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MULTIPLE SCLEROSIS: PLAQUES CAUSED BY 2-STEP DEMYELINATION?

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ABSTRACT

Selected studies concerning events at the contour of a progressive plaque are reviewed and an explanation of the subtle changes in periplaque white matter which various investigators have observed on autopsy or biopsy is presented. Recurrent exposure to toxic small molecular weight substances carried by arterial blood and capable of diffusing through the walls of blood vessels cause modification of protein or glycoprotein in the myelin sheath. These then act as allergens (modified native tissue considered as 'nonself' tissue by the immune system) which induce antibody formation (termed allo-auto-allergy). Phagocytosis of altered myelin, debris removal and cellular action to maintain homeostasis in the fluid surrounding neurons characterize the premorbid phase of multiple sclerosis.

We suggest that the accumulation in the perivascular space of macrophages with large lysosomes digesting myelin debris (visible in electron micrographs) causes bottlenecks in the lymphatic channels serving the extracellular space near nodes of Ranvier. This changes the chemical microclimate and leads to the second step of demyelination and degeneration of the oligodendrocytes, i.e. plaque formation.

Reference is made to outstanding problems. Research into the diffusion of small molecular weight substances into the extracellular spaces of white matter would aid in evaluating the hypothesis.

Key words: multiple sclerosis, demyelination, methyl alcohol, formaldehyde, fructose.

INTRODUCTION

In a table classifying demyelinating diseases multiple sclerosis and its variants are grouped under the heading of: 'immune (allergic) and virally induced disease' (13). That the classification is not necessarily final has been indicated by 'possibly'. Few scientists would disagree with this classification, but diverging opinions exist. In a discussion of the future direction of MS research an older etiological view has recently been restated: 'MS could be caused by a circulating compound of low molecular weight'. (29)

In the following we will test whether the insights of brain physiology permit this etiological model to be considered, i.e. whether this could explain demyelination in terms of molecules and cells.

For our discussion we will use methanol as the 'low molecular weight agent', as it is an endogenously occuring substance and as there is a remarkable similarity of the coeco central optic neuritis in MS (17) and in methanol poisoning. However, the model developed is applicable to any agent capable of entering the matrix of membranes and exerting an effect on myelin.

BACKGROUND

Fig 1 shows a section through the contour of a progressive plaque, with various authors findings and views given in telegraph style. Which region of the plaque they apply to is indicated diagramatically. More detailed information will be given where needed as the interpretation of data develops. The diagram of cell counts at the bottom of the figure is adapted from (7). In view of the difficulty of differentiating between the various types of small round cells, the information in the original concerning number of oligodendrocytes has been omitted. Also what was named total glia(?) cells includes in our interpretation all cells in the plaque contour, i.e. oligodendrocytes, astrocytes, microglia cells, macrophages, lymphocytes etc. NADH-dehydrogenase is representative of the oxidative enzymes – thus representative of energy input –; acid phosphatase is a hydrolyzing enzyme representative of decomposition of compounds.

For the ensuing discussion it is necessary to give a thumb-nail sketch of the pathogenetic process envisaged in the 'Methanol Hypothesis' (MeHyp) (9):

Under certain conditions simultaneous presence of methanol (mostly from pectins) and fructose (from sugar-rich food) can lead to competitive inhibition of critical enzyme-catalysed reactions. Due to the fact that alcohol dehydrogenase is common to the degradation pathways of both formaldehyde (the degradation product of methanol) and glyceraldehyde (the degradation product of fructose), formaldehyde may accumulate and bind to the NH_2-groups of amino acid side chains, forming a so called Schiff base. The change causes a new material, not present at birth, to be noted by the immune system and antibodies against this newly formed 'nonself' tissue (actually modified native tissue) is released. Venules are the 'locus minoris resistentiae' where methanol can continuously act by pathocline selection of damage on myelin and thus induce the growth of plaques.

A paper (12) which, as with the other findings referred to in fig 1 ought to be read in the original, shows the distribution of myelin associated glycoprotein (MAG) using an immunocytochemical technique. For the present discussion the following is of importance:

MAG is found in periaxonal regions of myelinated fibres. In tissue from normal white matter myelin sheaths are intensely stained. Diseased myelin shows decreased staining. The finding in MS lesions is the extension of decreased MAG immunostaining into white matter which appeared normal when stained with the antiserum for another associated protein (Basic protein). Distribution of the lightly staining MAG forms a kind of halo or corona effect around a plaque. It can be concluded that MAG is still in situ in the myelin, its altered staining behaviour being due to some modification.

Fig 6 shows that a plaque as identified at autopsy, i.e. a lesion surrounded by apparently normal white matter, really should be thought of as being surrounded by white matter which has undergone a subtle change. Truly normal white matter may occur only at a considerable distance.

For understanding the pathogenesis the findings and insights juxtaposed in fig 1 can give a clue if we ask the right question. White matter of all mammals and in particular of all primates is much the same, but MS is an exclusively human disease. The question arises as to why a small proportion, but nevertheless considerable number, of human beings should suffer from the microscopical abnormalities (the area of precursory change of figs 1 and 6) observed. This might be considered as rephrasing the fundamental question of MS research, but we hope to show that it has a useful twist.

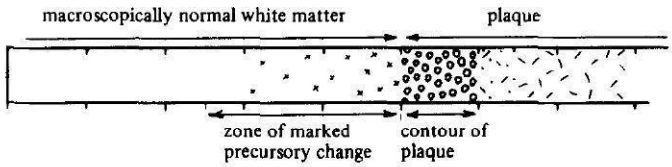
THE CELLULAR AND CHEMICAL ENVIRONMENT OF THE MYELIN SHEATH

A homeostatic system controls the fluid environment of nerve and glial cells. (14) (20)

Fig 2 shows that molecules can diffuse to and fro without meeting a barrier from the perivascular space to the node of Ranvier through a cleft approx. 20 nm wide. At the node ions move in and out of the axis cylinder with impulse and recovery, as nerve signals move from node to node. For neural function ionic composition of extra cellular fluid (ECF) at the node of Ranvier has to be maintained within narrow limits (homeostasis). The black arrows indicate

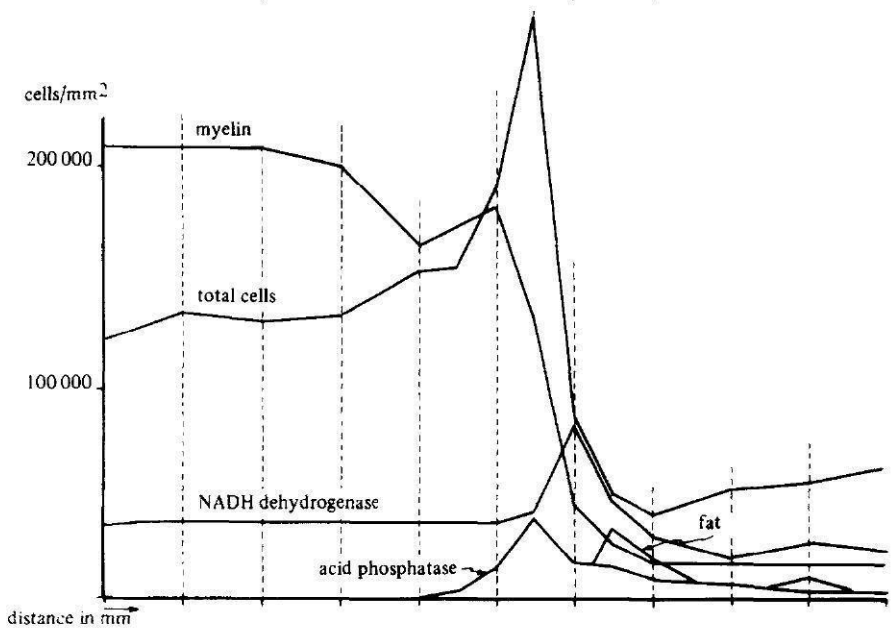
ig 1. **Juxtaposition of various authors findings/insights concerning events at contour of progressive plaque**

he diagram is adapted from fig 1 in *Enzyme Histochemical Studies in Multiple Sclerosis*, by R.L. Friede, Archives of Neurology Vol 5, 103-113 961. It shows: Numbers of cells, numbers of cells with acid phosphatase activity, numbers of cells with fat; densiometric measurements of mye- n (Sudan black staining), and NADH dehydrogenase activity. The counts are expressed in cells/square mm tissue, the densiometer measurements n scale parts. Each subdivision on the horizontal axis represents 1 mm along a line drawn across the contour of the plaque.



Zones intersected at right angles to contour of a progressive plaque (see fig 6 for plaque cross section and key)

uthor/Ref	Finding/insight (see text)
riede '61	zone of destruction of myelin sheath.
	zone of microglia (?) cells with acid phosphatase activity
	zone of cells loaded with fat droplets.
umsden '72	immunoantibodies responsible for demyelination.
rineas & aine '76	microglia cells contacting intact sheaths and effecting reduction in thickness.
rown '78	loops of split myelin being seperated by segments of macrophages.
toyama et al '80	decrease of MAG immunostaining.
lenzi '80	formaldehyde altering conformation of proteins.
rgyrakis '80	inclusive bodies in glia cells within and outside the lesion.
'on Allen '80	astroglial abnormalities in 'normal' white matter.
ourtelotte et al '80	IgG appears to be produced in and around MS plaques.



how molecules (and at times cells) can move in and out of the cerebro-spinal fluid (CSF), the blood and the cells bordering the cleft, Astrocytes are particularly in a position to influence ECF with ionic pumping etc. and so to maintain homeostasis. They presumably cooperate with endothelial cells of the capillaries to determine the chemical microclimate surrounding the myelin sheath.

In the bottom diagram of fig 2 a schematic cleft is shown with the black arrow indicating normal movements of molecules etc. Brain capillaries are characterized by tight junctions between endothelial cells. Under normal conditions blood solutes follow the black arrows, i.e. are exposed to endothelial cell cytoplasm before reaching the ECF. A small lipophilic molecule able to penetrate the membrane can however gain access by diffusion (white arrow) (4). Such illicit immigrants constitute an abnormal stimulus and we will class these as MCP = Molecules characterizing pathology. MCP would tend to diffuse throughout the cleft. Astrocytes then increase activity to remove such molecules through their membranes and/or flushing out towards perivascular space, thus maintaining homeostasis at the nodes of Ranvier (14,20,8,4). The graph in fig 2 showing the distribution of MCP over the length of the cleft is self-explanatory. According to the MeHyp the repetitive simultaneous presence of methanol, fructose and their metabolites induces pathology. Labeling techniques using methanol and fructose at physiological concentrations, may permit this to be mapped. Evidence of this sort combined with the obligatory venular relationship of MS plaques would give strong support to the hypothesis.

As pathology develops, MCP in our graph must contain all sorts of molecules besides methanol. These originate from the increasing and changing cellular activity in the cleft and are being flushed towards perivascular space which acts as a lymphatic channel (26).

The hyperactivity of astrocytes (increased molecular pumping etc.) referred to above is a well established phenomenon of MS pathology (23,5,8,4,1,15). Observation in 5 active pontine-medullary cases of MS (2) seems to tally very well with the deduction that in MS the blood brain barrier is at times breached by an agent capable of causing edema, and the consensus is recorded that edema occurs before cellular infiltration.

Two separate observations in the literature present corroborating evidence:

(i) The increase in sodium necessary to produce enzymatic changes in astrocytes in culture (experimental hyperactivity) was of the magnitude of the increase of sodium reported for edematous brain tissue (8).

(ii) White matter away from the zone of damage (necrosis due to methanol) showed mild astroglial hyperplasia (18). (This is from an autopsy report of a case surviving acute methanol poisoning for 13 months).

In view of the MeHyp concept of competitive inhibition, it is obviously of interest to consider whether fructose does occur in the brain. It seems probable that fructose is not transported by the endothelial cell into ECF as the hexose carrier (carrier protein in membrane of endothelial cell) exhibits significant affinities only for D-glucose, mannose, galactose, 3-0-methyl-D-glucose and 2-deoxyglucose. There is no measureable affinity for fructose or for L-glucose (20). Fructose can therefore not readily traverse the membranes of endothelial cells, i.e. it is unlikely to enter astrocytes. However there are reports that fructose occurs in normal lumbar CSF e.g. 4,0 mg/dl (extreme values 1,8 to 13 mg/dl) (6, table 6-1).

The fructose in CSF may of course have come from ECF or from elsewhere in which case it could diffuse into ECF. Table Geigy (7th edition) shows the relevant enzymes for fructose/glyceraldehyde degradation to exist in the brain.

No figures have been found for methanol occuring in CSF, but methanol in blood does reach the inner spaces of the brain. Diffusion has been demonstrated at concentrations several orders of magnitude below the levels measured in victims of acute methanol poisoning.

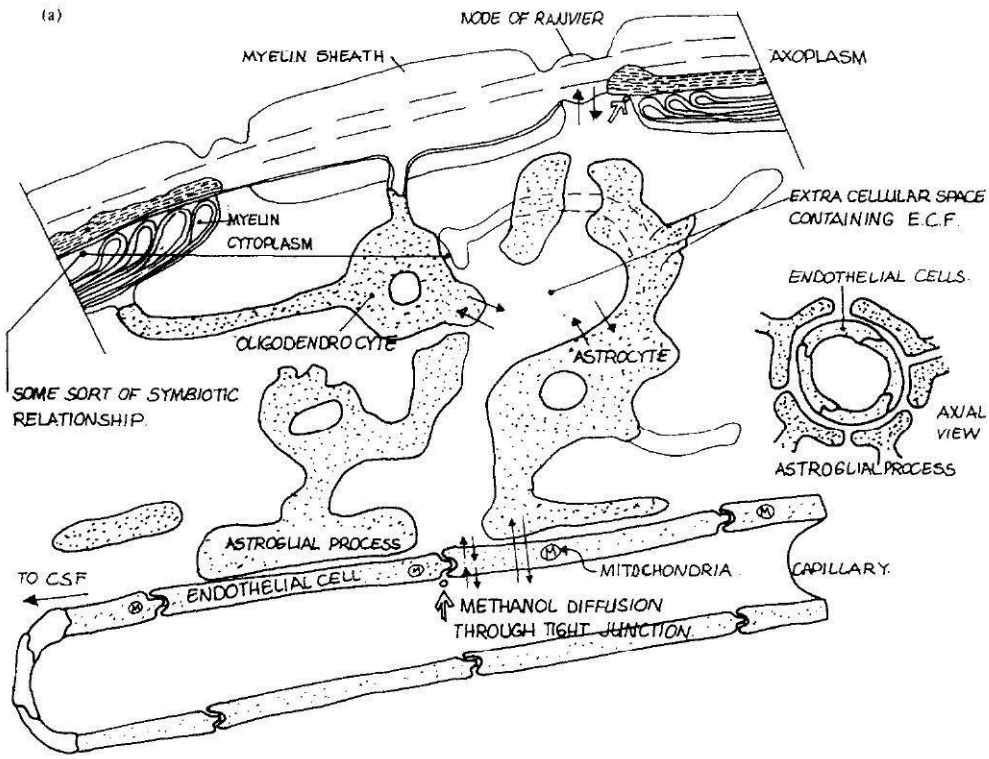
In experiments with well nourished adult male alcoholic volunteers a state of ethanol intoxication (blood ethanol level maintained at 200 to 400 mg/dl) of ten to 15 days duration was induced. This permitted the changed methanol degradation/elimination due to competitive inhibition of certain enzyme catalysed reactions (alcoholdehydrogenase!) to be monitored (16). Prior to the experiment, endogenous blood methanol content (we believe this stems at

Fig 2. **Cleft forming a direct pathway from capillary to node of Ranvier**

(a) is a map showing spatial relationship, dimensions not in proportion, adapted from Kuffler and Nicholls (1976) (14).
The cleft approx. 20 nm wide forms an aqueous extracellular pathway open to diffusion. Extra cellular fluid (ECF) influenced by movement as indicated by black arrows and diffusion to and from CSF. White arrow indicates additional movement in pathology (see text).

(b) shows the principle of the channel formed by the cleft and its continuation into the perivascular space. Astrocytes can influence ECF by ingestion and/or ionic pumping (outward flow of fluids) that will flush undesirable molecules towards drainage.

(c) shows the distribution of concentration of 'molecules characterizing pathology' (MCP) over the length of the channel as per (b). Experimental evidence (16) gives some support to the relative length of ordinate shown at node of Ranvier and at the perivascular space.
The heavy dotted line represents the influence of molecular pumping on chemical microclimate as necessary to maintain MCP at the node of Ranvier within permissible homeostatic limits.



least in part from pectins) was 0,1 mg/dl or below, after 4 to 8 hours experimental drinking of ethanol 0,2 mg/dl were recorded, and this increased progressively to reach values above 2 mg/dl within 5 days. From the symptoms observed at the end of the experiment it has been concluded that this methanol in circulation had a pronounced effect on the brain in the phase when ethanol had been degraded but methanol level was still elevated, i.e. it had breeched the blood brain barrier.

METHANOL TRANSFORMING HOST'S TISSUE INTO ANTIGEN

The data referred to above and the present understanding of the construction of capillaries and venules in white matter permits us to make the following postulate for the purposes of our model:

The pathologic event in the CNS of an MS patient may be a change in the chemical microclimate in the extracellular space surrounding the nodes of Ranvier of neurons. This could occur through episodic entry of methanol molecules into perivascular space from where they could diffuse into ECF.

As indicated in fig 2 methanol etc, i.e., MCP, could at times upset homeostasis at the nodes of Ranvier. In these episodes low molecular weight substances like methanol and fructose are free to soak in between myelin layers.

Myelin, an extension of the oligodendrocyte membrane, has a complex metabolic machinery not yet fully understood, but channels of cytoplasm and some form of molecular replacement are known to exist (5,19).

The chain of events postulated in the MeHyp can now be expected: 'Degradation of methanol to formaldehyde and attachment thereof to side chains of amino acids' (9). The changed immunostaining observed outside the contour of plaques in myelin-associated glycoprotein is in line with this concept (12).

In this manner, in all clefts affected, some myelin molecules would become 'nonself' molecules, i.e. antigens.

Simultaneously methanol must be expected to enter into the cell membranes surrounding ECF. Fructose would not traverse these membranes as the hexose carrier does not accept fructose, Methanol molecules entering the cytoplasm of neurons, oligodendrocytes, astrocytes endothelial cells will undergo normal enzymatic degradation. These cells serve as a sink for methanol, so unless there is another influx of molecules ECF would again be normalized.

In myelin, however, considering its slow molecular replacement rate as compared to a normal cell, the 'nonself' molecules are in existence for a significant time. These act therefore as antigens for an immune reaction. The various types of cells that have been observed by electron microscopists appear on the scene (see fig 1). As the traditionally utilized allusions such as immunopathologically mediated disease process, pathology associated with autoimmunity etc, are insufficiently precise for this detailed model, the term allo-auto-allergy has been introduced (9). The name defines an allergic response (allergy) to hosts own tissue (auto) in which antigenic determinants, which were not present at birth, have been created by an external factor (allo).

MOBILE CELLS IN PERIVASCULAR SPACE

In the course of this inquiry, while musing over possible disease processes in terms of molecules and cells and how they move and change, we found it helpful to give thought to the many different types of cells found by electron microscopy in the perivascular space in the white matter of MS patients.

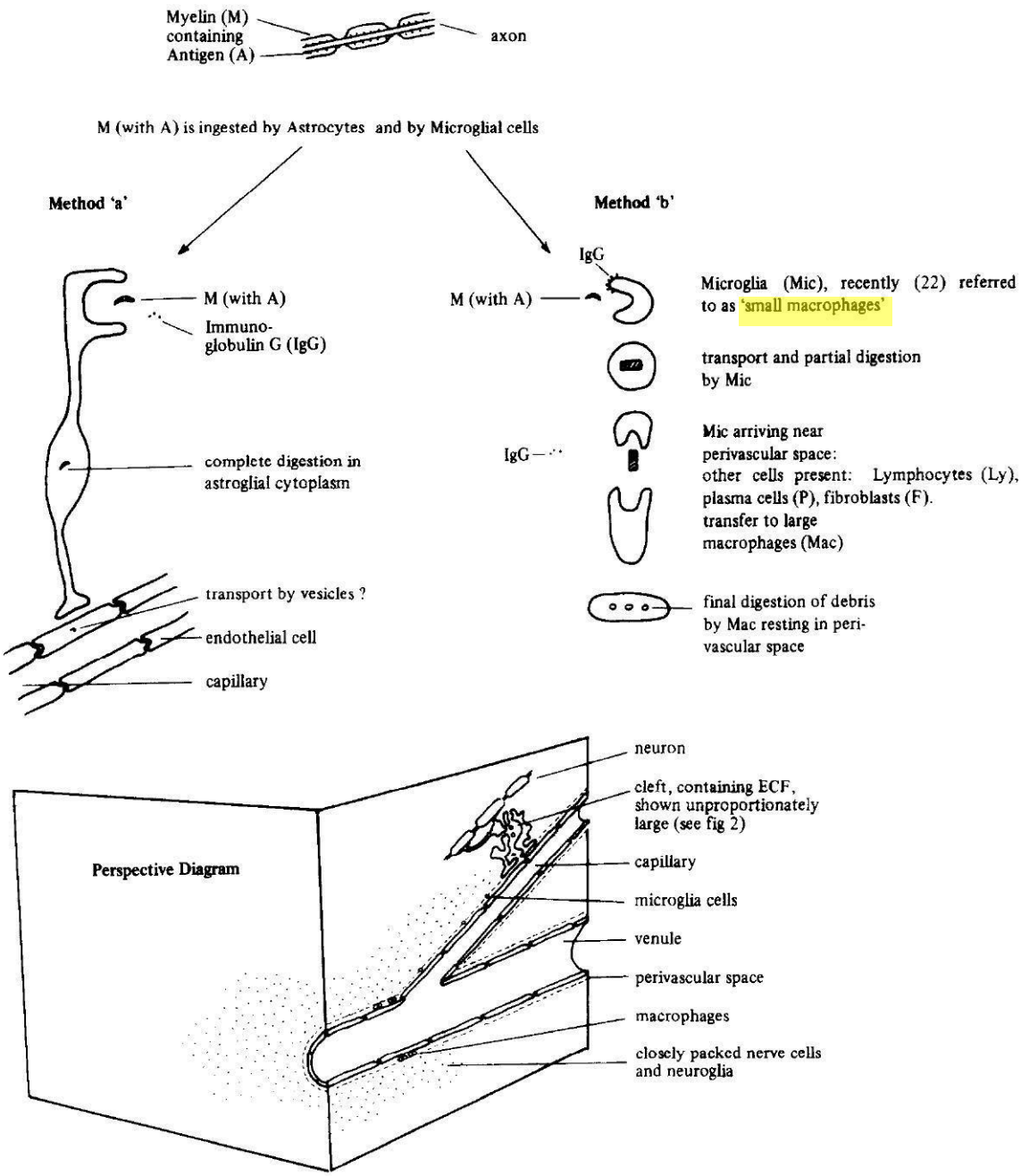
	Perivascular cells observed: As per table 2 in ref. 25	
	In uninvolved white matter	In a chronic plaque
	%	%
Lymphocytes	52,5	31,3
Macrophages	22,8	19,3
Monocytes	0,8	1,1
Plasma cells	3,8	15,5
Mast cells	0,1	0,2
Fibroblasts	17,4	26,1
Unclassifiable	2,4	6,5

Fig 3. **Pictogram flow sheet of myelin attenuation and disposal**

Flow sheet based on work by Prineas and collaborators (& other authors). It attempts simplification whilst preserving the essentials. (1, 2, 4, 6, 19, 21, 22, 23, 24, 25).

The process pictured in method 'b' takes place partly in the cleft and partly in perivascular space.

In the Perspective Diagram (dimensions not to scale) it should be imagined that macrophages from a great number of clefts will come together in the perivascular space of a venule where they remain during the lengthy period of myelin debris digestion.



In the sources referred to in fig 3 a wealth of information on immunological events in the periplaque white matter and the plaque contour is given. Together with the many electron micrographs they permit an interpretation of cellular dynamics. In the MS pathogenetic process there are apparently two methods of myelin attenuation and debris disposal operative side by side in the cleft leading from capillary to node of Ranvier:

(a) Through structural cells
Reactive astrocytes ingest and digest myelin. Other happenings, although infrequently observed, are ingestion of IgG by astrocytes or edema of astrocytic cytoplasm.

(b) Through mobile cells
Small macrophages (microglia cells? see fig 1) with IgG participation remove and ingest myelin and transport debris near perivascular spaces. En route myelin is only partly digested and on arrival the cells still contain recognizeable myelin debris. This is transferred to macrophages with large lysosomes in the presence of lymphocytes and plasma cells. The perivascular macrophages transform debris in lipid vacuoles and remain in situ in the perivascular space for a considerable time.

This 'considerable time' is important. The process may take up to a year (1). The Marchi-positive sudanophilic lipid that accumulates is mainly esterified cholesterol and is removed only slowly from the central nervous system.

Fig 3 shows in diagramatic form how these methods work. The perspective diagram shows how the macrophages with large lysosomes are sitting immobilized in the perivascular space of nearby venules. The flow sheets have deliberately been kept as simple as possible ignoring immune complexes etc. Method (a) can be presumed to become operative soon after astrocyte activation but must be of quite limited capacity. Method (b) would be introduced as soon as the immune reaction gets really under way. Electron microscopy revealed that both are operative in those areas of partial myelin loss which occur in macroscopically normal white matter, i.e. long before myelin is being removed in the substantial quantities that plaque development entails.

DISTINGUISHING STAGES HELPS TO VISUALIZE THE SEQUENCE OF EVENTS

Fig 4 shows MCP in action at various intensities in graphs of the type of fig 2c, again arranged below the diagramatic presentation of the channel as per fig 2b. In the top 3 graphs MCP at a node of Ranvier is either zero, or so minute as to hover just above the upper homeostatic limit of NM, these we will call stages t_0, t_1, t_2 and discuss them in turn.

Stage t_0: This is preliminary to real pathology. Metabolic complexities have brought about a 'methanol in blood episode' and methanol is diffusing through junctions of endothelial cells towards nodes of Ranvier. Astrocytes respond with molecular pumping and prevent methanol molecules from getting near the nodes. The episode passes, methanol gets eliminated, no MCP has entered myelin, normal conditions prevail again in cleft.

Stage t_1 : In this stage a somewhat higher methanol content in blood occurs or the episode is of longer duration, so that the presence of diffusing molecules at the node of Ranvier can not be completely avoided by the astrocytes molecular pumping. Methanol is penetrating into myelin, where its degradation product formaldehyde can attach itself and form antigen. The pathologic process has started, there is edema as lymphocytes and plasma cells are appearing. When the episode of 'methanol in blood' passes edema persists, as there is antigen left behind which the immune system will seek out and eliminate.

Stage t_2 : This is a later episode following t_1. Due to the presence of methanol and the immune reaction, myelin swelling and loosening and some attenuation is in progress as per the methods (a) and (b) of fig 3. The stage is reached in which macrophages with large lysosomes are settling down in perivascular space, digesting myelin debris.

Events in stages t_1 and t_2 have to be visualized as occuring during repetitive transient toxic periods, each MCP rise followed by a return of homeostatic conditions, but each time additional antigen will have formed, further fueling the immune reaction. The duration of t_1 and t_2 has to be thought of as weeks, months or years depending on frequency of 'methanol in blood' episodes and the level reached.

Fig 4. **Distribution of MCP (Molecules characterizing pathology) during the different stages**

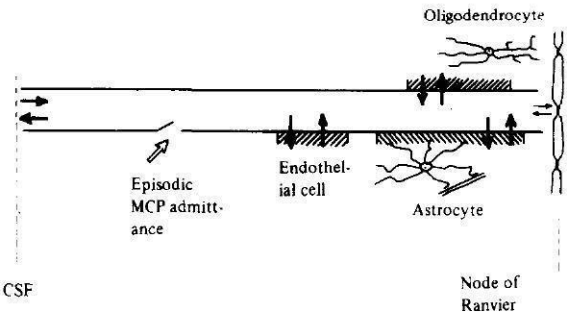
The diagram is a repeat of fig 2b; consult explanations under 2b and 2c. On the graphs the surmised distribution of MCP over the length of the cleft is shown. No scale is given for the ordinate; at this stage absolute values are not available. Relative values have been chosen in line with blood methanol values measured in the experiment quoted (16).

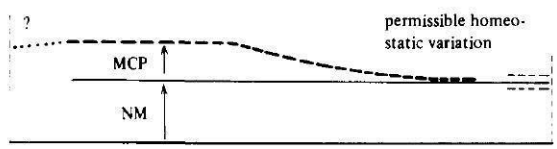
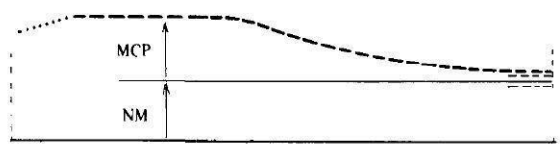
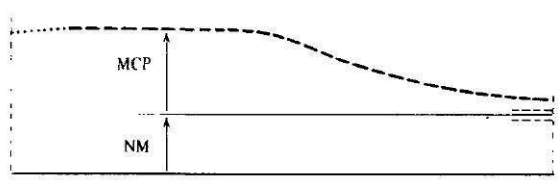
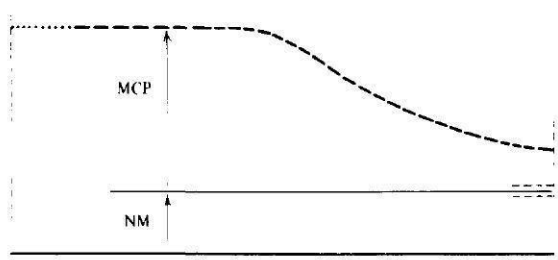
Note: (i) The chemical microclimate in the cleft during t_1 and t_2 is considered to be responsible for the subtle changes in white matter as observed in the area outside the contour in autopsy (23) and biopsy (4). The biopsy case permits judgement of premorbid change.

(ii) The chemical microclimate in the cleft during t_3 is considered to be responsible for plaque growth, i.e. the morbid phase of MS.

(iii) The chemical microclimate in the interior of the plaque (stage t_4) is not discussed at this stage.

NM denotes normal molecules at node of Ranvier under homeostatic conditions.



Stages:		**Activity of Astrocytes**	**Activity of Oligodendrocytes**
t_0		increasing level of oxidative enzymatic activity	normal (high) level of oxidative enzymatic activity
t_1		hyperactive, intense molecular pumping and starting to phagotize	as above
t_2		as above, but also enlarged astrocytes containing reaction products and IgG occuring	as above
t_2/t_3 transition		as above	MCP penetration of membranes, attenuation exceeding replacement, start of oligodendrocyte degeneration
t_3/t_4 transition	the cleft is changing to become scar tissue	active	degeneration proceeding

Astrocyte processes filling space formerly occupied by oligodendrocytes. Mainly a rearrangement, with the number of astrocytes in plaque interior remaining about the same as in normal tissue. (7)

The next stage of the pathologic process (a stage which clefts just outside the contour of a progressive plaque would have reached) is depicted in fig 4 under 't_2/t_3 transition' in the next lower graph. A considerable level of MCP is shown at the node of Ranvier. We assume that such a change of chemical microclimate can come about if many repeated episodes of 'methanol in blood' have caused so many macrophages and auxiliary cells to accumulate that their presence has a bottleneck effect on the lymphatic channel through which the drainage of MCP into CSF would normally occur. (Compare fig 3 and 5a).

This permits a discussion of the more intense myelinolysis and the start of oligodendrocyte degeneration occuring at the plaque contour in terms of the lipophilic methanol penetrating the matrix of membranes and playing havoc. Once started, lysis will aggravate the situation by releasing lysosomal enzymes from degenerating cells. Oligodendrocytes would obviously be more vulnerable than astrocytes, which via astroglial processes obtain what they need directly from the capillaries. Thus during stage t_3 the self agravating lysis would run its course, myelin sheath and oligodendrocyte disappear and astroglial processes are filling the space. In the t_3/t_4 transition the original cleft has disappeared and for that reason an MCP graph cannot be presented. Disappearance of myelin and oligodendrocytes is characteristic of the inner boundary of the plaque contour, where in the immunofluorescence test (15) a sharp boundary is visible between the outer antigen-containing (fluorescing) and inner non-antigen-containing (dark) tissue. This is in line with the model presented here, at the t_3/t_4 transition all antigen has been removed by lysis or by formation of immune complexes.

Clarification is still required regarding the origin and ultimate fate of the cells observed in the perivascular space (see table 2 quoted above and discussions in (1,5,24), as well as the pathophysiological significance of changes in B and T cells in MS (6).)

The model presented, which avoids the complexities of an aberrant immune system, may permit elucidation in due course. In view of the very different demyelinating mechanisms, it seems useful to speak of the immunological process in stages t_1 and t_2 (fig 3) as the first step of demyelination and the myelinolysis in stage t_3 as the second step of demyelination.

TENTATIVE APPLICATION OF INSIGHTS GAINED AT THE MICROSCOPIC LEVEL TO MACROSCOPICALLY VISIBLE PLAQUES

The expression 'plaque' was applied to a macroscopically visible area of scar tissue noted on autopsy. Many of these are roughly spherical or ellipsoid bodies, although special shapes occur. In this paper we are discussing the principle of growth only and are looking at a simple pattern of a progressive plaque as per fig 6, which could have started to grow from a venule situation as shown in fig 5.

Fig 5b indicates that the detail shown as fig (a) is a venule/capillary situation at the upper end of a group of venules that flow together into a vein coming out of the picture towards us. At the scale of detail (b) detail (a) would only be a dot, as capillaries become invisible.

The perivascular spaces along the system of venules have become occupied by macrophages and/or cells laden with fat droplets which are remaining in situ. Thus the clefts nearby get high MCP levels, oligodendrocytes start to degenerate etc. etc. Subsequently those further away are exposed to the high MCP level and so the tissue undergoes change which spreads radially outward and to some extent along the venules. A large number of such venules with changed tissue finally appears macroscopically as a plaque (15,1). Figs 5 and 6 with key and supporting remarks permit the process to be visualized. In fig 6 a curve indicating MCP level at a node of Ranvier is presented in relation to the cellular zones on a line at right angle to the contour of the plaque. On the abscissa the zones of the first and second steps of demyelination (allo-auto-allergic reaction and myelinolysis, respectively) are indicated.

WHY IS MS AN EXCLUSIVELY HUMAN DISEASE?

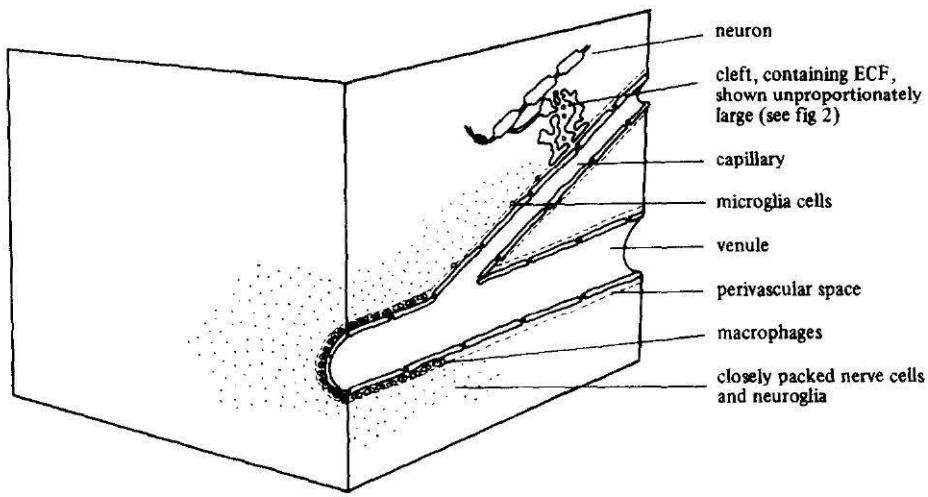
The final answer to this question is still unknown, but we wish to present the following scenario for discussion. Essentially primates have very similar metabolic processes adapted to the food supply in the realms they occupy. The genus homo in its hunting and gathering stage invaded all sorts of realms and is superbly adapted.

Fig 5. **Visualization of developing plaque around and along venules**

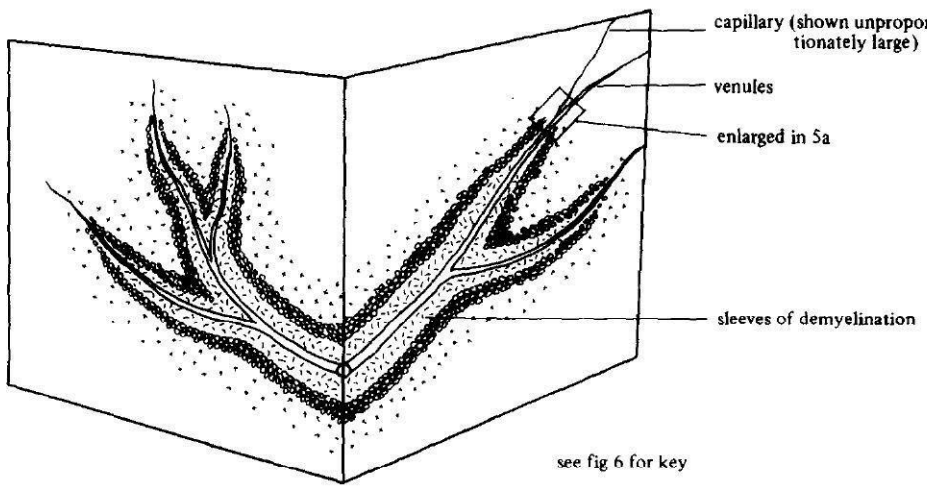
(a) Perspective view of same venule as in fig 3, but at a *later stage*. Macrophages with large lysosomes digesting myelin debris (auxiliary cells not shown) have accumulated in perivascular space, thus partially blocking the lymphatic channel for a great number of clefts.

(b) Diagram showing a venule/capillary situation in white matter. A toxic small molecular weight substance (methanol, in this specific model) has diffused out in repetitive episodes and an incipient progressive plaque is developing. The plaque growth process occurs radially outward and along the blood vessels by clefts (see fig 2) passing through stages t_0 to t_3 (after disappearance of clefts the area is in t_4). At the scale of the diagram this results in sleeves of demyelination which coalesce, as has been observed and discussed by Lumsden (15) and Adams (1).

(a)



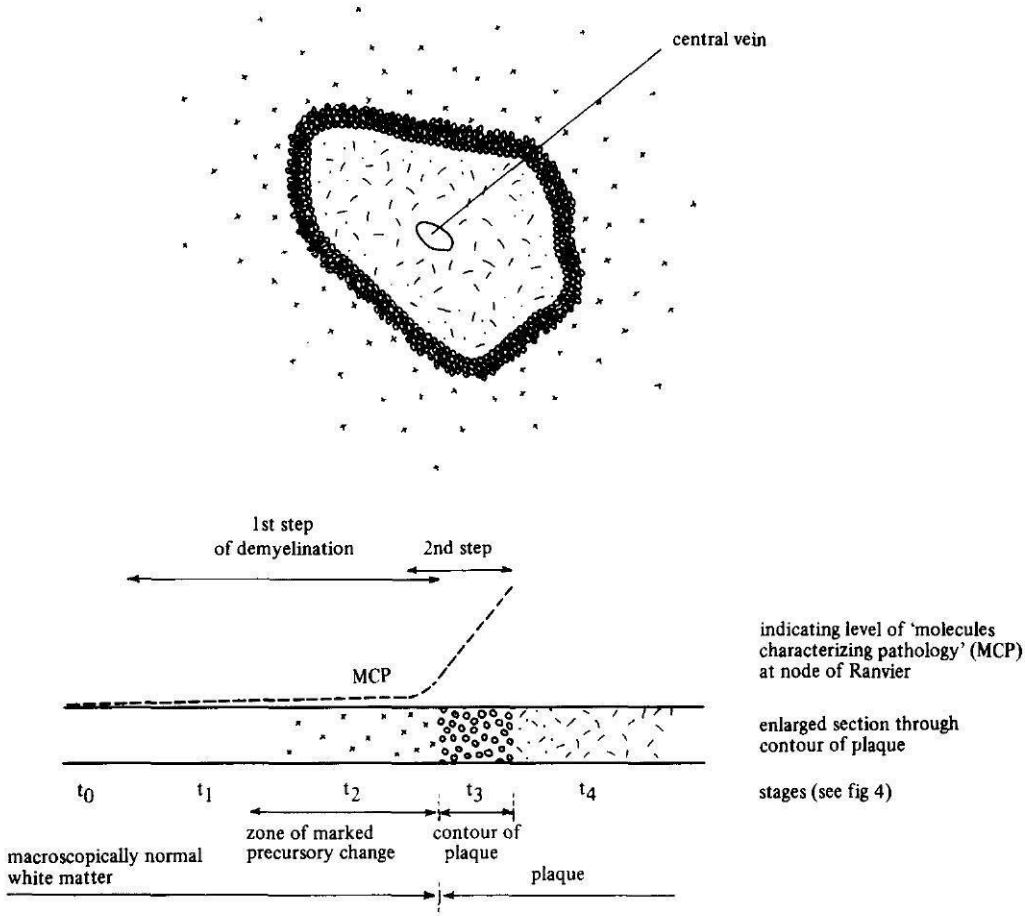
(b)



see fig 6 for key

Fig 6. **Cross Section of a progressive plaque**

The myelinated tissue is at the left, the plaque at the right. The macroscopically normal white matter is white matter in which subtle changes are visible microscopically. These are more marked near the contour of the plaque, i.e. are tailing off to the left into the unchanged white matter.



Key:

	Zones of plaque (see also figs 1 & 5)	**Cellular composition along cleft**	**Tissue condition**
	outer portion of area of macroscopically normal white matter with subtle changes	oligodendrocytes astrocytes	grading outwards from white matter with subtle changes into healthy tissue
	periplaque zone	oligodendrocytes astrocytes various mobile cells (see fig 3)	white matter with marked precursory changes
	contour of plaque	degenerating oligodendrocytes, proliferating astrocytes, large numbers of mobile cells	high cell density, in part due to proliferation of macrophages
	interior of plaque	cleft has disappeared	changed tissue and in outer portion fat laden cells

Modern man has departed from ancestral habits and the availability of sucrose as an inexpensive commodity early in the 19th century has led to new methods of utilizing foodstuffs and a profound change in diet.

Due to the additional fructose now ingested – ten to twenty-fold as compared to the time when the human metabolism adjusted to its food supply – many an individual's liver is strained. The liver's capacity for processing fructose is 2 to 3 gram per hour (11) and excessive doses of fructose lead to metabolic complexities. One of these is methanol and fructose circulating in arterial blood, which, depending on other factors (9), may lead to the microscopic abnormalities in the macroscopically normal white matter. This occurs in the so called 'premorbid' phase and in the morbid phase. Evidence is accumulating that these subtle changes in white matter are the hallmark of the MS syndrome and that the plaques which have given the disease its name are an aftermath. It appears that an intricate immunological defence mechanism becomes so active that the host ends up with tissue damage.

This view has led to plausible explanations of various puzzling features of the MS syndrome and to a therapy which in cooperative patients permits the MS disease process to be arrested in most cases.

CONCLUSION

In an attempt to understand events at the contour of a progressive plaque, findings and plausible assumptions as recorded in the literature were compared. There is a consensus that the central portion of the plaque is the area where pathologic change from serviceable white matter began and the plaque contour observed on autopsy or biopsy is a more recent phase of the pathologic process. We have applied the methanol hypothesis (9) and the working hypothesis (8) on the astrocytes role in maintaining a constant environment for the nerve cells to an interpretation of the MS disease process. Current work in brain physiology, cytochemistry and electron microscopy allows discussion of what happens in macroscopically normal white matter and at the plaque contour at the cellular level. In this discussion the inner fluids of the brain (14,20) have been considered, in particular the interaction of CSF and ECF. In this context the concept of MCP (Molecules characterizing pathologic conditions in the extra cellular fluid of clefts leading to nodes of Ranvier) was introduced. Results of MS-specific research were than applied to the problem. Information on mobile cell populations (21,22) in cleft and perivascular space proved particularly useful, as it gave an outline of a dynamic process. By introducing the concept of stages a clearer distinction between the pathologic process which exists already in the premorbid phase (changes in macroscopically normal white matter here called the first step of demyelination) and the additional process in the morbid phase (changes at plaque contour, here called the second step of demyelination) of MS became possible at the cellular level.

This permits the view that in the premorbid phase there is a tug of war between the disease and the cells which attempt to put matters right, but then the cells called up in defence lymphocytes, macrophages, monocytes, plasma cells, mast cells, fibroblasts etc.) plug a vital drainage channel. This leads to degeneration of the myelin forming cells ushering in irreversable damage in the CNS.

This microscopic model has to be transposed to the macroscopic level. The present state of knowledge of the network of capillaries, venules and veins in the white matter is unsatisfactory, however plaque growth by perivenous sleeves and coalescence of these as has been discussed by earlier investigators (1), (15), is suggested.

We expect corroborating evidence to come from the subtle techniques being developed for assessing blood and CSF, as such approaches may permit estimates of ECF variation during the course of the disease. Current work with electron microscopes can be expected to clarify the problem of fat laden cells, which appear eventually to enter the blood stream. Hand in hand with this the role of the vein, the population of plasma cells, and the gliofibrillogenesis in the central area of the plaque may become more fully understandable.

MS pathology cannot yet be fathomed but an outline of events can be perceived from ongoing studies of the fundamental arrangements of the cells in macroscopically normal white matter and at the plaque contour.

At the moment it seems that small molecular weight substances (29) precipitate a cascade of events and that further investigation in this direction may lead to insights useful to physiologists and pathologists involved with the human brain.

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