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AETIOLOGICAL ASPECTS OF MULTIPLE SCLEROSIS

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PART I

Although a hundred and twenty years of phenomenal advance in medicine have passed since multiple sclerosis was first described, we remain ignorant not only of its cause but even of its general nature. Is this because it is due to an entirely new kind of causal agent, as yet unthought-of? Is some as yet unidentified agent belonging to a known category responsible? Or does the disease depend on some unusual combination of pathogenetic factors already familiar? That multiple sclerosis will yield its secrets to a merely heuristic approach is unlikely, but the crucial observations or experiments which ultimately elucidate its nature may well originate in some speculation.

In few diseases can we recognize the operation of a single "cause" such as the genetic anomaly of Huntington's chorea or the typhoid bacillus, and we are increasingly reconciled to thinking in terms of multiple aetiological factors of differing valency, and of extended disease processes involving a complex succession of patho-physiological mechanisms, rather than of frozen "disease-entities." Such an approach, while discomfiting to the tidy-minded, has the advantage that it permits the isolation of various stages in the disease process as appropriate subjects both for investigation and for therapeutic intervention. After all, truly aetiological information about peptic ulcer remains sketchy, but fragmentary knowledge of its pathogenesis has furnished the theoretical basis for various forms of effective treatment.

The history of aetiological theories in multiple sclerosis throws as much light on the development of medical thought in general as on the nature of the disorder. Carswell (1838) and Cruveilhier (1829-42), who first described the condition, respectively attributed the plaques of the disease to ischaemia, and the disorder in general to the suppression of "insensible perspiration." Early histopathological observers such as Rindfleisch (1863) and Moxon (1875) stressed the inflammatory and perivascular nature of early lesions, and Leyden (1863) postulated the aetiological role of non-specific incidents such as acute illness, trauma, exposure, and emotional disturbance—factors enumerated unchanged in the textbooks of to-day. Charcot (1868, 1872) supported Moxon in implicating infectious diseases as a causal factor: that such a relationship was consistent and central to the problem of aetiology was first postulated by Pierre Marie

(1895), and accepted by many, including Gowers (1893). However, on the basis of one of the earliest personal series of cases reported, Krafft-Ebing (1895) regarded body-chilling as more significant, while Strümpell (1896) envisaged the role of an inborn vulnerability of the nervous system. The latter view appealed to Bramwell (1917), who sought to combine it with the hypothesis of "auto-intoxication," on which Dawson (1916) had speculated in his unequalled pathological study.

The last fifty years have seen the unsuccessful search for a specific infective agent which has revolved chiefly round the spirochaete and the virus. Even allowing for its notoriously elusive nature, evidence incriminating the former is frankly unconvincing. The question of a viral aetiology for multiple sclerosis has been reviewed by Innes and Kurland (1952): there is no positive evidence in its favour, nor does the evidence preclude such a possibility.

Acute Disseminated Encephalomyelitis

Glanzmann's (1927) study of the acute disseminated (perivenous demyelinating) encephalomyelitic syndromes which occasionally complicate measles and Jennerian vaccination opened a new chapter of speculation and investigation into the aetiology of multiple sclerosis, and it is to this aspect of the problem that the present paper is chiefly addressed. Obscure though the exact pathogenesis of these rare disorders might be, they possessed the signal advantage as objects of study and comparison that each such illness was the outcome of a single identifiable aetiological event. Furthermore, it was soon established that whether the encephalomyelitis was caused by measles, chicken-pox, influenza, vaccination, or merely a non-specific respiratory infection, the characteristic pathological lesion encountered was the same, suggesting the intervention of some common pathogenetic factor between the varied initial insult and the uniform sequel; in this connexion Glanzmann speculatively invoked von Pirquet's (1907) concept of allergy.

The clinical and pathological similarities of these syndromes to acute episodes of multiple sclerosis were soon appreciated, and as early as 1928 Pette described three cases exhibiting a gradient of pathological changes progressing from acute perivenous demyelinating encephalitis to a more subacute syndrome of four months' duration with marginal gliosis which he interpreted as an unequivocal instance of the chronic disease.

The relationship between acute disseminated encephalomyelitis and multiple sclerosis is still debated.

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McAlpine (1931) drew attention to the frequency in encephalomyelitis of certain symptoms such as clouding of consciousness, meningism, high fever, severe limb pains, and radicular lesions with flaccid palsy and areflexia; and to the rarity of other clinical features such as euphoria, bilateral retrobulbar neuritis, and diplopia, which are often encountered in multiple sclerosis. Recovery from a frankly post-infective lesion such as transverse myelitis has also been widely regarded as usually more rapid and more complete than from a comparable episode of the chronic disease. However, an appreciable proportion of cases originally diagnosed as encephalomyelitic have subsequently declared themselves to have been initial episodes of multiple sclerosis.

Opponents of Pette's unitary view who conceded the symptomatic overlap between the two syndromes claimed that the subsequent history of patients with acute disseminated encephalomyelitis established the condition as a clinical entity independent of the chronic disease. That the two conditions could hardly be regarded as identical was supported by the observation that out of a total of 75 such cases followed up by Thygesen (1949), van Bogaert (1950), and Miller and Evans (1953), no fewer than 42 showed no recurrence of neurological symptoms over a period of years. Furthermore, even when relapse or recurrence did occur in encephalomyelitic cases, the progressive disability associated with strangulation of the long tracts by massive fibrous gliosis characteristic of chronic multiple sclerosis was lacking. This last observation can, however, hardly be regarded as more than tautological: any case in which chronic disability of this kind followed an encephalomyelitic illness would almost certainly be omitted from such a series by hindsight as an instance of multiple sclerosis.

Histopathology

Histopathological differentiation is similarly controversial, such studies being hampered especially by the infrequency of death during an acute exacerbation of unequivocal multiple sclerosis: many of the earlier cases so described prior to 1927 would generally be regarded to-day as instances of acute disseminated encephalomyelitis. It is, however, now widely accepted that, while the characteristic plaques of chronic multiple sclerosis show no consistent relationship to vascular territories, the initial lesion of the disease is usually if not always perivascular, and very similar in nature to that of the encephalomyelitic syndrome. The main difference appears to be that, while perivascular cuffing and demyelination following measles or vaccination are generalized and uniform, the similar changes in multiple sclerosis are essentially focal, and the cuffing intermittent along the course of the vessels. Such a difference might, for instance, be regarded as analogous to that seen in the field of systemic disease between the solitary generalized exudative explosion of acute serum sickness and the localized chronic lesions of polyarteritis nodosa, which appear to be due either to repeated exogenous antigenic insults or to the initiation of some self-perpetuating process of iso-immunization such as has recently been demonstrated in thyroid disease.

It is not difficult to equate the more global encephalomyelitic lesion with the greater frequency of symptoms indicating generalized involvement of the neuraxis, such as clouding of consciousness and symmetrical involvement of optic nerves, long tracts of the spinal cord, and nerve-roots—in contrast to the

characteristic clinical asymmetry of early multiple sclerosis. Such a statement must be qualified by the observation that the polymorphic symptomatology of encephalomyelitis itself indicates that the apparent pathological uniformity is far from absolute, and that this difference is probably one of degree. Somewhat similar though less acute pathological changes are encountered at the margins of chronic plaques, a finding which has led some authorities to suggest that, despite its episodic clinical manifestations, the pathological course of multiple sclerosis may nevertheless be insidious rather than intermittently explosive.

The most untiring advocate of the unitarian view that the disease represents in its pathological essence nothing more than a chronic recurrent disseminated encephalomyelitis of allergic origin is Ferraro (1937, 1944, 1958), who regards the chronic plaques as the result of coalescence of multiple acute perivenous foci, and glial scarring as merely the outcome of relapses causing repeated damage to areas previously involved.

Most patients who die of acute disseminated encephalomyelitis do so within a few days of its onset, and histopathological evidence is scanty regarding the changes found in patients who recover or who have survived for longer periods. *Complete resolution* of the acute changes has been recorded, though both *coalescent demyelination* (Herkenrath, 1935; Schaltenbrand, 1938) and *extensive gliosis* (Schlesinger, 1909; van Bogaert, 1932) have occasionally followed such an illness.

Experimental Allergic Encephalomyelitis

The demonstration that a perivenous demyelinating encephalomyelitis widely accepted as analogous to the human post-infective syndrome discussed above can be regularly provoked in animals by repeated injections of sterile brain emulsion, and that its development can be effectively inhibited by the prior administration of corticotrophin, has clinched the fact that this lesion can arise *independently of infection*, and has lent strong support to its allergic origin.

To have induced acute disseminated encephalomyelitis in animals is not, however, to have reproduced multiple sclerosis, and these important observations have thrown no new light on the crucial problem of the relationship between these acute self-limited clinical and experimental syndromes on the one hand and the relapsing self-perpetuating course of the chronic human disease on the other.

Neurological Sequelae of Rabies Vaccination

In this connexion, however, important evidence has recently been furnished from Japan by Uchimura and Shiraki (1957), who describe the findings in nine patients dying after subacute neurological illnesses which followed preventive inoculation against rabies—a form of human prophylaxis which closely parallels the animal experiments noted above, in that it involves repeated injections of heat-treated animal neural tissue. Their illustrations show widespread massive demyelinated lesions, clear-cut, often closely related to the ventricular margins, and characterized by marked gliosis; it can hardly be doubted that these represent a later evolution by confluence of the perivascular foci found in earlier cases, which appear entirely similar to those familiar in the more commonly encountered forms of acute disseminated encephalomyelitis. The unique iatrogenic illnesses from which these patients suffered were of

subacute encephalomyelitic type, and not classical multiple sclerosis. The significance of these observations is pathological: they present human lesions of known aetiology (and almost certainly allergic pathogenesis) which are more strikingly similar to those of multiple sclerosis and Schilder's disease (diffuse sclerosis) than anything previously described.

Some Clinical Considerations

Any current hypothesis on the aetiology of multiple sclerosis must be compatible with certain established facts in the natural history of the disease. In relation to its age incidence we would merely record that we have encountered its acute onset in classical form at all ages between 6 and 60 years.

Differing standards of medicine preclude a comprehensive view of geographical incidence, but the disease is commoner in the northern than in the southern hemisphere, and in the northern than in the southern parts of the former. We do not know whether this greater prevalence in cold climates is related, as has been suggested, to a higher incidence either of infections of the upper respiratory tract or of vasospastic disorders, nor whether removal to warmer conditions would protect patients against recurrence as it does in rheumatic fever.

Implications of a Genetic Factor

The fact that a second patient with multiple sclerosis is found in the families of between 6 and 7% of cases (McAlpine, 1957) has been taken to imply a genetic factor in the production of the disease: if so it is remarkable that recent investigations (Pratt, 1951; Thums, 1951; Mackay and Myrianthopoulos, 1957) have conspicuously failed to show any significant degree of concordance in the occurrence of multiple sclerosis in monozygotic twins. In the most recent of these observations, Mackay and Myrianthopoulos reported 27 instances of the disease in one identical twin, and in 21 of these the other was unaffected. The situation is even further complicated by the fact that other members of such families show an incidence of multiple sclerosis strikingly in excess of that encountered in the general population. We have encountered one such instance in our unpublished series of more than 600 cases of multiple sclerosis personally examined in the course of a regional survey.

Case 493.—In 1948, at the age of 36, a woman, one of nine sibs, developed sudden diplopia. In April, 1954, she became unsteady and weak on her legs, and was found to have typical signs of mild multiple sclerosis with nystagmus, pallor of the disks, and an asymmetrical ataxic paraplegia. Re-examination in 1958 revealed more gross signs, with marked cerebellar ataxia of all limbs and a spastic quadriplegia, in addition to advanced bilateral optic atrophy with nystagmus. Her 46-year-old identical twin was also examined at this time, ten years after the onset of the patient's illness. At no time had the twin sister suffered any neurological symptoms, and physical examination of the nervous system was completely normal. The identical nature of the twinning was established by serial photographs and blood-grouping. However, another sister (*Case 418*), born in 1918, six years after these twins, developed classical multiple sclerosis in March, 1955, with gross ataxia and loss of vision in the right eye, diplopia, and nystagmus. The spinal fluid at this time showed a paretic Lange curve, and the diagnosis of multiple sclerosis was confirmed by rapid recovery from this episode and by a relapse with loss of proprioceptive sensation in the right arm and leg in February, 1958. A fourth sib, born in 1901 (not accepted

in our survey as an authenticated case of multiple sclerosis), suffered from acute unilateral retrobulbar neuritis in 1936, but has remained well since. Five other sibs, including another pair of heterozygotic twins, were normal with regard both to history and to neurological examination, but a paternal cousin born in 1901 developed an acute paraplegic syndrome in 1935 and exhibited classical signs of advanced multiple sclerosis on re-examination in 1958.

On the other hand, the rarity of conjugal cases militates equally against a contagious explanation of the familial incidence.

The occasional evident influence of one of a number of non-specific factors (trauma, exposure, fatigue, infection, and probably emotional disturbance) in provoking the onset or exacerbation of multiple sclerosis is strongly supported by clinical evidence not necessarily invalid because it is drawn from individual cases. This evidence is indeed so suggestive that it remains impressive in spite of the fact that no such relationship is consistently encountered, and that in many cases none whatever can be traced. The cause of these well-authenticated phenomena remains obscure: some kind of reflex circulatory disturbance seems to be the most plausible guess at a common factor.

Relationship with Trauma

On the face of it, for example, an aetiological relationship between trauma and multiple sclerosis appears unlikely. There is, however, a group of cases in which not only a temporal but also a topographic relationship to injury is so striking that such a connexion can be denied only in the light of preconceived notions which are themselves of dubious validity in the light of recent observations on the traumatic provocation and localization of paralytic poliomyelitis.

Case 501.—In March, 1958, a 23-year-old dental student was struck on the left cheek by a hockey ball. A large haematoma developed below the zygoma and there was a good deal of pain in the cheek and the inside of the mouth. This pain gradually cleared, but the haematoma was still present six days after the injury, when he developed numbness and tingling over the left cheek. This spread rapidly to the palate and the inside of the lower jaw, and involved the whole of the left trigeminal distribution within 24 hours of its onset. In view of the haematoma, and although there was no radiological evidence of fracture, this condition was thought possibly to be traumatic until three days later, when he developed similar tingling in the right arm and leg. Signs of local injury cleared up within two weeks, but it was five weeks before his neurological symptoms disappeared. Six weeks later he developed a typical episode of acute disseminated sclerosis with ataxic nystagmus, diplopia, and a right hemiparesis. Again disability on this score cleared rapidly, and the only abnormal findings four weeks later were absence of the abdominal responses and an extensor plantar response on the right side, with minimal nystagmus.

Case 453.—In November, 1954, a 47-year-old man sustained an extensive superficial electrical burn to his left hand, and within six days of this he noticed an abnormal sensation of numbness in the hand and half-way up the forearm. When the dressing was removed the limb was found to be clumsy, and within a few days the numbness spread to the left face and leg, and also to the tips of the fingers of the right hand. The only abnormal finding at this stage was a left hemihypaesthesia, which included the face. Diagnosis was obscure, but a tentative suspicion of multiple sclerosis was confirmed by the development in 1957 of fatigability and unsteadiness of gait, when examination revealed ataxia, sustained vertical nystagmus, right lower facial weakness, left intention tremor, absent abdominal reflexes, a right plantar response, and patchy

impairment of sensation over the left side of the body. With the exception of spinal fluid examination, which showed a marked rise in gamma-globulin content, all ancillary investigations were negative.

The sensory nature of the initial post-traumatic symptoms in these cases is worthy of note: signs of initial involvement of afferent pathways from the affected part have characterized other such cases in the literature.

Non-specific Infections

Non-specific infections have gradually replaced the epidemic fevers of the nineteenth century as putative aetiological factors in multiple sclerosis, but in fact clinically evident infection of any kind is often entirely lacking in the recent history of early cases. Although Abb and Schaltenbrand (1956) claim to have traced it in more than two-fifths of patients, the figures given by most other workers are much lower. Störtebecker's (1951) claim to have revealed a high incidence of miscellaneous antecedent infections in cases of multiple sclerosis by means of agglutination, antistreptolysin, and antistaphylococcal titres is suggestive, but as yet unconfirmed. Nor—although reliable figures are entirely lacking—has the gradual conquest of the bacterial infections during the past two decades been followed by any apparent decline in the frequency of new cases of multiple sclerosis comparable with that of which we cannot fail to be aware in the case of such frankly post-infective disorders as acute rheumatism or acute nephritis.

Again, occasional cases are impressive.

Case 90.—In December, 1949, a 26-year-old woman developed a severe head cold with fever and influenzal symptoms, followed within 24 hours by the sudden appearance of a partial transverse spinal-cord lesion at the mid-dorsal level. This improved rapidly after a few days, and 10 weeks later there was no residual disability. During the next seven years she had six similar episodes, each involving the spinal cord at the same level, always in winter and always immediately preceded by a frank and sometimes febrile upper respiratory infection. The three later episodes also involved the arms, and one of these was accompanied by double vision and one by pronounced left hemiparesis. Each attack lasted for less than 12 weeks, and each cleared up, leaving minimal disability. The only other episode was in the summer of 1952, when she had an attack of nystagmus and double vision lasting for two weeks, quite unrelated to clinically evident infection. Examination in 1957 revealed a mild spastic paraparesis with appropriate reflex changes. Astereognosis was found in both hands, and vibration sense was lost in the left hand and leg.

Allergy

Much the same reservations apply to the role of allergy, reviewed by Prigal (1956). Occasional cases are striking in which frank allergic disturbance appears to have provoked the onset or exacerbation of the disease (Compston, 1951), but statistics are unimpressive. However, anamnestic investigation of allergy is mainly limited to obtaining evidence of its more striking manifestations, such as atopy, of which evidence may be entirely lacking in other diseases which we know to arise on an allergic basis. The observations of Alexander *et al.* (1950) that multiple sclerotics show an incidence of transfusion reactions (mostly allergic) thirty times as great as that encountered in control cases is suggestive clinical evidence in favour of some instability in the machinery of immunity in these cases, while the demonstration of a frequent increase in the spinal fluid

gamma-globulin (Kabat *et al.*, 1942; Yahr *et al.*, 1954) and of an abnormal response to the intrathecal injection of tuberculin (Smith *et al.*, 1957) have been similarly interpreted. The significance of these last findings, however, remains obscure: they may represent secondary results of the vascular and meningeal changes of the disease rather than evidence of a primarily immunological disturbance.

[The conclusion of this article, together with a list of references, will appear in our next issue.]

THE ARTIFICIAL KIDNEY

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Severe renal failure is evidenced clinically by the syndrome of uraemia. This is believed to be due to the accumulation in the body of a number of substances, only a few of which have probably been identified. The artificial kidney is a device for removing from the body some or all of these substances. Various types of machine have been used for this purpose, and their historical development has been reviewed by Merrill (1955) and by Sorrentino (1956). All of them have employed the principle of dialysis, using a semi-permeable membrane that separates a bathing solution from the patient's blood.

Dialysis with any type of artificial kidney is a complicated and time-consuming procedure, and its greatest therapeutic value has been in the treatment of patients with acute reversible renal failure.* It has also been used for the treatment of patients with exacerbation of chronic renal failure (Parsons and McCracken, 1957) and barbiturate (Kyle, Jeghers, Walsh, Doolan, Wishinsky, and Pallotta, 1953) and other acute poisonings (Doolan, Walsh, Kyle, and Wishinsky, 1951; Danzig, 1955; Merrill and Weller, 1952). It has a limited use in maintaining life in order that diagnostic procedures can be undertaken in patients presenting with the more obscure types of renal failure. The artificial kidney also provides an opportunity of obtaining information about the uraemic state, and its potentialities as a research tool are largely unexplored.

Following the pioneer work of Kolff and Berk (1944), reports of experience with artificial kidneys have appeared chiefly from the U.S.A. (Skeggs and Leonards, 1948; Merrill, 1950; Kolff, 1957), Scandinavia (Alwall, 1947; Anthonisen, Brun, Crone, Lassen, Munck, and Thomsen, 1956; Thaysen, Gjørup, and Killmann, 1957), and the mainland of Europe (Legrain, 1953; Hamburger and Richet, 1956). Use of the apparatus in Great Britain prior to 1956 has been confined to its occasional employment between 1947 and 1949 (Bull, Joekes, and Lowe, 1958); since 1956 machines have been in use in two centres, and preliminary reports of these have been

*The term "acute reversible renal failure" is used in preference to others, such as lower nephron nephrosis, tubular necrosis, etc.