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The Aetiology of Disseminated Sclerosis

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Abstract

Based upon a Dissertation on "Disseminated Sclerosis" given before the Society on Friday, 10th January 1958. Disseminated sclerosis is the commonest nervous disease in this country; in the north of Britain at least one in 1300 adults is affected. If any rational or successful therapy is to be introduced the cause must be found and I therefore propose briefly to discuss the main theories of its aetiology.

Disseminated sclerosis is one of the primary demyelinating diseases (as opposed to those causing secondary demyelination such as infarcts) which can be defined as "diseases of the central nervous system showing destruction of myelin sheaths with relative sparing of axon cylinders and supportive tissues usually occurring in multiple foci."

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THE AETIOLOGY OF DISSEMINATED SCLEROSIS

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By J. G. TURNBULL

Le pronostic jusqu'ici est des plus sombres. En sera-t-il toujours du même? On peut espérer que lorsque la maladie sera mieux connue, le médecin apprendra à tirer parti de ces tendances spontanées aux rémissions que se trouvent signalées dans un bon nombre de ces personnes. Charcot. 1865.

Disseminated sclerosis is the commonest nervous disease in this country; in the north of Britain at least one in 1300 adults is affected. If any rational or successful therapy is to be introduced the cause must be found and I therefore propose briefly to discuss the main theories of its aetiology.

Disseminated sclerosis is one of the primary demyelinating diseases (as opposed to those causing secondary demyelination such as infarcts) which can be defined as "diseases of the central nervous system showing destruction of myelin sheaths with relative sparing of axon cylinders and supportive tissues usually occurring in multiple foci."

The main theories of aetiology are:—

- (1) The Strumpell-Muller hypothesis of dysplastic glial development.
- (2) Infective theories.
- (3) Biochemical and chemical theories.
- (4) Vascular theories.
- (5) Allergic theories.

Also various precipitating and aggravating factors such as climate, geography, trauma and infection, can be twisted and turned to fit most of the above theories.

The Strumpell-Muller theory arose from a mistaken concept of the pathogenesis of disseminated sclerosis, namely that the astrocytic overgrowth and occurrence of atypical monster astrocytes, seen otherwise in the malignant glioma, were evidence of a neoplastic process. However, in the earliest lesions astrocytes are not abundant and workers now agree that demyelination or loss of the satellite oligodendroglia is the first change. Oligodendroglia are absent even in the earliest lesion, and studies have shown that, when viable, their processes encircle the myelin sheaths like ribbons and it is likely that the integrity of the myelin depends to a great extent on these cells. They are the most sensitive cells in the C.N.S. and for this reason I would like to introduce the concept that the disappearance of these cells and perhaps therefore demyelination is the response to the least noxious agent able to harm the C.N.S. Indeed all the demyelinating diseases could then be considered as steps up the scale of destruction due to a variation in one of many possible factors, and it is interesting to note that in very acute disseminated sclerosis softening and liquefaction have occurred.

The infective theories arose from the occurrence of "epidemics" of disseminated sclerosis in different localities though many other factors such as those mentioned above could play a part. Indeed there is little clinical evidence that contact or similar factors are involved. Pathologically the lesion is not typical of infection; the perivascular cuff, absent in the early lesion, is probably a response to degeneration rather than to an organism.

The infective agents incriminated fall into three groups:

- (a) An exogenous organism might secrete a myelinolytic toxin acting via the circulation. Many bacterial toxins can cause experimental demyelination but attempts to incriminate any have repeatedly failed. It is interesting to note here that a high incidence of unsuspected sinus infections are uncovered at autopsy.
- (b) Older workers, including Steiner, thought that disseminated sclerosis was an atypical form of syphilis and the apparent response to arsenicals strengthened this theory. Steiner claimed to have found spirochaetes and silver staining debris in the C.S.F. at autopsy in disseminated sclerosis patients. Various claims for culture of these organisms were made at this time. Rabbits injected with C.S.F. of patients developed symptoms and lesions more similar to acute disseminated encephalomyelitis than disseminated sclerosis; both spirochaetes and silver staining debris were found at autopsy. However, better controlled experiments showed the organisms occurring in the control group as well, and these organisms were later proved to be normally present in rabbits. Why then did the previous animals show demyelination and why were spirochaetes found in human subjects? The answers to these questions are perhaps that the disease might be due to allergy or a virus in the rabbits and the organisms found in human beings might be a manifestation of post-mortem organismal dissemination analagous to that of *B. Coli* or *Cl. welchii*. The last word on this subject came from Ichelson in America, who claims to have cultured spirochaetes similar to Steiner's organisms from the C.S.F. in a high percentage of a large group of disseminated sclerosis patients and in none of a control group. Immunological evidence was also cited.

A virus has, of course, been suspected as the cause of disseminated sclerosis and not all work on this has been negative. In 1930 Chevassut stated that she had cultured a virus which she called Spherula Insula, from the C.S.F. of a high percentage of disseminated sclerosis patients and from none of a control series. Animal inoculation was inconclusive and though she claimed that a therapeutic vaccine gave clinical improvement and that the sera from vaccinated patients inhibited the growth of the spherula, her work has since been discredited.

In 1946 Margoulis compared acute disseminated encephalomyelitis (A.D.E.) with disseminated sclerosis clinically, pathologically and experimentally and noted the following points:

- (a) The occasional clinical transition of A.D.E. to disseminated sclerosis.
- (b) The pathological differences were merely an expression of acuteness or chronicity of the lesions.
- (c) The isolation of a virus from the C.S.F. of A.D.E. patients and its neutralisation by the sera of fifty per cent. of a group of disseminated sclerosis patients and seventy per cent. of A.D.E. patients.
- (d) Vaccine therapy giving apparent improvement in disseminated sclerosis patients.

A more critical investigation published only this year discredits the above.

Perhaps it is appropriate to say here that all workers claim some improvement for therapies based on their ideas of the aetiology.

Before leaving the infective theories it should be pointed out that the hypothetical organism need not liberate a demyelinating toxin or cause demyelination itself as the demyelination might be due to the endogenous release of a myelinolytic agent in response to some organismal irritation.

Therefore the various theories still to be discussed do not necessarily contradict the above.

Many chemical agents such as carbon monoxide, bacterial toxins, and sodium taurocholate cause demyelination, but the most studied is cyanide. Variation in the size and frequency of doses given to animals caused lesions from acute cortical necrosis to chronic demyelination. Massive doses produced liquefaction and death, medium doses caused a picture akin to A.D.E., and small doses led to lesions like disseminated sclerosis. It has been suggested that while the large doses affect their high immediate oxygen requirements, the neurones are able to resist the small repeated doses because of their adequate oxidative enzyme systems and circulation.

Marburg postulated that a circulating lipase might produce the demyelination and produced this possibility *in vitro*. He claimed to have observed raised lipase levels in the urine of disseminated sclerosis patients and advanced liver or pancreatic disease as the possible cause. Although later work failed to confirm this, a lipase might be produced locally from cellular ferments and if this were so, it would be "used up" locally and it is unlikely that much would reach the general circulation. Along similar lines Lumsden thinks that the enzymes for manufacture and breakdown of myelin might exist side by side in the oligodendroglia and an imbalance in these might be the cause.

Could disseminated sclerosis be a deficiency disorder like pernicious anaemia or a heavy metal poisoning? Campbell in 1947 reported that four out of seven scientists working on swayback "contracted" disseminated sclerosis, and though other factors may be involved this incidence is striking. Swayback is a disease of lambs born in certain areas and it is characterised by low copper levels both in the ewe and in the lamb; the pasture is not deficient in copper. Pathologically it resembles another human demyelinating disease called Schilder's disease. High lead levels have been found in areas with swayback and in areas with disseminated sclerosis, but this relationship is by no means constant for either. Swayback notoriously occurs in highly limed areas. If a swayback producing ewe is taken to a non-swayback area and even fed on a low copper diet she does not produce swayback lambs. Obviously something in the pasture has interfered with the absorption or metabolism of copper. We can postulate (a) high lead levels preventing absorption of copper, (b) a virus acting in the presence of, or causing, copper deficiency. Admittedly there is no evidence of copper deficiency in disseminated sclerosis but an important role is played by this element in some enzyme systems.

Lead poisoning has been incriminated as symptoms and signs, similar to those in some chronic neurological conditions, have been observed in plumbism, and early workers reported raised levels of copper in the tissues of patients. Again recent work by better methods has contradicted these findings and it has been pointed out that in disseminated sclerosis other clinical stigmata of plumbism were absent. Here again lead may be completely involved in enzymic activity.

Hyperinsulinism has been shown to have a relationship to disseminated sclerosis in a very high percentage of cases and disseminated sclerosis is very rare in diabetics. Could glucose starvation affect the myelin?

Before leaving this field of speculation, one of the latest theories from Canada must be considered. Noble thought that disseminated sclerosis might be due to a deficiency of those fatty acids which are essential for myelin formation. He therefore fed a small group of patients with fatty acids of beef cerebroside and claimed therapeutic improvement. When the

allergic theories are discussed it will be seen that this was perhaps a dangerous experiment.

The vascular and allergic theories are the most attractive and convincing of all.

Putnam noticed thrombi in some autopsy specimens and thought that these might be the cause of disseminated sclerosis particularly in view of the perivascular plaques. He conducted experiments in which he observed: (a) Demyelination akin to A.D.E. as a result of various thrombosing procedures in dogs; and (b) that in disseminated sclerosis the coaguability of the blood was increased. Other workers, however, though admitting the perivascular distribution of plaques and occasional thrombi, said that these were either secondary to vascular spasm, intimal damage, venous stasis and exudation which were seen histologically or due to a thromboplastic substance released from the plaques. The blood coaguability was lowered more often than it was raised in disseminated sclerosis.

Interesting evidence was put forward by Brickner who noticed vascular spasm in the fundal vessels with an associated scotoma. Vasodilator therapy cleared up these signs and he has even treated some patients with a continuous alcohol drip. This does not conflict with the findings of more permanent lesions since prolonged vascular spasm would obviously lead to changes which drugs could not affect.

Other workers have noticed general vascular changes such as spasm in the small vessels, and degrees of tortuosity and dilatation, which they believe are secondary to the spasm. While these changes were most noticeable in the lower extremity the effects of general vascular disease would surely occur first in the highly sensitive C.N.S.

Finally, in considering allergy in the C.N.S., some of the hypotheses tend to find a common denominator.

Clinically, the evidence for allergy is almost overwhelming: (1) the high incidence of other allergies, (2) the onset of these allergies just before the onset of disseminated sclerosis, (3) the course of the disease and the precipitation and aggravation of the disease by factors acting similarly on other allergies; nevertheless the poor response to A.C.T.H. and anti-histamines and the somewhat more promising results of histamine-diphosphate therapy must be borne in mind.

Ferraro in 1946 compared the extent of the pathology with the manifestation of allergy, and abhorred the tendency of creating new disease entities out of minor histological differences. All these diseases, he said, could be understood and explained on an allergic basis.

Experimental parenteral injection of heterogenous or damaged homologous brain has produced demyelination in rabbits varying in intensity and character with the size and frequency of dosage and at the same time brain specific antisera were produced. The antigen was abundant in the white matter of the brain used, and it was never present in foetal brain in portions which had neither myelin nor oligodendroglia. How then can this be correlated with disseminated sclerosis?

By and large, attempts to incriminate known antigens have failed and the degree of correlation between disseminated sclerosis and other allergies of the C.N.S. is small. Perhaps, therefore, the secret lies in the property of damaged homologous brain tissue to act as an antigen and provoke a response within the brain. Anything which damages the myelin or oligodendroglia might set up a self-perpetuating auto-sensitisation. An antibody-antigen reaction would cause demyelination and provoke further release of antigen, in its turn increasing antibody production. The antibodies would of course

have to attain a critical level before a perceptible reaction could take place, thus explaining the relapsing and remitting course of the disease.

What conclusions can be drawn from this account? It is suggested that demyelination can follow a diversity of antecedents and is probably the least response of the C.N.S. to noxious agencies. The most satisfying explanation is auto-sensitisation to nervous tissue. "Disseminated sclerosis," said Kurland, "is not a specific disease but a syndrome with multiple aetiological agents and several mechanisms. An initial damage to the central nervous tissue with release of antigen finally perpetuates auto-sensitisation to nervous tissue."

INTERRUPTED FERTILITY *(continued from page 22)*

begins now to recover her appetite & gets strength, the bones always come away with a purging & some coagulated blood with, & after, her stools with a sharp tresmus.

During the summer she had passed several small bones, but her appetite & strength is much mended, having gone in a coach to Twittenham 4 miles distant from London, she was so ill from the jolting that she was obliged to be brought home in a chair and the day following seventeen bones mostly ribs were extracted, & as most of them lay transversely I was obliged to turn them & bring them away lengthways, this could not be effected without a great effusion of blood and the most excruciating pains. In October the remaining bones of the cranium came away all but one, these bones having three edges were always followed a profuse haemorrhage. In November she was troubled by the Whites & a heat in her urine. In December the largest and only remaining bone of the cranium was extracted, the swelling of her belly subsided, & she has recovered her strength greatly. In February 1776 her courses appeared & the next ensuing period, but both times by the anus, of which she made grievous complaint, I assured her they would soon come the natural way, which happened the May following, since the above she has been married to a second husband, by whom she had three childrine. The girl which she was delivered in October 1775 is still alive and a fine healthy girl.

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