appears at this stage to ignore vascular territories, and which suggests the possible diffusion of some demyelinating agent or process. Experimental evidence has shown that a somewhat analogous lesion can be provoked in animals without the participation of any infective agent, and apparently in the form of an antigen-antibody reaction resulting from tissue-sensitization. The initiating aetiological agent in this experimental disorder is the injection of sterile extracts of animal nervous tissue.

In the closely similar human clinical syndrome, acute disseminated encephalomyelitis, it is clear that either virus infection—for example, measles, varicella—or the injection of various sterile antigenic substances—for example vaccination—may play a similar aetiological part. In experimental encephalomyelitis and in the human disorder as it follows sterile inoculation there is good reason to believe that the initial perivenous lesion which is the first visible pathological sign of the disease represents in itself the larval manifestation of neural hypersensitivity. If for a moment we accept the hypothesis that multiple sclerosis may have a similar allergic pathogenesis, *the nature of the primary aetiological insult* which initiates the process of sensitization in the human disease still remains to be sought. In this instance also it seems to us probable

that the initial perivenous exudation may represent merely the beginning of the secondary hypersensitive reaction, evidence of the true aetiological agent being buried in the past. Speculation on the nature of this primary aetiological factor is even less securely based than what has gone before, but both clinical evidence and historical considerations suggest that it may be non-specific, and that except in the occasional iatrogenic instances in which the disease has followed the deliberate introduction of antigenic substances into the human body it can best be tentatively regarded as a late sequel of various infective processes.

On the other hand, it is at any rate possible that the primary exudative lesion in the case of the human disease might in itself represent the point of attack of an initial infective agent, possibly of a viral nature: in herpes simplex we are familiar with a recurrent exudative reaction arising in ectodermal tissues which is strikingly and repeatedly potentiated by a wide variety of exogenous and endogenous factors such as infection, trauma, and emotional disturbance, in a manner not dissimilar to that seen in the case of multiple sclerosis. It is possible to envisage some similar recurring process in the central nervous system, each episode of which might reactivate a local process of tissue-sensitization releasing a further quantum of demyelinating fluid. The usefulness of so speculative an approach may well be questioned, and the last variant of the hypothesis castigated as seeking to combine the best of both worlds. On the whole the postulation of a specific virus, even as a link in the allergic hypothesis, is supported by less in the way of circumstantial evidence than a non-specific and multiple primary aetiology, though it has perhaps the advantage that it focuses attention on two possible avenues of investigation and of prophylactic or therapeutic interference—an infective aetiology and an allergic pathogenesis.

Indeed, the only excuse for a speculative hypothesis of this nature is that analysis must succeed synthesis in leading to observations or experiments which will provide evidence to confirm or refute it. In our view the allergic or immunological theory of multiple sclerosis, with all its loose ends and inadequacies, provides the most useful working hypothesis at present available from this point of view. In the pathological field the nature of the perivascular exudate, the problem of whether in fact this results from exudation or is formed *in situ*, and its relation to the increase in spinal fluid gamma-globulin, all await illumination. From the immunological point of view the investigation of multiple sclerotic patients for antibodies to neural tissue or for abnormal immunological responses to known viruses has hardly begun, while the examination of unaffected relatives for evidence of constitutional abnormalities in the mechanisms of hypersensitivity and immunity offers a completely unexplored field. Finally, from the therapeutic aspect a definite answer is awaited on whether the clinical course of multiple sclerosis is in any way influenced by the administration of substances known either to inhibit antigen-antibody reactions or to suppress their inflammatory manifestations. The fundamentalist view that such investigations must await elucidation of the intimate neurochemistry of the myelin sheath shows a curious misreading of the lessons of medical history.

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STEROID METABOLISM IN A CASE OF CONGENITAL ADRENAL HYPERPLASIA

BY

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During recent years the metabolic disorder in congenital adrenal hyperplasia that leads to pseudohermaphroditism in females has been a subject of great interest. This was stimulated by the dramatic demonstration by Wilkins *et al.* (1950) that administration of cortisone led to a remarkable relief of the symptoms and apparently restored the disordered metabolism to normal. Many diseases of uncertain aetiology are relieved by cortisone even when adrenal steroid metabolism appears to be normal, so that no conclusions could be drawn from the relief of symptoms alone. But it was soon shown that two manifestations of the disordered steroid metabolism—the excessively high 17-ketosteroid excretion in the urine and the excretion of the unusual steroid pregnantriol in the urine—are both promptly brought under control with return to normal values after cortisone administration. These points indicated clearly a gross disorder of adrenal cortical metabolism which was corrected by cortisone administration.

Evidence then collected that production of hydrocortisone by the adrenal cortex was seriously impaired in this disorder. Thus both Ely *et al.* (1953) and Bongiovanni *et al.* (1954) showed that the blood levels of circulating hydrocortisone were abnormally low in this disease, and soon afterwards Eberlein and Bongiovanni (1955a) found that the metabolites of hydrocortisone in the urine were also present in abnormally small amount.

To explain this syndrome of high 17-ketosteroid excretion, excessive pregnantriol excretion, and defective hydrocortisone production, Jailer (1953) postulated an enzymatic block of congenital origin in these subjects whereby they were unable to convert 17-hydroxyprogesterone, the probable normal precursor, to hydrocortisone itself. This would normally involve the action of a 21-hydroxylase, and this enzyme he suggested was lacking in congenital adrenal hyperplasia. This suggestion of Jailer's went far to explain the metabolic anomaly in the disease, and has found wide acceptance.

But hints began to appear that the condition was not as homogeneous and the explanation not always so simple as Jailer's hypothesis would suggest. It had been recognized since 1951 (Shepard and Clausen, 1951; Wilkins *et al.*, 1951) that a variant of the clinical disorder exists in which hypertension is a major feature. In 1955 Bongiovanni and Eberlein investigated one such patient and found strong evidence that the derangement of steroid metabolism was different in this patient from that previously encountered. There was, for instance, a relatively small pregnantriol excretion, but an excessively large excretion of a steroid, commonly called tetrahydro S, which differs from the usual metabolites of cortisone and hydrocortisone in having no hydroxyl group on the 11 carbon atom. In the urine of this patient no metabolites were found which contained the 11-hydroxyl grouping, and it appeared, therefore, that the defect in this variant of the disorder was not of the more usual 21-hydroxylase, but of a different enzyme, 11-hydroxylase. A unified concept of the derangement in congenital adrenal hyperplasia was thus no longer tenable. Other

The International Labour Office has produced two large volumes entitled *International Directory of Institutions Engaged in Study, Research, and Other Activities in the Field of Occupational Safety and Health*. These volumes list organizations in 40 countries concerned with research and other activities in the field of occupational safety and health. Further information about obtaining copies of this compilation may be obtained from the Chief of the Occupational Safety and Health Division, International Labour Office, Geneva.