

EDITORIAL

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The Aetiology of Disseminated Sclerosis

In spite of much hypothesis and, more recently, experiment, the essential causal factor of disseminated sclerosis remains undiscovered. Most of the theories that dominated neurological thought during the latter part of the last century and the earlier part of the present were the result of conjecture based upon histological interpretation. Thus, some considered the disease was due to an inborn dysplasia of one or other elements of nerve tissue, either a maturation defect of myelin or a hyperplasia of glial cells, whereas others considered the disease to be an inflammatory response to some unknown organism or toxin gaining entry via the blood stream or the Virchow-Röbin spaces.

The modern view is that the histological changes in disseminated sclerosis give little clue to its aetiology, since the central nervous system will react only in a limited number of ways, and these depend upon the intensity rather than upon the specificity of the noxa. Focal demyelination with subsequent gliosis is one such 'reaction form.' The production of perivascular demyelination in animals by widely different experimental methods supports this contention.

There has been no unanimity in the results of those who have sought to prove the infective origin of disseminated sclerosis. However, considerable interest has recently been aroused by the claim of Margulis, Soloviev and Schubladze (1946) to have isolated the same virus from two cases of encephalomyelitis. This virus they state is neutralized by the serum of 50 per cent. of patients suffering from disseminated sclerosis but not by serum from patients with other neurological diseases. Their material has not been made available for others to study, so that until their work is confirmed their claim must remain *sub judice*.

Good and Campbell (1948) demonstrated that artificially induced herpes simplex encephalitis in rabbits may remain inactive for long periods and be reactivated at will by the administration of histamine or the induction of an anaphylactic state with foreign protein. By analogy, therefore, a virus aetiology is not incompatible with the relapsing nature of disseminated sclerosis.

Recently it has been found that a spontaneous demyelinating disease of lambs, swayback, only occurs in those animals reared on pastures deficient in copper, and that the disease can be prevented by feeding additional copper to the ewes. Swayback is analogous to Schilder's Disease rather than disseminated sclerosis, but nevertheless it was obviously worth while to investigate copper metabolism in disseminated sclerosis. This has been done by Mandelbrote and his colleagues (1948); no differences of statistical importance were found between normals, patients with disseminated sclerosis or other neurological controls. Despite these negative results the possible role of trace elements in the maintenance of the normal health of nervous tissue must be borne in mind.

A claim that disseminated sclerosis is caused by venous thrombosis has been put forward by Putnam (1935). His original claim was based on the interpretation of the histological appearance of blood vessels in postmortem material, and he subsequently supported it by producing foci of demyelination in animals by the obstruction of venules. His work has been criticized adversely by Greenfield and King (1936), and by Dow and Bergland (1942), who were unable to agree with his histological interpretation. Recently Lumsden (1948) has shown that the histological appearance in man resulting from widespread venous throm-

bosis in the central nervous system bears no similarity to that of disseminated sclerosis.

Ferraro (1937) has conceived all the spontaneous demyelinating diseases as being varying degrees of reaction of a hypersensitivity type in the nervous system. The primary aetiological factor in such a case would be the factor that renders the central nervous system hypersensitive, and this Ferraro does not consider. McAlpine, when reviewing the subject (1946), suggested that the central nervous system might become sensitized by an infection which had occurred months or even years before, and instanced the skin as a possible source of such infection. Considerable impetus has been given to the theory of hypersensitivity by a series of animal experiments commencing with the work of Rivers *et al.* (1933, 1935). He and his co-workers produced a form of encephalomyelitis by the repeated injections of heterologous brain emulsions. Subsequently the induction of such an encephalomyelitis, now usually termed allergic encephalomyelitis, has been simplified by the addition of various adjuvants (notably dead tubercle bacilli) to the emulsion. With such adjuvants the disease can be produced with emulsion of homologous brain tissue. By varying the dosage, chronic forms of encephalomyelitis can be produced. This experimental disease is possibly analogous to the acute encephalomyelitis that follows vaccination or infectious fevers and sometimes occurs spontaneously in man. The disease, once induced, has no power to spread or relapse. Valuable as such work undoubtedly is, it should be emphasized that disseminated sclerosis has not been reproduced in animals. Allergic encephalomyelitis will, however, prove to be a useful experimental weapon for the study of the demyelinating process.

The production of focal demyelination in animals by the use of poisons that interfere with the oxidation of nerve tissue has suggested that the disease is due to a primary enzyme disorder (Weston Hurst, 1942). Lumsden (1948), as a result of intensive histological study of demyelinating diseases in man, is struck by the absence of oligodendroglia in plaques of disseminated sclerosis. He postulates that the essential ferment required for myelin metabolism

is produced by this cell, and either spontaneously or under the influence of exogenous agencies in disseminated sclerosis the enzyme systems are upset and a myelinolytic substance is produced.

Certain additional factors appear to be of importance in the genesis of disseminated sclerosis. They require study because knowledge of their mode of action may throw light upon the primary causative agent. Additional importance should be given to these secondary factors because in any individual case they may play a dominant role in governing the course of the disease, including the time of its onset and the time and frequency of its relapses.

Among the more important of such factors are trauma, sepsis, infection, pregnancy, emotional stress and dietary deficiency. Von Hoesslin (1934) found the onset of the disease to follow trauma in 11 per cent. of his large series of 516 cases. He and other workers have found that trauma may also influence the localization of initial symptoms. Sepsis plays a similar role. It is of interest that Orr and Rows (1914) and Wail (1935) have demonstrated histological changes in the spinal cord of both man and animals dying of severe sepsis of a limb. The site of these changes in the cord were related to the site of the sepsis and a similar mechanism may operate in localizing the lesions of disseminated sclerosis in the root entry zone of an infected dermatome. Brickner and Brill (1941) reported a deficient food intake in 27 out of 34 patients in the period preceding onset. The deficiency was particularly in relation to the fat intake. In their pamphlet 'Multiple Sclerosis: Diagnosis and Treatment,' the National Multiple Sclerosis Society of America state that the onset of multiple sclerosis or relapses are precipitated in about 40 per cent. of female patients by pregnancy.

Other factors, geographical, racial, familial and social may play some part in the occurrence of disseminated sclerosis. The disease is very rare in South Africa in the white, and does not occur in the black population; it is very rare in the Far East and India, and unduly common in Switzerland and in this country. Within countries of high incidence, many cases may be grouped within small localities. The familial factor is of proven significance in the incidence of the disease. Curtius

(1933), whose work has been criticized on the grounds of diagnosis, found another case of disseminated sclerosis in relatives of 10 of 106 patients. McAlpine (1946), who excluded any doubtful cases, found an incidence of 5 per cent. in 142 patients, and he and his collaborators have found this incidence to be maintained in a much larger series (unpublished work). In view of the estimated incidence of the disease in this country of approximately 1 in 6,000 (Russell Brain, 1930), these figures are significant. No evidence has so far been produced to show whether the increased familial incidence of the disease is due to intra- or extra-chromosomal factors. The Registrar-General's decennial supplement for the years 1921-1931 reveals an increased incidence of disseminated sclerosis in Social Groups I and II compared with other social groups. The chance of accurate diagnosis will obviously operate differently in different groups, but separate figures for males and females show a much steeper gradient of incidence from Group V to Group I for females than for males. As there is no reason why diagnostic accuracy should vary greatly between the sexes of each class, the figures for females are probably significant.

The modern conception of the aetiology of disseminated sclerosis can be summarized as follows.

There is a primary aetiological factor which remains unknown, but which operates more readily when certain secondary, or conditioning, factors are present, but as the process of demyelination in animals is a reaction form produced by numerous widely different agents, it cannot be denied that the lesion of disseminated sclerosis may also be a reaction form to a primary factor varying from case to case.

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BIBLIOGRAPHY

- BRAIN, W. RUSSELL (1930), *Quart. J. Med.*, **23**, 343.
 BRICKNER, R. N., and BRILL, N. Q. (1941), *Arch. Neurol. and Psychiat.*, **46**, 16.
 CURTIUS, F. (1933), 'Multiple Sklerose u. Erbanlage,' Leipzig.
 DOW, R. S., and BERGLAND, G. (1942), *Arch. Neurol. and Psychiat.*, **47**, 1.
 FERRARO, A. (1937), *Arch. Neurol. and Psychiat.*, **37**, 1100.
 GOOD, R. A., and CAMPBELL, B. (1948), *Proc. Soc. exper. Biol. and Med.*, **68**, 82.
 GREENFIELD, J. G., and KING, L. (1936), *Brain*, **52**, 445.
 HURST, E. W. (1942), *Aust. J. exper. Biol. and Med. Sci.*, **20**, 297.
 LUMSDEN, C. E. (1948), 'Studies in Demyelinating Disease,' M.D. Thesis, University of Aberdeen.
 MCALPINE, D. (1946), *Brain*, **69**, 233.
 MANDELBROTE, B. N., STANIER, M. W., THOMPSON, R. H. S., and THRUSTON, M. N. (1948), *Brain*, **71**, 212.
 MARGULIS, M. S., SOLOVIEV, V. D., and SCHUBLADZE, A. K. (1946), *J. Neurol. and Neuropsychiat.*, **9**, 63.
 ORR, D., and ROWS, R. G. (1914), *Brain*, **36**, 271.
 PUTNAM, T. J. (1935), *Arch. Neurol. and Psychiat.*, **33**, 929.
 RIVERS, T. M., SPRUNT, D. H., and BERRY, G. P. (1933), *J. exper. Med.*, **58**, 39.
 RIVERS, T. M., and SCHWENTKER, F. F. (1935), *J. exper. Med.*, **61**, 689.
 VON HOESSLIN, R. (1934), 'Uber multiple sklerose,' Munich.
 WAIL, S. S. (1935), *Virchow's Arch. f. path. Anat.*, **295**, 414.

Bovine Tuberculosis in the United States

Livestock production is an important industry in the United States. Dairy and dairy-beef production has been attracted by the big cities, particularly in the East and in the Lake States, whilst beef-production predominates in the prairie and mountain areas. The resulting widespread movement of cattle, whether for show purposes or for seasonal changes of pasture, has and will always afford an enormous opportunity for the spread of contagious disease throughout the country.

To counteract this, the Bureau of Animal Industry was formed in 1884. Its first big task was

to fight contagious pleuro-pneumonia which was then spreading to become a menace. Its eradication was completed by 1892. Further experience was obtained with foot-and-mouth disease, tick fever and sheep and cattle scab, which all in turn yielded to concerted measures so that by 1917 both cattle breeders and general public were to some extent aware of the possibilities of animal health control.

Demands for action against bovine tuberculosis were first made by public health authorities whilst the livestock industry was expanding to meet population needs. The Koch's tuberculin diagnostic reaction had been in use since 1892.

The Bureau began its wide-scale tests in 1906, and was soon able to show that infection was heaviest where cattle were concentrated, as in the milk-sheds of large cities, whilst large-scale movements of cattle gave ideal conditions for spread of the disease. Attempts of local authorities to deal with the disease proved useless. Only a comprehensive attack could succeed.

As a result of a meeting called by the U.S. Livestock Sanitary Association in Chicago in 1917 during the first World War, plans were drawn up which subsequently received both Federal and State backing. They provided for:—

1. The testing of all cattle by qualified veterinary practitioners.
2. Slaughter of all infected animals, with appropriate indemnity to the owner beyond the salvage value.
3. Cleaning and disinfection of all premises on which the disease had occurred.
4. Re-testing at stated intervals to detect re-infection.
5. Quarantining of infected herds.
6. Tuberculin testing of all cattle moving from one state to another, except those being shipped directly for slaughter.

Fortunately ample trained veterinary help was available. Short courses were given at State Agricultural Colleges, so that when the programme began 8,000 trained personnel were accredited to perform tuberculin testing.

For the first five years the 'accredited herd plan' was followed. It became immediately popular and 30,000 herds were accredited on a voluntary basis. Subsequent re-testing however showed that clean herds were being reinfected by adjacent infected animals. In 1922 the 'area plan' was adopted which allowed areas desirous of so doing, usually counties, to require testing of all cattle within their boundaries and the removal of all infected animals for slaughter upon payment of indemnity to the owner. The same stringent rules applied as under the 'accredited herd' plan. Non-infected animals in infected herds must pass three negative tuberculin tests before they are considered to be free from the disease. In areas where an infection rate of more than 2 per cent. is found, all cattle are retested after three years.

Where the infection rate is less than 2 per cent. State and Federal officials agree on the proportion of animals to be re-tested as a check.

There can be no doubt that the 'area plan' was the key to the situation. In the peak year of 1933, 25 million cattle were tested. The infection was found to be present in all areas but varied within wide limits, from almost nil up to 80 per cent. in some small areas where cattle were highly concentrated. In 1918, 4.9 per cent. of all cattle tested showed a positive reaction. This percentage fell gradually but steadily throughout the years between the wars to 1.5 in 1935. In 1936 it fell for the first time below 1 per cent.; in 1941 it was 0.3 per cent. and for the past five years has remained about 0.2 per cent. In 1948, 8,000,000 tests were carried out and less than 16,000 (0.19 per cent.) proved positive.

These figures were confirmed by the Bureau of Meat Inspection Division. Its officers, in the first year of the programme, either condemned or sent for sterilization 49,214 carcasses, representing 0.53 per cent. of all cattle slaughtered. By 1948 the percentage had fallen to 0.02, whilst in 1949 only 0.01 per cent. of 14 million cattle were involved. Savings from this item alone would almost pay the operating expenses of the programme.

So much for the effectiveness of the campaign, what has it cost? Since 1917 a total of 269,650,000 dollars has been spent, considerably more than half of the sum coming from state and county sources. Two-thirds of the sum has been paid directly to farmers as indemnity for the more than 4,000,000 infected cattle which have been slaughtered. The cost per infected animal has been roughly 67 dollars, of which 45 have been paid directly to the farmer. The total cost considered over the 32 years since the inception of the scheme has been approximately 10 cents per head per year for all the cattle on United States farms. For the year 1948 the total cost of the programme was 3,370,000 dollars, or about 4 cents per head of cattle throughout the country.

Surely this is cheap insurance.

From a paper by Dr. B. T. Simms, U.S. Department of Agriculture.

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1947, 1948, 1949, 1950, 1951, 1952, 1953, 1954, 1955, 1956, 1957, 1958, 1959, 1960, 1961, 1962, 1963, 1964, 1965, 1966, 1967, 1968, 1969, 1970, 1971, 1972, 1973, 1974, 1975, 1976, 1977, 1978, 1979, 1980, 1981, 1982, 1983, 1984, 1985, 1986, 1987, 1988, 1989, 1990, 1991, 1992, 1993, 1994, 1995, 1996, 1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025, 2026, 2027, 2028, 2029, 2030, 2031, 2032, 2033, 2034, 2035, 2036, 2037, 2038, 2039, 2040, 2041, 2042, 2043, 2044, 2045, 2046, 2047, 2048, 2049, 2050, 2051, 2052, 2053, 2054, 2055, 2056, 2057, 2058, 2059, 2060, 2061, 2062, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2070, 2071, 2072, 2073, 2074, 2075, 2076, 2077, 2078, 2079, 2080, 2081, 2082, 2083, 2084, 2085, 2086, 2087, 2088, 2089, 2090, 2091, 2092, 2093, 2094, 2095, 2096, 2097, 2098, 2099, 2100, 2101, 2102, 2103, 2104, 2105, 2106, 2107, 2108, 2109, 2110, 2111, 2112, 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