1961

Etiologic aspects of multiple sclerosis with emphasis on metabolism

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ETIOLOGIC ASPECTS OF MULTIPLE SCLEROSIS WITH EMPHASIS ON METABOLISM

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Submitted in Partial Fulfillment for the Degree of Doctor of Medicine

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April 1, 1961

Omaha, Nebraska

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INTRODUCTION

The combination of what circumstances, the presence or absence of what agent, or the decrease, increase, or stoppage of what process will alter normal human physiology and result in a specific disease entity? For multiple sclerosis not only is the answer not known but neither is the question to be answered. This paper proposes to approach the question through a consideration of an aberration of metabolism as the etiology of demyelination in multiple sclerosis. The disease will be considered and a brief consideration of other theories will be noted followed by a discussion of myelin and the newer knowledge about it. Then the experimentation on and elaboration of the metabolism in multiple sclerosis, myelination and demyelination will be focused in an attempt to provide some evidence that multiple sclerosis is the result of an abnormality of metabolism.

HISTORICAL OUTLOOK (162,163,63,114)

Search for a metabolic deficiency or an agent interfering with or enhancing a metabolic process was possibly first noted by Marburg in 1906, who believed he had noted that the plaques of multiple sclerosis were from enzymatic lysis. This approach remained stagnant

until 1930 when Brichner demonstrated a myelinolytic agent in the blood. Crandall and Cherry (29) studied the lipase, diastase and esterase activity on multiple sclerosis in 1932, and Weil and Cleveland in the same year noted lipase activity and a decrease serum inorganic phosphorus which they related to disturbed phospholipid metabolism. Since then reports from these and other workers have reported enzyme abnormalities in patients with multiple sclerosis. When it was shown by Bennetts and Chapman in 1937 that copper was the cause of swayback in sheep, a study of possible electrolyte deficiencies had been hoped to yield the clue to the etiology of demyelination. Olafson in 1942 noted that copper deficiency resulted in a type of ataxia in foals and yearlings, and in 1948 Tosic and Mitchell showed an illness in sheep from cobalt deficiency which it was held might lend a clue to the etiology of demyelination. Studies with other animals and diseases resembling the demyelinating diseases of man have been investigated without results. Altmann and Goldhammer in 1937 studied lipase and cholesterol levels of patients with multiple sclerosis and in 1951 Lesny found abnormal lipase activity in patients with multiple sclerosis. Innes in 1939 reports the prevention of demyelinating diseases in lambs with copper. As Richards and Wolff also

studied the esterase activity in multiple sclerosis in 1940, and Weil supported the myelolytic toxin theory in 1935, Seuberling-Schaltenbrand in 1938 denied the theory. Studies on pyruvic and carbohydrate became prominent and were enhanced by Jones et al in 1950. Since these early experiments and reports, the literature has enlarged, and the reported cases are more numerous with contradictory reports and confirming ones, but with no final conclusions or correlation of the findings to give a decisive answer as to the etiology of multiple sclerosis.

MULTIPLE SCLEROSIS

Historical Outlook (162,163,63,114)

Although the etiology of multiple sclerosis has long remained an enigma, the signs, symptoms, history, epidemiology, pathology, and course of the disease have been well elaborated. The earliest report and description of multiple sclerosis was presented by Cruveilhierin in 1835, and in preparation of some pathological illustrations Carswell describes a condition like multiple sclerosis but gave no clinical details other than the mention of paralysis. The first diagnosis was by Frerichs in 1849, and later his pupil published their history and autopsy reports in 1856. This was followed by

pathological reports by Rikitansky in 1856 and Rindfleisch in 1863, and in the same year, in summarizing the existing knowledge, Leyden showed that multiple sclerosis and chronic myelitis were the same entity. Then it was Charcot in the 1860's who integrated the knowledge of the pathology and symptomatology into a distinct disease entity. Bourneville and Guerard, pupils of Charcot, published the first book on multiple sclerosis in 1869, and Oppenheim in 1887, Strumpel in 1896, and Uhthoff in 1889 elaborated on the symptoms and signs. Early notable workers trying to establish the etiology were Ribbert in 1882, suggesting thrombosis, and Marie in 1884 who considered infection. Notable names have been involved in developing an exacting description of the disease with good results; but, while the theories and postulations on the etiology are covering more pages and becoming more numerous, little conclusive results are being obtained.

Course (23)

In magnitude, it is said to be the most frequent organic neurological disorder and the second most common neurological disease, the first being neurosyphilis; however, with the decrease of neurosyphilis and reported increase in the incidence of multiple sclerosis, it may soon be the most important neurologic

disorder. Its course is variable, but in over 90 per cent of cases it is a relapsing and remitting sequence, but it may proceed in a slowly progressive or rapidly progressive course. Young adults between the ages of 20 and 40 years are most frequently affected, but the age spread is from 10 to 60 years, with an average age of 24; but Kurland and Westlund (92), in their epidemiologic survey, set the average age of onset at 30 years for females and 34 for males, with an earlier onset in areas of prevalence. Reports have stated a greater incidence in females, and others indicate that males are more often affected. The first attack may last from one day to several months, with the frequency of relapses occurring 0.50 per year, and tending to be more frequent within the first five years of the illness, and the duration of relapsing increasing later and leaving more residual disability (2). The average life expectancy is 21 years, but may vary from eight weeks to 64 years.

Signs and Symptoms (10)

The signs and symptoms of multiple sclerosis are explainable through multiple involvement of the nervous tissue and present a myriad of findings. Charcot proposed the triad of nystagmus, scanning speech, and intention tremor as the pathognomonic signs and

since the recording of signs and symptoms have elaborated a multiplicity of these. The motor symptoms are weakness, ataxia, change in muscle tone, and tremor. Sensory disturbances were paresthesias, thermal dysesthesia, pain, and deep superficial and cortical sensory loss. The cranial nerve disturbances manifest themselves in visual disturbances which are usually unilateral, decreased visual acuity, blurring, and diploplia, and others being difficulty in swallowing, vertigo, trigeminal neuralgia, speech difficulty, and tinnitus. Other symptoms were urgency, mental changes (13,20), impaired skill, and loss of libido. Presenting signs are ocular, changed superficial and deep reflexes, nystagmus, intention or action tremor, weakness, ataxia, clonus, atrophy, positive abnormal reflexes, slurring and scanning of speech, vibratory and position sense loss, impaired skill, and euphoria or depression.

Prognosis (21,23)

Factors assuming importance in the prognosis and progression of multiple sclerosis are trauma, cold, pregnancy, infection, emotional disturbances (18), fatigue, exertion, and general poor health. McAlpine et al. (114) concluded that the risk of disability was increased in cases showing a progressive character,

incomplete remission of the first attack, frequent relapses, pyramidal or cerebellar signs or disturbance of sphincter control, and a more benign course was indicated by a good recovery from the first attack, mild relapses with infrequent occurrence, a lengthy remission following the first attack, and initial disturbances being optic, cranial nerve or sensory.

Pathology

Plaques of demyelination are the main pathological findings in the disease. Grossly they present well demarcated areas, the early ones being pinkish, and the later ones grayish. No gross abnormalities of the meninges or blood vessels are observed; however, some atrophy of the spinal cord may rarely be noted. Microscopically the plaques have sharp margins, show no perivascular distribution, tend to be found more frequently in the long tracts of the spinal cord or subependymally with little affinity for peripheral nerves. They may be of any size and shape, showing some tendency towards symmetry. Peripherally there is active myelin disintegration, microglial proliferation, astrocytic hypertrophy surrounding a zone of gliosis and increasing numbers of astrocytes with an amorphous center. The myelin shows swelling, varicosity, decoloration, fragmentation, peripheral globules of myelin, and the focal erosion

forming the plaques. Astrocytes are prominent in the early lesions and at the periphery of older lesions, being first protoplasmic and later fibrous, laying down a scar; concomitantly with the appearance of the astrocytes, microglial proliferation occurred with phagocytosis of fat and lymphocytic and plasma cell infiltration. Later a connective tissue response and fat-granule cell response occurred. The oligodendrocytes disappear in the vicinity of the lesion. The axis cylinder is affected to a lesser degree and may show no alteration, although some varicose swelling, fragmentation, granular degeneration, vacuolation, thickening, and endbulbs may occur. McAlpine (114) summarizes the pathology in relation to etiology describing the process as "a chronic progressive expanding lesion, restricted to the central nervous system and caused by a myelinolytic agency in the ground substance, focally distributed but showing a tendency to symmetry and some relationship, in the early stage at least, with the venous system."

Epidemiology (31)

Epidemiological studies to discover the natural history of the disease have met with good result; however, it does not lend itself conclusively to the

support of any one etiology. The disease is more prevalent in the northern hemispheres and certain localities; however, this may support the vascular, or infective theories. Attempts to find racial prevalence have indicated a possibility of a greater occurrence in the white race, but they have been inconclusive, and recent reports show multiple sclerosis to occur in African natives which was heretofore unreported.

THEORIES OF ETIOLOGY (63)

Allergic

The earliest theory on the etiology of multiple sclerosis was dysplastic glial development by Strumpell-Muller from which began the voluminous literature and speculation as to the etiology. Among the present theories, the allergic one is highly considered. It was suggested by von Pirquet in 1906; Glanzmann, in 1927, suggested that the neurologic manifestations of smallpox, chickenpox and vaccines were due to allergy; and van Bogaert in 1932 considered this as the possible cause of multiple sclerosis. Experimentation became concerned with experimental allergic demyelination, and Ferraro, in 1944, proposed that an allergic etiology was the cause of all demyelinating diseases. Pette's neuroallergic thesis proposes as the pathogenesis vessel dilatation

with increased permeability, allowing plasma and cellular infiltration followed by myelin disintegration and proliferation of glia. Attempts have been carried out to demonstrate skin reactions and an increased incidence of allergic disease in multiple sclerotics has been claimed. The inciting agent has been considered as infective, auto-immune, and non-specific.

Infective

The infective theory has long been considered being proposed first by Pierre Marie in 1892. Bullock, now Gye, first claimed to have transmitted the disease in 1913, and other investigators have reported positive and negative results but none conclusively. Amongst the infective agents proposed are Brucella, mycobacterium, virae, spirochetes, protozoa, and unclassified organisms. The remitting course has been compared to other infections, notably brucellosis; however, the lack of fever, leukocytosis, and demonstration of an organism has dimmed support of this theory.

Vascular (5)

A third theory having many proponents is the theory of vascular occlusion or spasm, being first proposed by Putman. Brickner (16) states that the unsystematic distribution of the lesions, the sudden onset of attacks,

the occurrence of sudden milk attacks with limited manifestations, and the observation by Franklin in a patient with sudden loss of vision that the superior temporal artery had shrunk to a white streak and the neighboring vessels gave a box-car appearance are the supporting features of multiple sclerosis for the theory of vascular spasm as the cause. The perivascular distribution of the lesions and claimed obstruction of the vessels also lend support to this theory. Alexander and Parker (2) related a fall in blood pressure as indicative of a poor prognosis in a relapse, and a high blood pressure as a favorable sign. Blood coagulation has been studied with no conclusive results. Increased capillary fragility, sludge formation, platelet abnormalities, increased bleeding time, and variable plasma fibrinogen levels have been implicated (1) without conclusive evidence.

Toxigenic (7,8)

Exogenous toxins have been observed to cause demyelination such as carbon monoxide, triorthocresylphosphate, mipafox, potassium cyanide, sodium azide, cobra venom and snake and bee venoms. Along with these, some endogenous toxins have been implicated in porphyria, eclampsia, uremia, hepatic disease, and subacute degeneration as proposed by Baker.

Nutritional and psychogenic

Various nutritional deficiencies have been proposed, but none conclusively, and the psychogenic proposals are not favored. As is seen from the numerous theories, the picture of multiple sclerosis is open to diverse interpretation and difficult to evaluate. The possibility of more than one cause acting either primarily or secondarily also exists requiring a correlation and consideration of the two conditions to arrive at the solution.

Hereditary

In attempting to decide the etiology of multiple sclerosis, the possibility of a genetic disease has been proposed. Landing (44) believes that "one or two per cent of theoretically possible hereditary metabolic diseases of humans are recognized," and proposed the following seven rules for classifying a disease as such.

1. All hereditary diseases are hereditary metabolic diseases (HMD).
2. HMD's result from defects in single genes with resultant defects in single enzymes.
3. Enzyme defects are due to protein abnormalities.
4. The enzyme defect is present in all cells of the body.
5. All clinical and biochemical aspects of HMD's must be accountable directly or indirectly to the defect.

6. The heterozygots for abnormal genes are half abnormal by tests.

7. A defective enzyme is present.

A hereditary factor was believed as a possibility by early workers, Charcot, Gowers, Strumpell, and Muller; but the earliest mention of familial occurrence was by Gowers in 1893, and Eichhorst in 1896, and Cestan and Buillain in 1900; Reynolds, in 1904, presented cases of familial occurrence. Von Rad, in 1905, categorically denied any familial incidence, but since, Davenport, in 1922, and Goldflam, in 1930, emphasized the hereditary character of the disease and the work of Curtius in 1933 has augmented this possibility. Mackay (106), in making a survey of the reported cases of familial occurrence, reports 79 cases which he considered as acceptable and believed from his study and review of the literature that, although there is a hereditary vulnerability to the disease, the hereditary factor is not potent enough alone to cause the disease, but requires a secondary cause. Waelsch (169,170), in experimenting with mice, noted the susceptibility of some strains to experimentally induced disseminated encephalitis, and some strains with resistance, indicating the possibility of a hereditary disposition towards the disease. Others, notably Harman (64,65), have been experimenting with the

wabbler-lethal mouse in trying to show a hereditary link as a possibility in demyelination. Plum and Fog (121,122) mention the finding of increased diameters of leukocytes and reduced bone marrow function as indicative of a developmental abnormality of the bone marrow, which, with the known fact that developmental anomalies are more frequently found in the presence of others, might indicate some hereditary anomaly in the formation of myelin as a possible etiologic agent in multiple sclerosis. Pratt, in 1951, studying the occurrence in monozygotic and dizygotic twins, concluded that, as the disease does not appear in both always, an exogenous factor must be working. Presently the incidence of multiple sclerosis appears to have some familial prevalence, but any relation to etiology still remains obscure.

MYELIN

Embryology and Formation (11)

Studies into the embryology and formation of myelin are adding much to the understanding of the metabolic process and elements involved necessary to myelin production, which adds some impetus to the study of a possible metabolic defect in demyelination in the primary demyelinating diseases. The production of the myelin sheath has been thought to take place in the

Schwann cell, the axoplasm, the blood (being deposited herefrom), the surrounding stroma with the axon as a stimulus towards production, oligodendrocytes centrally, or by wrapping of the Schwann cell. That the Schwann cell is invaginated by the axon with either the cell or the axon rotating to create layers of myelin is the commonly accepted theory of peripheral myelin formation. In vitro studies, showing the association of Schwann cells to myelinating nerves with the formation of cytoplasmic vesicles, increased lipid droplets, prominent Golgi membranes, and many mitochondria in the cell cytoplasm during the process of myelination, point to an active part of myelin production in these Schwann cells. The necessity of an axon being present for myelin formation indicates that perhaps the nerve provides the stimulus for activating in the Schwann cell or oligodendrocyte the metabolic activities for myelin formation, or reacting with products from the oligodendrocytes to form myelin. The observation of the appearance of nissel substance with the formation of myelin suggests the possible stimulating effect of the axon on myelin formation and the possible necessity of co-operation and coordination between these two elements in creating a metabolic and chemical equilibrium favorable to myelin formation. The association of oligodendrocytes with

myelin and their appearance coincident with myelin formation indicates them as the site of central myelin formation. And the finding of Koenig (86) that during myelination they develop large perinuclear caps of basophilic cytoplasm thought to be PNA reveals some metabolic activity increased during this period. Terry and Harkin (158) report the finding of a degenerating and healthy sheath simultaneously in a healthy Schwann cell, demonstrating the necessary stimulus from the axon for maintenance of myelin.

Anatomy

The formed myelin consists of a concentric laminated sheath with periods radially of 171 A^{o} and consisting of two double layers of lipid and one to two layers of protein and water alternating with the lipid layer. Schmitt (145) believed that "all nerve fibers are enclosed by satellite cells and by the lipid-protein membranes of these cells in varying amounts and types of structural and biochemical differentiation," and that these membranes constitute an extension of the metabolically active satellite cell. That Luse could not demonstrate finding myelin either in the presence of Schwann cell, oligodendroglia or axon alone supports a theory of some interaction between these elements in

forming myelin. Murray (119) observed numerous fine lipid droplets congregated juxtanuclearly in the Schwann cell during myelin formation, indicating that the lipid production for myelin occurs in this cell. Interesting is the fact pointed out by McAlpine et al. (114) that the onset of nervous activity and myelin formation occur concomitantly, indicating the possibility that acetylcholine is the trophic substance of the axon inciting the satellite cells to lay down myelin, and also the need for insulation at this time. Conclusions as to the permanency of myelin once formed have been indecisive with studies on the incorporation of radioactive substances taking the lead in this aspect. Support has been given both ways and studies have included the persistence of radioactive substances once incorporated into the brain. This study is important in deciding the possibility of an imbalance in the anabolism and catabolism of myelin resulting in a tendency towards greater myelin anabolism. This is likewise important in considering whether an early defect in myelin construction, giving a debilitated structure which makes it more susceptible to demyelinating forces, is the causative factor, or whether a later disruption in the metabolic processes of myelination may interrupt the anabolic forces, allowing the catabolic forces to become dominant. These are some of

the problems in considering the metabolic etiology of multiple sclerosis which, when solved, will be a road sign along the way. Consensus at present tends to favor the dynamic rather than the static theory. Electromicroscopically, the ultimate structure of myelin is being studied at a molecular level, and with the aid of lipid and protein digestive agents the anatomical structure and framework of myelin is becoming a knowledgeable form. Moshe Wolman and Lerner (180) have presented a recent theoretical scheme which is pictured in Fig. 2. The intricate and complex anatomy of myelin as seen obviates that the possibility of minute changes which may lead to a weakness of construction or vulnerability to myelinolytic agents needs to be pointed out; however, demonstration of such a defect has no research support.

METABOLISM

Lipid

Lipid composes a large part of myelin structure and the possibility of a defect in its metabolism has been under consideration as the etiology of multiple sclerosis. The classification of cerebral tissue lipid is shown in Tables 1 and 2, as classified by two authors. The myelin lipids as proposed by Holm are phosphosphingosine (sphingomyelin), galactosphingosine (cerebroside),

cholesterol, phospatidylserine (cephalin), and diphosphoinositide (cephalin). He noted that in the second stage of Wallerian degeneration these myelin lipids disappear and cholesterol is esterified. That these lipids are an important part of myelin and that phosphosphingosides, glycosphingosides, and cerebrosides are believed to be found only in myelin demands that they be considered in any ailment in which myelin alone is affected or primarily affected. The pathways of synthesis of these lipids is being studied and the enzymes concerned. Epidemiologic studies have been believed by some to indicate that the prevalence of multiple sclerosis, where there is a high intake of fat, points toward this substance as the etiologic factor. Courville (27) has favored this hypothesis and has compared the pathology of fat embolism to the process of multiple sclerosis. He believes that the fat globules or chilomicron entering the blood stream after a high fat meal act as emboli blocking the small blood vessels and capillaries which accounts for the perivascular arrangement of lesions found in multiple sclerosis. He further hypothesized that the action of heparin in increasing lipase activity would benefit patients, and in two series (26,28) he reports of seven patients with good results in four, fair in two, and none in one; and in another series of twenty-five he

reports the treatment benefited the patient in seventeen cases and failed to create any improvement in seven. A major drawback to this theory is that other organs are not affected by these emboli. Folch (51) has shown that during myelination there is an increase in proteolipids, cerebrosides and cholesterol, and that prior to myelination proteolipids and cerebrosides are absent. Plum and Fog (121), from their studies, could not demonstrate any significant deviation of the serum lipid, phospholipid, phosphoglyceride, cephalin, lecithin, sphingomyelin, or cholesterol, and from their experimental observation state "no abnormality in lipid metabolism can be demonstrated with certainty by an examination of serum." Studies of the cerebrospinal fluid by the same authors showed an increase in cholesterol and an abnormal distribution of lipoprotein without coinciding change in the serum. This points to some defect within the central nervous system in the metabolism or catabolism of these products. In demyelinative diseases, the finding of cholesterol esters which normally are not present implicates again lipid metabolism. Production of myelin is now thought to occur in the central nervous system. Webster (173) points out in multiple sclerosis the loss of total lipids especially cerebrosides, sphingomyelin, and cholesterol with the finding

of esterified cholesterol in the plaques and further reports that these findings to a lesser degree are true of the uninvolved myelin which points toward some original defect in the lipid metabolism, making it more susceptible to demyelinating forces.

Radioisotopes have been used, to study whether the production of myelin continues or if (which is, of course, true of the neurons) once formed myelin is a permanent structure, with no conclusive results. Waelsch (169) reports that fatty acids and cholesterol are synthesized in the brain, and that the rapid turnover of fatty acids and cholesterol in the early stages of myelination decreases later and with cholesterol is non-existent. Davison and Dobbing (32,33,34) report the persistence of (3-14) labeled serine when incorporated into myelin. Karnovsky, Moser, and Majno (80) point out the specific activity from birth to maturation of cerebroside galactose, fatty acids, and cholesterol fall respectively 150-fold, six-fold, and fifteen-fold, demonstrating that, although all anabolic activities do not necessarily stop, they do decrease. Also, the oligodendroglia have been given a trophic role in maintaining myeline in the adult which introduces the disturbance in their activity as a possible cause, and this may be related to lipid metabolism.

DiLuzio (38) believes that the reticuloendothelial system is concerned with cholesterol metabolism or excretion, and its involvement in other demyelinating diseases brings it into suspicion; however, little has been found to suggest any relation to multiple sclerosis. Correlation between the vascular and metabolic theories in relation to lipid metabolism derives from the occurrence of phospholipids, not only as a component of myelin, but also as a component in the structure of thromboplastin. This may account for some of the disturbed defects reported in the hematology of multiple sclerosis patients while the main etiologic factor may rest primarily in disturbed lipid metabolism. Holm (72) also lays emphasis on diphosphoinositide which he classifies as a myelin lipid and which is also a component of antithrombokinase which is a possible second link between a vascular and metabolic etiology coexisting.

Protein

With the increasing knowledge concerning synthesis of the elements of myelin, the important role of proteins and amino acids is becoming more apparent as they are involved in the metabolic pathways. Koenig (86) showed the active assimilation of labeled methionine by myelin protein and that the outermost layers of myelin

or the glial cytoplasm accumulated the labeled elements. It was also found that in myelinating pathways the oligodendrocytes showed marked assimilation of labeled adenine and orotic acid into PNA, and at the same time possessed large basophilic cytoplasmic caps, not observed in mature oligodendrocytes, which are thought to be RNA revealing active sites of protein synthesis. As the oligodendrocytes are thought to be trophic in regard to myelin, this presents evidence as to the possible function of protein synthesis in the central nervous system with regard to possibly maintaining an enzymatic or structural duty. Levine (101) believed that oligodendroglia show an active turnover of protein and nucleic acid, and this represented in regard to myelin a trophic function which probably persists through life. Waelsch (169,170) points out the extensive turnover of proteins in the brain. Rossiter and Berry (133) demonstrated an increase in the specific activity in labeled precursors, of phosphatides, as choline, ethanolamine, serine, and cytidine diphosphate choline, using the degenerating sciatic nerve of a rat. Associated with the increased activity was a proliferation of Schwann cells indicating that these increases were the result of an increased potential of myelination. The study of neurokeratin is another line of research in seeking the part protein

plays in myelin. Folch et al. (51) defines neurokeratin as a proteolytic enzyme resistant residue, and it is present in both central and peripheral myelin, being a part of a myelin tridimensional framework. Tewasi and Bourne (159) describe the neurokeratin network as forming hexagonal prisms radiating through the myelin, and demonstrate many enzymes within these prisms, believing them to be the center of metabolic activity in the peripheral myelin. That a defect in this network might result in demyelination is a possibility, but there is little to indicate that this exists. The synthesis of the lipids and protein of myelin may provide a vulnerable area resulting in demyelination. In this regard the importance of ceramide as an intermediary substance in the formation of cerebrosides and sphingomyelins is being observed. Watts (172) states that ceramides are amides of sphingosine with a higher fatty acid and that sphingomyelins are choline or ethanolamine phosphoric acid esters of the ceramide, and cerebrosides are ceramide with the fatty acid linked to galactose or glucose (with the normal occurring one being galactose). Kennedy (81), in his study, indicates that sphingomyelin is formed from the action of N-acylsphingosine and cytidine diphosphocholine under the influence of phosphorylcholine ceramide transferase requiring a

sphingosine derivative with a configuration which differs from the one heretofore thought to occur in sphingolipids. Studies more basic describe the carbon atoms 2 and 3 of serine as the source of carbons 1 and 2 of sphingosine, and palmityl CoA as the precursor of carbons 3 and 18 of sphingosine. Further investigation also revealed that where palmitic aldehyde in the absence of CoA is capable of serving as a precursor to sphingosine, ethanolamine can not. This basic biochemical research into the building blocks of the substances found in myelin, while still requiring more elaboration, holds some consideration from those trying to demonstrate a structural or metabolic defect in myelin and those trying to determine the point at which certain demyelinating agents act. Holm (72) determines the steps essential for choline synthesis as consisting of glycine plus formate giving serine which gives ethanolamine while utilizing a methyl group from methionine gives choline. Further, considering that for the formation of phosphosphingosides choline is essential, the demonstration of decreased glycine reserves in multiple sclerosis as revealed by a decreased excretion of hippuric acid in the urine following administration of benzoic acid which normally combines with glycine to form hippuric acid implicates glycine in the disease process. Holm (72)

lays great emphasis on inositol and the diphosphoinositides in the etiology of multiple sclerosis. He states as his reasons that inositol is lipotrophic and is found in considerable quantity in the cell cytoplasm of the brain. Inositol-n-diphosphate is the only phosphorus containing compound traveling at three millimeters per twenty-four hours, which is the rate that the nerve grows; inositol is essential to glucose metabolism; inositol antagonizes the neurotoxic properties of streptomycin, diphosphoinositide disappears with the myelin in the second stage of Wallerian degeneration; diphosphoinositide is a myelin lipid; inositol-n-diphosphate is thought to be either a co-enzyme or component of an enzyme concerned with synthesis of myelin lipids; and diphosphoinositide is a component of antithrombokinase which would explain the finding of abnormal hematologic reactions. Holm (72) concludes, from his studies, that the three fundamental alterations in multiple sclerosis are an inhibition of the glycine reserve, a shortage of magnesium, and a shortage of inositol. Though presenting an intriguing case, there is no conclusive evidence that this is the cause and not the result of the condition, and scanty support of his hypothesis is found in the literature or adhered to as conclusive.

O'Conner *et al.* (120) report the finding of a

decreased glutathione in the serum of multiple sclerosis patients. Extensive studies on serum and cerebrospinal fluid to demonstrate abnormal constituents or abnormal concentrations of constituents have been carried out. These studies, although not conclusively supporting any theory as to etiology, add much to the knowledge of the disease. Volk et al. (167) report finding in 85 per cent of their cases a decreased albumin and A/G ratio, increased alpha-2 and beta globulin fractions, a normal or slightly elevated gamma globulin fraction, and a normal alpha-1 globulin fraction, with the others showing many but not all of the changes. Sixty-six per cent gave positive cephalin-cholesterol flocculation reactions indicating changes of the electrophoretic albumin content, and 21 per cent showing positive thymol turbidity, indicating changes in the beta globulin fraction. A minor number of positive zinc sulfate turbidity and ammonium sulfate-sodium chloride turbidity reactions were recorded, these tests reflecting an increased or normal serum gamma globulin. The above studies were done using an electrophoretic method, and the authors determined values using a quantitative protein flocculation-ninhydrin procedure which corresponded with the above findings. Bronsky et al. (19) demonstrated an increased total serum protein in patients

with multiple sclerosis and demonstrated no abnormal partition of serum protein in these patients. He noted that in the patients demonstrating an increased serum protein with a normal gold curve there was also a decreased beta-globulin and increased serum albumin. Hill et al. (70) states that, from their studies, "any acute neurologic disease may be accompanied by a triad of findings, consisting of increased alpha-2 globulin, increased total glycoprotein, and increased alpha-2 glycoprotein in the serum." They failed to demonstrate an increase in the serum of alpha-2 globulin in multiple sclerosis, and further noted that the increased gamma glycoprotein was not accompanied by a concomitant rise in alpha-1 and alpha-2 glycoprotein. Field and Miller (47), while demonstrating no difference in the gamma globulin between patients with multiple sclerosis and normal controls, state that the ratio of gamma globulin to total serum protein was increased in multiple sclerosis. Plum and Fog (121) demonstrated no abnormality in serum of serum protein other than a report of decreased neuraminic acid. Jones et al. (77,78) report low values for serum albumin and the albumin/globulin ratio, positive cephalin flocculation tests, and increased thymol turbidity indices. They believed that the latter two tests indicated liver function impairment. Decreases

in the serum albumin, albumin/globulin ratio, and cholinesterase values were noted to indicate an impending exacerbation. Correlation of these findings to indicate an etiological agent has been unsuccessful, and most of the changes are considered non-specific and not pathognomonic of multiple sclerosis. Cerebrospinal fluid examination has provided more results which have been more thoroughly tested. Bronsky (19) reports in the cerebrospinal fluid an increased gamma globulin and a decreased albumin. Volk et al. (163), in more extensive studies, reports 80 per cent of patients with an increased gamma globulin and an increased gamma globulin/total protein ratio, while Yahr et al.(181) report an increased gamma globulin in the cerebrospinal fluid in 66½ per cent of patients with multiple sclerosis. Freedman and Merritt (55) also report increased cerebrospinal fluid gamma globulin in 80 per cent of their cases. Plum and Fog (121) also demonstrated a distinct rise in the gamma globulin fraction of the cerebrospinal fluid, while stating, however, that the total protein remained mostly within a normal range in multiple sclerosis patients. They further believed that, because this rise in cerebrospinal fluid gamma globulin was not accompanied by a corresponding rise in the serum, the increased production occurs within the central nervous

system itself. Their finding of an increased neuraminic acid in the cerebrospinal fluid was noted to be accompanied by a decrease of neuraminic acid in the blood. While aiding in better determining and possibly diagnosing multiple sclerosis, these findings lend no conclusive evidence as to the etiology. The increased gamma globulin has pointed to either an allergic or infectious phenomenon, but from the findings no conclusions can be promoted with any degree of finality.

Carbohydrate

The implication of carbohydrate metabolism has been considered, but here again, while much research and investigation has been carried out, the findings do not confirm any hypothesis and often produce varying and indefinite findings. In this regard, pyruvate metabolism has often been studied.

Jones, Jones, and Bunch (77), in 1950, were the earlier workers. They found in a study of 40 patients with multiple sclerosis that the blood pyruvate level was raised when they were in a state of relapse and that, following the ingestion of glucose, the rise in these patients was greater than in a control group of 30 patients. Other investigators have reported varying findings.

McCardle *et al.* (115), using 41 patients, found

that the mean fasting pyruvate level in the control and those with multiple sclerosis were nearly identical. Following glucose ingestion, however, they demonstrated at 60 and 90 minutes a significant rise in the pyruvate level from the control. They also noted that there was no difference in the alpha ketoglutarate levels between those with multiple sclerosis and the control. A finding which they laid importance to, for which its significance is not determined, is the finding of low levels of fasting plasma citrate in patients with multiple sclerosis. Though believing that "the existence of an abnormality of pyruvate metabolism in some cases of multiple sclerosis seems reasonably certain," they conclude by stating that "a disturbance of pyruvate metabolism is unlikely to be causally related to the disease." In 1954, Jones et al. (78) demonstrated an abnormal rise in the pyruvic level in relation to lactic acid following glucose feeding, and noted that the decrease of inorganic phosphorus was less following glucose ingestion in patients with multiple sclerosis than in normals.

Droller and Powell (39) observed three types of glucose tolerance curves: a flat curve, a curve with a steep rise and return to initial level within the second hour (lag curve), and a diabetic curve. They, however, noted that in people maintaining a poor nutritional

intake altered glucose tolerance curves and abnormal plasma pyruvic acid levels could be observed, and thought that as many multiple sclerosis patients maintain a poor diet this may be the cause of the finding of abnormalities in these two respects.

Jeanes and Cumings (75) found increased levels of fasting blood pyruvic acid in four of 26 patients with an increased rise over that found normally following glucose ingestion in 15 of the 26 patients. They also noted an increased pyruvic to lactic acid ratio in 14 of their series of 26 patients. Holm, using methylene blue in sodium chloride, mixed with citrated blood, noted that normal decolorized this in six hours, while blood from patients with multiple sclerosis required more than six hours in 38 of 44 female and 45 of 50 male patients, concluding from this an insufficiency in the oxidative decarboxylation of pyruvic acid. He also noted a wider range in the rate of glycolysis in patients with multiple sclerosis; however, he laid this to a shortage of magnesium.

The significance of these findings, while pointing toward the possibility of some metabolic defect, remains obscure, being left for further research and correlation.

Enzyme

An aspect which has more recently become prominent in the search for the etiology of demyelination is the enzyme and enzyme systems in myelin and the nervous system.

Tewasi and Bourne (159), in studying the neurokeratin framework of myelin, note in the prisms constituted by this network finding adenosine triphosphatase, creatine phosphatase, numerous other phosphatases, cytochrome oxidase, succinic dehydrogenase and non-specific cholinesterase; and the finding of acid phosphatase and specific cholinesterase in the axon which gives some insight into the numerous enzymes and intricate interaction of substances which occur not only in the axon and surrounding tissues, but in the myelin sheath itself.

Foster (52) also states the finding of certain enzymes in the myelin indicative of a metabolic potential. Much import has been given to the study of cholinesterase and its division into specific and non-specific cholinesterase. Webster and Mackenzie (174) found that, while serum cholinesterase in multiple sclerosis had a wider range than normal, no abnormality was demonstrated in pseudocholinesterase. Differentiation of the specific (true) cholinesterase and the unspecific (pseudo) cholinesterase is accomplished as both systems will

hydrolyze acetylcholine, while only the former will break down acetyl-beta-methyl-choline (mecholyl) and only the latter will break down benzylcholine.

Another difference between the two is that unspecific cholinesterase activity is greatest in glial elements and Schwann cells, while the specific cholinesterase is found mostly in the neurons. Unspecific cholinesterase is also noted in arterial walls.

Thompson (160) found that cholinesterase was found in greater amount in the gray than in the white-matter, that specific was greater than non-specific cholinesterase in the brain, and that non-specific was found in greater quantity than specific in myelin. He made note of the fact that certain inhibitors of cholinesterase cause demyelination, such as tri-orthocresyl phosphate, and further noted that in the distal segment in Wallerian degeneration the specific cholinesterase was decreased by 60 per cent.

Lumsden (104) noted that in the plaque tissue of multiple sclerosis patients there was a decrease of 25 to 50 per cent activity of pseudocholinesterase, while the true cholinesterase was the same as in the normal tissue. He concluded from his findings that the true cholinesterase is in the axon, and interpreted his findings as indicating that pseudo cholinesterase was due to

the decreased numbers of histiocytes and that there was a dual source of the enzyme with one of the sources persisting in the plaque. He also confirmed that the pseudocholinesterase production resides in the oligodendrocytes and microglia.

Plum and Fog (121) note that specific cholinesterase predominates in the cerebrospinal fluid, and only unspecific cholinesterase is found in plasma. They found that in multiple sclerosis cholinesterase is greatly reduced, and that there is no difference in the unspecific cholinesterase.

Many believe that the importance of these above findings is that myelination occurs at the time when nerve conduction increases and that perhaps cholinesterase is the stimulus for this formation and, when lacking or reduced in later life, may result in demyelination.

The finding of myelolytic agents has been reported. Birkmayer (12) claims to have produced myelolysis, using the serum of patients with multiple sclerosis, which spared the axon. He stated that the myelolytic property was located in the albumin fraction and was thermostabile, being inhibited by thiamine disulfide, vitamine B, serum hemolyzed by cobra toxin, hydrocortisone, and prednisolone. Weil (176) found a myelonolytic substance in the urine of patients with multiple sclerosis

and this was also noted by Wolfgram and Rose (173). Vignais (116) claimed that a relatively strong activating enzyme of the central nervous system for long chain fatty acids exists and that it is for longer chain fatty acids than is the case with the liver enzyme. They also demonstrated an enzyme which reduced indophenol in the presence of palmityl coenzyme A. Haine (62) pointed out that the cerebrospinal enzymes of glutamic-oxalacetic transaminase lactic dehydrogenase, and malic dehydrogenase were increased in multiple sclerosis. Plum and Fog (121), however, could demonstrate no difference in the serum or cerebrospinal fluid glutamic oxalacetic transaminase between normal controls and patients with multiple sclerosis. The possibility of a defect in lipase is brought out by Courville (26), using heparin to enhance the lipase activity which he claims benefited multiple sclerosis patients.

Brady (14) believed that in the synthesis of sphingosine an enzymatic system was necessary to catalyze the reduction of palmityl coenzyme A and a second enzyme system was necessary to oxidize palmitic aldehyde. Porcellati and Curti (124) report an increase in the enzymatic activity of proteinase following transaction. Thompson (160) notes that following a crush injury to a nerve the alkaline phosphatase activity is increased,

and he also demonstrated acid phosphatase in the Schwann cell and myelin. Green et al., using spectrophotometric determination, showed that in all cases of multiple sclerosis the glutamic oxalacetic transaminase values were elevated, while Fleisher et al. claimed normal levels. Kennedy (81) carried out studies of the enzymatic synthesis of phospholipids and triglycerides showing that the synthesis of 1,2-diglycerides from phosphatidic acids occurs as a result of the enzyme phosphatidic acid phosphatase. He also claims that the enzyme in the action of cytidine diphosphocholine with N-acylsphingosine to give sphingomyelin is phosphorylcholine ceramide transferase.

Mandel, Birth, and Weill (110) note that the young brain is more adapted for anaerobic glycolysis than the adult, and that this may be why multiple sclerosis shows up late; they also noted that, while citrate doesn't change the oxygen consumption of the young, it increases the oxygen consumption of the adult brain. Also the importance of oxidative phosphorylation in myelin metabolism has been pointed out. The importance of these enzyme systems, or the part they play in demyelination has not been established, and a correlation of the facts now gathered has not been put together, but the possibilities are there and some minor abnormalities have been noted.

Electrolyte

Copper was one of the earlier elements which was considered as the possible cause of multiple sclerosis when present in insufficient quantity, but since, its likelihood has decreased; however, other elements and electrolytes have been studied.

Holm (72) indicates that a deficiency in magnesium is involved, supporting this hypothesis by noting that the formation of choline requires activated methionine which is formed under the influence of adenosine triphosphate and magnesium, and that the reduction of methylene blue with blood is increased on the addition of phosphate more in multiple sclerosis than in the normal, due to the binding of magnesium.

Plum and Hansen (122) demonstrated no abnormality in the sodium, potassium, calcium, magnesium, phosphorus, or chloride in the cerebrospinal fluid or serum of patients with multiple sclerosis; however, they note an increase in the standard deviation of calcium.

Spiegal (151) notes an increase before birth in the copper of both the white and the gray matter of the brain, while an increase in copper continues after birth in the white matter, and a similar course was observed with magnesium. As myelination occurred, a decrease was noted by the sodium and calcium content of the cerebral

spinal fluid, noted by Wender and Hierowski (177), as potassium remained steady which they considered as one of the primary chemical developmental phenomena. Among other electrolytic findings reported is a normal inorganic phosphorus, and sometimes as decreased. The decrease in water content with increasing age has also been recorded, but any relation of the above to demyelination in multiple sclerosis has not been recorded.

SUMMARY AND CONCLUSIONS

At present most of what is known are isolated facts, a pricri experimentation, and inconclusive interpretation. Until the normal values and physiology are more fully determined and understood, the answer will remain unknown, and it is through the basic sciences that our knowledge will be extended and the boulder of normal values and functions will be lifted so that we may see the underlying pathology.

While numerous abnormalities are being associated with multiple sclerosis, it is not known whether these are the cause of or are caused by the disease. We are circling now in what is a spiral which will lead to the answer in the center, and now our position is much like that stated by the poet Robert Frost:

> We dance around the circle and propose,
> But the answer lies in the center and Knows.

APPENDIX I

Table 1

Classification of Cerebral Tissue Lipids (72)

A. Phospholipids (phosphatides)

1. Phosphoglycerides
   Phosphatidyl choline (Lecithin)
   Phosphatidyl ethanolamine
   Phosphatidyl serine : Cephalide
   Phosphoinesicides

2. Phosphosphingosides

B. Glycolipids : Sphingolipids

1. Cerebrosides (glycosphingosides)

C. Sterole

1. Cholesterol

2. Dicholesterol ester

D. Neutral fat

APPENDIX II

Table 2

Classification of Cerebral Tissue Lipids (147)

I. Cholesterol (unesterified only in normal nervous tissue)

II. Sphingolipids (sphingosides containing sphingosine in each fraction)

A. Glycosphingosides (hexose containing sphingolipids)

1. Cerebrosides (galactose *sphingosine * fatty acid)

2. Gangliosides (hexoses, hexosamine, neuraminic acid * sphingosine * fatty acid

B. Phosphosphingosides (Phosphorus containing sphingolipids)

Sphingomyelin (phosphorylcholine * sphingosine * fatty acid)

Cephalins B (P-bound? * sphingosine * fatty acid)

III. Glycerophospholipids (phosphoglycerides including glycerol in each fraction)

A. Lecithins

1. Phosphatidyl choline
P-bound choline * glycerol * fatty acid

B. Cephalins

1. Phosphatidyl ethanolamine (P-bound ethanolamine * glycerol * fatty acid)

2. Phosphatidyl serine (P-bound serine * glycerol * fatty acid)

3. Phosphoinositide (P-bound inositol *glycerol * fatty acid)

C. Acetal phospholipids (plasmalogens)
(P-bound ethanolamine * glycerol * fatty aldehyde)

APPENDIX III

Table 3

DEMYELINATING DISEASES (147)

I. PRIMARY DEMYELINATING DISEASES

A. Cerebral lipidosis

1. Cerebroretinal degeneration.
   Variants:
   a. Infantile type or amaurotic family idiocy (Tay-Sachs disease)
   b. Late infantile type (Dielschowsky)
   c. Juvenile type (Spielmeyer-Vogt)
   d. Late juvenile type (Kufs)
   e. Cerebroretinal degeneration with hepatosplenomegaly (Niemann-Pick disease)

2. Infantile lipoid histiocytosis (Gaucher's disease)

3. Cranial xanthomatosis (cholesterinosis) (Hand-Schuller-Christian disease)

4. Chondro-osteodystrophy (gargoylism) (Hurler's disease)

B. Diffuse sclerosis

1. Degenerative familial type (leukodystrophy)
   a. Simple type, with sudanophilic ("neutral fat" and cholesteros ester) products of myelin degeneration
      (1) Chronic infantile type (Pelizaeus-Merzbacher disease)
   b. Globoid-cell type, with prelipid products of myelin degeneration in multinucleated giant cells (Greenfield)
      (1) Acute infantile type (Krabbe)
      (2) Subacute juvenile type (Scholz)
      (3) Chronic adult type (Ferraro)
      (4) Late adult type (van Bogaert-Nyssen)
   c. Metachromatic type with golden-brown or red-brown prelipid products of myelin degeneration when stained by toluidine blue or basic

aniline dyes (Einarson and Neel, Norman, Braun and Greenfield)
d. Degeneration of interfascicular glia (Greenfield)

2. Inflammatory degenerative type (nonfamilial)
a. Giant plaque type or encephalitis periaxialis diffuse (Schilder's diffuse sclerosis)
b. Concentric type (Balo's concentric sclerosis)

3. Inflammatory type of myelinoclastic sclerosing leukoencephalitis (viral?)
a. Inclusion-body leukoencephalitis (Dawson)
b. Subacute sclerosing leukoencephalitis (van Bogaert)

C. Disseminated sclerosis

1. Multiple sclerosis (Charcot's disease)
a. Acute form
b. Chronic relapsing encephalomyelopathic form

2. Optic neuromyelopathic form or neuromelitis optica (Devic's disease)

D. Acute disseminated encephalomyelitis (acute perivascular melinoclasis or "allergic" perivenous encephalomyelitis)

1. Postimmunization types (after rabies, smallpox, and other types of immunization)

2. Postinfectious types
a. Postexanthem (after vaicella, variola, rubella, rubeola, scarlet fever)
b. Nonspecific infection (after grippe, upper respiratory infection and so forth)

3. Idiopathic or "primary"

4. Acute hemorrhagic leukoencephalopathy (Hurst), leukoencephalitis (Russel)

II. SECONDARY DEMYELINATING CONDITIONS

A. Wallerian degeneration (secondary to primary neuron lesion)

1. Neuron damage due to known causes (physical trauma, infection, neoplasm, infarction, and so forth)

2. Neuron loss due to unknown cause (neuronal "abiotrophies")
   a. Heredodegenerative diseases of the central nervous system (cerebellar-system atrophies, Friedreich's ataxis, spastic paraplegia and so forth)
   b. Sporadic degeneration (amyotrophic lateral sclerosis and so forth)

B. Metabolic disorders and deficiency syndromes

1. Hypoglycemia

2. Porphyria

3. Subacute combined sclerosis (pernicious anemia)

4. Nutritional and vitamin deficiency

C. Anoxic anoxia

1. Respiratory arrest or low concentration of atmospheric

2. Circulatory
   a. Anemia
   b. Chronic cyanotic heart disease
   c. Thromboembolic cerebrovascular occlusion (including malaria, arteritis)

3. Carbon monoxide intoxication

D. Exogenous intoxication (enzyme poisons)

1. Triorthocresylphosphate (inhibition of pseudocholinesterase)

2. Isoniazid (inhibition of coenzyme, pyridoxine)

3. Carbon monoxide (inhibition of cytochrome oxidase)

E. Endogenous intoxication

1. Uremia

2. Eclampsia

3. Hepatic failure

4. Dysentery

F. "Melinoclastic" viral infections

1. Sclerosing inclusion-body leukoencephalitis (van Bogaert, Dawson)

2. Other virus encephalitides

G. Miscellaneous

1. Cerebral edema

2. Surrounding cerebral glioma

APPENDIX IV

Table 4

Chemical Constitution of Mammalian Brain (51)

(G/100 gm. fresh tissue)

Constituent	White Matter
H_2O	67-74
Total ash	0.7 - 2.7
Acid-soluble N	0.11 - 0.47
Amino N	0.082 - 0.105
Na	0.10 - 0.23
K	0.18 - 0.38
Ca	0.014- 0.016
Mg	0.026- 0.041
Cl	0.09 - 0.19
Total S	0.092- 0.150
Org. P	0.33 - 0.48
Inorg. P	0.011-0.060
Acid sol. P	0.060-0.186
Lipids:	
Total L.	16.0 - 22.0
Total P lipids	6.2 - 9.3
Phosphatidyl choline	0.9 - 1.9
" serine	1.4
" ethanolamine	
Phosphasphingosides	1.8 - 4.3
Glycosphingosides (cerebrosides)	4.1 - 7.4
Aldehydes in acetyl phosphatide	0.63 - 0.75
Inositol phosphatides	
Strandin) Gangliosides)	0.06 - 0.07
Sulfatide	0.9 - 1.2
Phosphatido-peptides	0.1
Total non-saponifiable material	6.0 - 8.3
Cholesterol	3.6 - 5.4
Hydrocarbons	
Proteins:	
Total protein	6.0 -12.7
Proteolipide protein	2.0 - 2.5
Globulin extractable with 20% NaCl.	1.0
Alb. " " " "	0.3

Constituent	White Matter
Neurokeratin	
Collagen	
Elastin	
Protein-bound - fraction	
Total residual P	0.025 - 0.042
PNA ≠ P	0.004 - 0.005
PNA - P	0.005 - 0.006
Phosphoprotein-P	0.002 - 0.003
Inositide-P	0.019 - 0.023

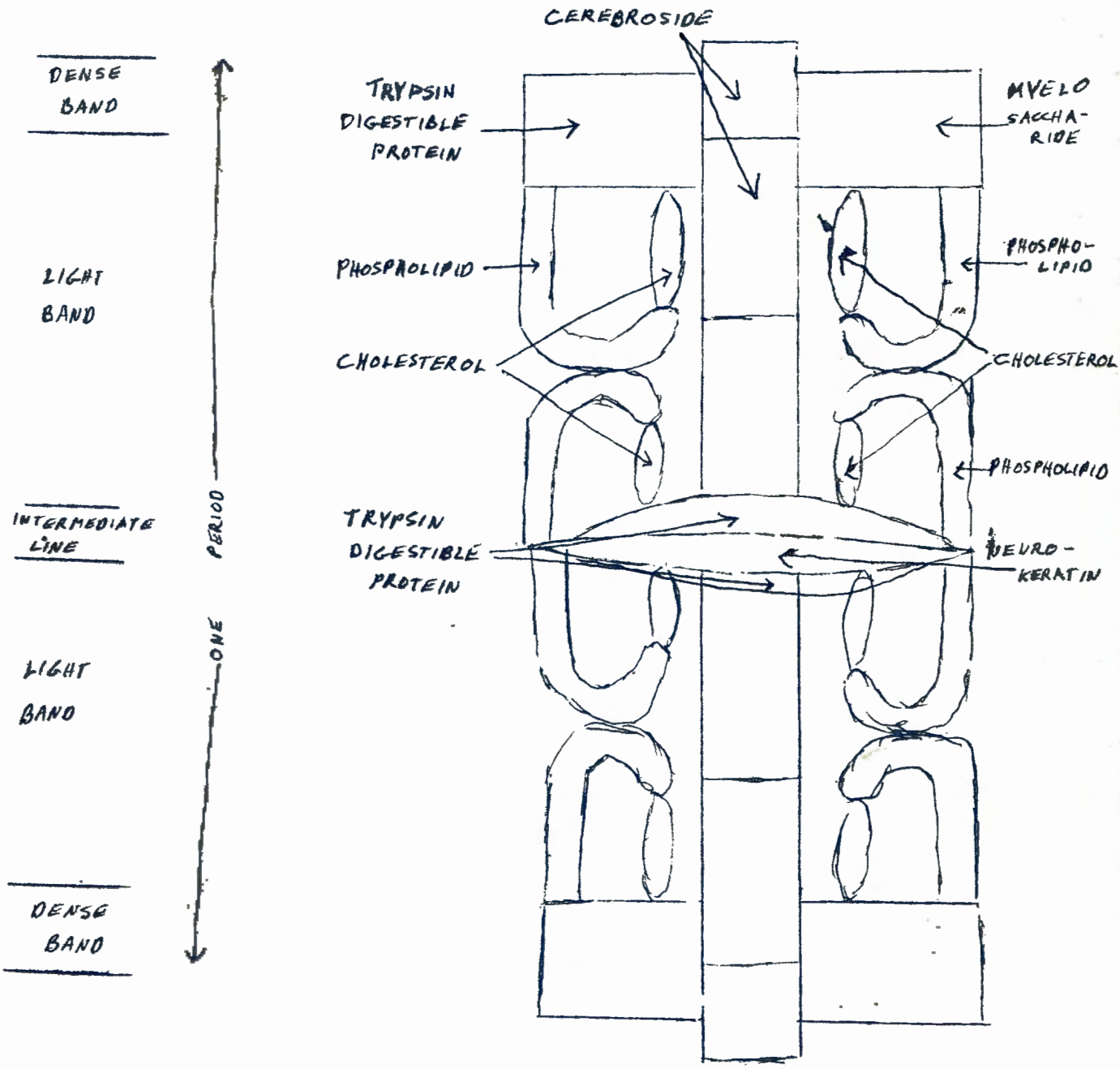
Constituent	Whole Brain
Glycogen (or kerose)	0.087 - 0.128
Glucose	0.058 - 0.102
Lactic acid	0.013 - 0.023
Phosphocreatine	0.061 - 0.080
ATP	0.106 - 0.154
PPN	0.0099- 0.018
Thianone	0.00008 - 0.00015
Glucose-1-PO_4	0.0026- 0.026
Glucose-6-PO_4	0.0026- 0.052
Fruct-6-PO_4	0.0026- 0.0078
Fruct-1,6-di PO_4	0.0010- 0.0023
3 Phosphoglycoaldehyde ≠ ..... Dihydroxyacetone-PO_4	0.0051
Phosphoglyconate	0.019 - 0.0093
Phosphenol pyruvate	00.13
Pyruvate	0.00088- 0.00176
Phosphoethanolamine	0.0419
Phosphoethanc choline	0.0066 - 0.0081
Glycerby phosphoryl ethanolamine ..	0.0023

APPENDIX V

MYELIN MOLECULAR ANATOMY (180)

Electron-Microscopical Appearance

Fig. 2



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