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The next issue will treat of: MYASTHENIA

Editorial

Las primeras publicaciones referentes a la Esclerosis Múltiple fueron hechas en Francia por Cruveilhier en 1815 en su "Anatomie Pathologique du corps Humain" y en Inglaterra por Carswell en 1838 en su "Pathological Anatomy. Illustrations of the Elementary forms of Disease".

Pero en el diario de Augusto D'Estré aparecido anteriormente se encuentra ya una descripción que no puede corresponder a otra cosa que a una Esclerosis Múltiple.

Charcot hizo la primera descripción completa en 1868 con enfermos suyos y de Vulpian y denominó la afección "Sclérose en plaques" y configuró su característica triada para el diagnóstico: ataxia, nistagmus y palabra escandida. Charcot conocía además los otros síntomas que pueden estar presentes, ambliopía, diplopía, vértigos, cambios emocionales e intelectuales, síntomas bulbares, paresias de las extremidades, etc.

Bourneville y Guérard de la escuela de Charcot publicaron en 1869 el primer libro sobre la enfermedad. Charcot dio con cierto detalle datos acerca de la anatomía patológica: desaparición precoz de la vaina de mielina, relativa conservación del cilindro eje excepto en el centro de la placa, aumento de los elementos gliales; en la periferia de la placa acumulación de glóbulos grasos alrededor de los vasos sanguíneos; la sustancia gris a veces es invadida y hay atrofia de las células.

En Alemania en el siglo pasado se hicieron estudios por Frerichs (1849), Türck (1855), Valentiner (1856), Rokitansky (1850), Leyden (1863), Zenker (1870).

Moxon (1875) hizo una de las primeras descripciones en Inglaterra y Seguin (1875) la primera americana.

Pierre Marie (1874) insistió en la relación de la Esclerosis Múltiple con enfermedades infecciosas; este autor ha sugerido también que la Epilepsia es de origen infeccioso.

Eduard Müller (1904) de Breslau publicó un libro "Die Multiple Sklerose des Gehirns und Rückenmarks" en el cual menciona más de 1100 referencias, lo cual indica el interés que ya entonces había despertado la enfermedad.

La esclerosis múltiple es una afección que evoluciona a menudo con agravaciones y remisiones.

Los síntomas que se presentan con cada agravación, no desaparecen totalmente durante la mejoría que sigue, de manera que con el transcurso del tiempo van acumulándose efectos permanentes.

El curso de la enfermedad puede ser lento o rápido y su comienzo puede ser gradual o brusco.

Las lesiones se observan en cualquier sector del neuroeje desde la corteza del cerebro hasta el cono terminal. La sintomatología puede describirse a gran-

des rasgos en la siguiente forma: En lo motor, el hecho más común es una paresia espástica de uno o los dos miembros inferiores; debilidad en los miembros superiores y temblor intencional.

En lo sensitivo es frecuente observar parestesias sobre la cara, brazo o pierna. Si se flexiona el cuello del enfermo, este experimenta una sensación de electricidad en el cuerpo. En algún momento de la evolución, en el 50 % de los casos aparece una anestesia.

La sintomatología oftalmológica es muy importante y fundamental para el diagnóstico. La neuritis óptica retrobulbar aguda y unilateral aparece en el 50 % de los pacientes durante el curso de la enfermedad. La palidez temporal es de instalación más gradual. Un nistagmus es de frecuente observación, en general horizontal, raramente rotatorio. Con cierta frecuencia hay diplopía. Por el contrario es rara la parálisis de la desviación ocular conjugada.

El líquido cefalorraquídeo es a menudo normal. Frecuentemente se observan leves modificaciones en uno o más de los elementos estudiados de rutina en el laboratorio hospitalario. Se mencionan cambios en la curva del oro coloidal y aumento de la gamma globulina.

La esclerosis múltiple pertenece al grupo de las enfermedades desmielinizantes. Se caracterizan ellas por presentar destrucción de las vainas de mielina y relativa conservación de los cilindroejes, las células nerviosas y los tejidos de sostén. Las lesiones dentro del sistema nervioso central aparecen en focos múltiples.

En el grupo de las enfermedades desmielinizantes están comprendidas la esclerosis múltiple, la encefalomielitis aguda diseminada, la encefalopatía hemorrágica necrotizante aguda y la esclerosis cerebral progresiva del tipo desmielinizante.

Estas afecciones si bien tienen anatómicamente caracteres comunes, evidencian también elementos que permiten distinguirlas por lo cual su diagnóstico por lo general no es difícil.

En la esclerosis múltiple las lesiones son de 1 mm. a 4 cm. de diámetro y se observa siempre una tendencia a la localización perivenosa. Se las encuentra en la médula espinal, en el tronco cerebral, cerebro, cerebelo y nervios ópticos.

En el cerebro su localización es casi constantemente adyacente a los ventrículos laterales.

La apariencia de las lesiones varía con la edad de las mismas, las crónicas se caracterizan por ser cicatrices gliales, con ausencia de degeneración secundaria encima y debajo. Las agudas o recientes (de casos crónicos) presentan además de lo señalado en las vainas de mielina, infiltración perivascular con linfocitos, plasmazellen, histiocitos.

Los cilindroejes presentan escasos signos de degeneración salvo cuando la enfermedad ha sido muy prolongada.

Las incógnitas que presenta esta cruel enfermedad son muchas, siendo de destacar en primer término su origen totalmente desconocido y la falta absoluta de tratamiento curativo. El mecanismo de las lesiones, la evolución habitual con empujes y remisiones son entre otros, enigmas a resolver. Un hecho curioso es el de que a pesar de la frecuencia y riqueza que presentan estos pacientes síntomas piramidales, la sintomatología sensitiva es relativamente escasa, aun en casos avanzados con notables trastornos motores, a pesar de que las lesiones anatómicas de las vías motoras no son más frecuentes que las de las vías sensitivas. Sin embargo algunas correlaciones anatomoclínicas son muy claras: los síntomas y signos piramidales se explican por el daño a la vía piramidal que puede estar en la médula, el tronco cerebral o el cerebro; la diplopía por lo general es un síntoma de oftalmoplejía internuclear y se debe a la lesión de la cintilla longitudinal posterior; la neuritis óptica retrobulbar es consecuencia

del daño del sistema vestibular (vías o núcleos) y las lesiones de los pedúnculos cerebelosos en el tronco cerebral explican la ataxia y la inseguridad.

Mucho se ha discutido acerca de las relaciones entre la encefalomielitis (la post-infecciosa y la espontánea) y la esclerosis múltiple. En las últimas décadas Ferraro y Jervis (1940), Kabat, Wolff y Bezer (1947) y otros comenzaron la producción experimental de encefalomielitis por la inyección de emulsiones de cerebro homólogas o heterólogas.

Induciendo en animales de experimentación reacciones tisulares hiperergicas y observando las alteraciones cerebrales, se han desarrollado conceptos para explicar la anatomía patológica de las enfermedades desmielinizantes espontáneas del hombre.

También se han empleado las técnicas de cultivos de tejido al estudio de la encefalomielitis alérgica experimental y las afecciones desmielinizantes en el hombre. Estas investigaciones van en apoyo de la hipótesis de que en la encefalomielitis alérgica experimental estamos frente a una reacción del tipo antígeno anticuerpo. En estos experimentos se ha observado remielinización, lo cual de cumplirse en el proceso espontáneo podría explicar las remisiones que siguen a las exacerbaciones en la esclerosis múltiple. Por ser la esclerosis múltiple una enfermedad desmielinizante, los estudios realizados en la biología de la mielina son de fundamental importancia. Particularmente interesantes son las observaciones hechas con microscopía de fase y electrónica sobre la desmielinización experimental.

Estudios histoquímicos practicados en las placas lesionales han señalado cambios en la actividad enzimática (enzimas oxidativas, enzimas hidrolíticas) mitocondria, etc. Algunos autores han identificado un virus que sería el causante de la enfermedad. Pero esto aun no ha tenido confirmación.

En los últimos tiempos se han acumulado evidencias acerca de particularidades geográficas y epidemiológicas de la enfermedad. Si bien puede encontrarse en todas las razas y en todas las regiones, en Europa prevalece en las regiones nórdicas; la enfermedad decrece en frecuencia a medida que se está más cerca del Mediterráneo. En los Estados Unidos la afección es más común entre los habitantes de origen escandinavo que entre los descendientes de otras razas.

Indudablemente que cualquier teoría acerca de la causa de la esclerosis múltiple debe explicar estos hechos.

Agradecemos en nombre de los editores de la Revista Internacional de Neurología, a los autores de este número por el honor que significa haber contado con sus valiosísimas colaboraciones, Drs. Edith y Heinrich Pette (Alemania), M. Bonduelle y R. Albaranes (Francia), D. J. Lyle (U.S.A.), C. M. Plum (Dinamarca), E. P. Bharrucha y R. M. Umarji (India) y G. A. Schumacher (U.S.A.), quienes nos dieron la oportunidad de ofrecer a nuestros lectores los frutos de sus investigaciones y amplia experiencia sobre la Esclerosis Múltiple.

VICTOR SORIANO.

Editorial

The first publications concerning multiple sclerosis were written in France by Cruveilhier in 1835 in his "Anatomie Pathologique du Corps Humain" and in England by Carswell in 1838 in his "Pathological Anatomy-Illustrations of Elementary Forms of Disease".

But previously in the diary of Auguste D'Esté there was found an accurate description that no doubt fits the multiple sclerosis picture.

Charcot made the first complete description of this illness in 1868 in his and Vulpian's patients and called this disease "Sclérose en Plaques" and established his triad nystagmus, scanning speech and intention tremor. He also was well aware of the other symptoms that could be present like amblyopia, diplopia, vertigo, emotional and intellectual changes, bulbar symptoms, paresis of limbs, etc.

Bourneville and Guérard of the Charcot school published the first book on multiple sclerosis in 1869.

Charcot gave descriptive data with certain details of the pathological anatomy of it, like early disappearance of the myelin sheath, relative sparing of axis cylinder except in the plaque's center, glial elements augmented, accumulation of fat cells around the blood vessels at the plaque's periphery; the grey matter sometimes is invaded and there is atrophy of the cells.

In Germany in the past century, studies were made by Frerichs (1849), Türck (1855), Valentiner (1856), Rokitansky (1850), Leyden (1863), Zenker (1870).

Moxon (1875) made one of the first descriptions in England and Seguin (1875) the first one in America.

Pierre Marie in 1884 stressed the relationship between multiple sclerosis and infectious diseases. This author also has suggested that Epilepsy is of infectious origin. Edward Müller (1904) of Breslau published a book "Die Multiple Sclerosis des Gehirns und Rückenmarks" with a bibliography of more than 1100 references which indicates the great interest which this illness had aroused at that time.

Multiple sclerosis is an ailment that very often evolves with alternating exacerbations and remissions.

The symptoms that appear at every exacerbation do not totally disappear during the period of remission, and in this way with time permanent deterioration takes place. The evolution of the illness can be slow or rapid, its onset can be gradual or sudden.

Lesions may be observed in any sector of the central nervous system from the brain cortex to the terminal conus.

A general outline of the symptomatology is the following: Concerning the

motor function, a spastic paresis of one or both of the lower limbs, is the most common occurrence; frequently also weakness in the upper limbs and intentional tremor.

In regards to the sensibility, parestesias on the face, arm or leg is frequent, upon flexing the neck of the patient he experiences a sensation of electricity in his body. At some stage of its evolution, an anesthesia appears in 50 % of the cases.

The ophtalmologic aspect of the symptomatology is very important and fundamental for the diagnosis. A unilateral and acute retrobulbar neuritis of the optic nerve appears in 50 % of the cases. The temporal pallor has a more gradual beginning. A nistagmus often usually lateral, rarely rotatory. Frequently there is diplopia. A paralysis of conjugate ocular deviation seldom occurs.

The cerebrospinal fluid is often entirely normal. Frequently there can be seen slight to moderate change in one or more of the different elements studied in routine hospital laboratory. Have been reported colloidal gold changes; altered distributions of protein, notably a rise in the gamma globulin content in the spinal fluid.

Multiple sclerosis is an illness belonging to the demyelinating group of diseases. Characteristic of this kind of ailment is the destruction of the myelin sheaths, and a relative conservation of the cylinder axis, the nerve cells and the supporting tissues. The lesions of the central nervous system appear in multiple focus. In the group of demyelinating diseases are included multiple sclerosis, acute disseminated encephalomyelitis, acute necrotizing hemorrhagic encephalopathy and progressive cerebral sclerosis of the demyelinative type.

These diseases even though they have similar anatomic characteristics, posses features which allow generally without defficulties their differentiation and thus a correct diagnosis.

In multiple sclerosis the lesions are from 1 mm. to 4 cm. in diameter and always a to be located around the veins is noticed. They may be found in the spinal cord, in the brain stem, brain, cerebellum and optic nerves.

In the brain they are almost always located next to the lateral ventricles. The appearance of the lesion varies with their age, the chronic ones are glial scars, with an absence of secondary degeneration above and below the lesion. The more recent or acute (of chronic cases) evidence besides the already described in the myelin sheaths, perivascular infiltration with lymphocytes, plasmacells and histiocytes.

The axis cylinders present few signs of degeneration except when the illness has been very prolonged.

There are many unsolved questions of this cruel illness, the two most important being its completely unknown cause and the absolute lack of a curative treatment. The mechanism of the lesions, its habitual clinical evolution with relapses and remissions are as the other problems needed to be solved.

One remarkable fact among the extraordinary richness these patients present in pyramidal symptoms is that the sensory loss is relatively scarce, even in the most advanced cases with marked motor disturbances, and in spite of that the anatomical lesions of the motor tracts are not more frequent than those found in the sensory ones.

However some anatomical relations are very clear; the pyramidal symptoms and signs are explained by the damage to the pyramidal tract that may be located in the spinal cord, the brain stem or the brain; the diplopia generally is a symptom of an internuclear oftalmoplegia due to the lesion of the medial longitudinal fasciculus, the optic retrobulbar neuritis is due to a lesion of the

nerve, nystagmus is a consequence of the damage of the vestibular system (tracts or nuclei); and the lesions of the cerebellar peduncles in the brain stem explain the ataxia the unsteadiness and incoordination.

Very much has been discussed about the relationship between encephalomyelitis (the post infectious and the spontaneous) and multiple sclerosis. In the last decades Ferraro and Jervis (1940) Kabat, Wolff and Bezer (1947) and some others began the experimental production of encephalomyelitis by the injection of heterologous or homologous brain emulsions.

Concepts based on what has been able to be observed in the brains of animals with induced hiperergic tissue reactions have been proposed as an explanation of the morbid anatomy of the spontaneously occurring human demyelinating diseases.

Experiments with tissue culture have application to the study of experimental allergic encephalomyelitis and demyelinating disorders in man. It seems to support the concept that in experimental allergic encephalomyelitis we are dealing with an antibody antigen type of reaction. In these experiments remyelination has been observed which may give an inkling to the remissions after exacerbations in multiple sclerosis. Since the multiple sclerosis is a demyelinating disease, the studies made especially in the biology of the myelinating sheath are of prime importance. The enlightening observations made with the use of phase and electron microscopic of experimental demyelination are of the greatest interest.

Histochemical studies in the plaques of multiple sclerosis demonstrated changes in enzymatic activity (oxidative enzymes, hydrolitic enzymes) mitochondria, etc.

Several authors have reported identification of a virus as a cause for multiple sclerosis. But still no specific virus has been unequivocally demonstrated.

In recent times evidence has been accumulated about the geographic and epidemiological particularities of this illness. Even though it can be seen in every race and region in Europe it is prevalent in the nordic regions. The frequency decreases moving toward the Mediterranean. In the United States this ailment is more frequent among the inhabitants of Scandinavian origin than among the descendants of another ethnic strains.

Any theory aiming to explain multiple sclerosis ought to have an explanation for these differences.

In the name of the Editorial and Advisory Board of the International Journal of Neurology we express our deply-felt gratitude to the authors who have tackled the different aspects of this puzzling disease Drs. Edith and Heinrich Pette (Germany), M. Bonduelle and R. Albaranes (France), D. J. Lyle (U.S.A.), C. M. Plum (Denmark), E. P. Bharucha and R. M. Umarji (India), G. A. Schumacher (U.S.A.), who have thus given us the opportunity to offer our readers the fruits of their excellent research and wide experience concerning Multiple Sclerosis.

VICTOR SORIANO.

The Immunological Aspect of the Problem of the Demyelinating Encephalomyelitis

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Research on the demyelinating encephalomyelitis has experienced a considerable impetus in the past two decades with regard to its etiopathogenesis. This is due to the introduction of animals as experimental tools in immunological research and to the serological and immunochemical methods *in vitro*.

In 1929 we classified the acute inflammatory diseases of the central nervous system (CNS), which were not of a bacterial etiology into two groups: 1) the acute inflammatory diseases predominantly in the grey matter and 2) the acute inflammatory diseases predominantly in the white matter. To the first group belong the viral infections of the CNS (poliomyelitis, rabies, arbovirus-infections a.o.) and to the second group the acute demyelinating encephalomyelitis (DEM) i.e. diseases of a primary and selective degeneration of the myelin sheath for which a living agent as an etiological factor could not yet be traced. The agent formerly suspected by some authors (spirochets, viruses of various kinds) did not stand up to later tests. We have carried out investigations with the JHM virus on monkeys which according to Bailey, Pappenheimer, Cheever and Daniels (1949) should produce a destruction of the myelin sheath in mice. The degeneration of the myelin sheath was found to be merely a manifestation of a tissue necrosis and, therefore, not specifically caused by the virus disease.

In 1946, the Russian authors Margulis, So-

loviev, Shubladze isolated the virus (SV) from cases of encephalomyelitis (EM).

According to virological, serological and histological findings the virus turned out to belong to the rabies group. The virus did not cause lesions of the myelin sheath in monkeys.

Sigurdsson and Associates isolated a virus from the brains of paralysed sheep and considered it to be the causative agent of MS. In subsequent investigations the sheep were infected intracerebrally and an inflammatory granulomatous process was evoked with an intense reaction of the reticuloendothelial system (RES). This in turn caused a necrosis located in various points of the brain and spinal cord. The process has nothing in common with MS.

Definition of Concept, Clinic and Histology

In the course of different research periods, the concept of the Demyelinating Encephalomyelitis has undergone various different interpretations. During the 1920s, the concept was applied solely to the disseminated encephalomyelitis and the acute multiple sclerosis (H. Spatz).

Later on, the postvaccinal and parainfectious encephalomyelitis were also included in this group of diseases. This terminated the long controversy over the problem whether the diffuse DEM should be fundamentally separated from the disseminated DEM and the acute MS resp. In our opinion

there is no fundamental etiopathogenetic difference between these diseases, neither clinically nor histologically. From a clinical point of view the onset and the evolution of the diseases are different from those of neurovirus infections, which show: acute appearance of the morbid manifestations without prodromes. On the other hand, in many cases of DEM the neural process is preceded by catarrhal infections, vaccinations of different kinds, hormonal crisis, climatic affections (exposure to wetness, chills, intense sun radiations), etc., within a certain time interval. In the acute phase one observes a dilatation of the capillary blood vessels with a dissolution of the endotheliums of the vascular walls. This causes an alteration of the wall permeability thus enabling the plasmatic proteins to outflow. The process, therefore, starts from the vascular system.

A differential diagnosis between a parainfectious encephalomyelitis and the first attack of a multiple sclerosis is often impossible.

In 1950, Van Bogaert reported that out of nineteen cases of parainfectious encephalomyelitis (diffused) observed in Belgium between 1927 and 1932, 4 turned out afterwards to be the first attack of multiple sclerosis. It has been reported several times that certain cases show histologically the characteristic plaques for MS together with alterations observed in diffuse encephalomyelitis. Lehoczky found in numerous cases of chronic multiple sclerosis besides old plaques, fresh foci of a diffuse encephalomyelitis. We have also seen and described similar cases.

Neuroallergy as a Pathogenic Factor

In 1929 we discussed the possibility of immunobiologic factors and in 1938 the possibility of an allergic reaction in the genesis of a DEM. In 1942, in our Monograph "The Acute Inflammatory Diseases of the Nervous System", we discussed the hypothesis of an antigenic-antibody reaction as a basis for the pathogenesis of the DEM. At that time, the hypothesis was based on an analysis of the clinical process combined with a dynamic aspect of the anatomic-

pathological alterations. It was then that the conception of the Neuroallergy was created.

In 1927, Glanzmann considered for the development of a postvaccinal and parainfectious encephalomyelitis an anaphylactic reaction as a responsible factor. On the first International Neurological Congress at Berne in 1931 Van Bogaert posed the following question: "May not the classical multiple sclerosis be considered an ordinary hyperallergic reaction of a special type characterized by a phasic development?" However, the problem was not dealt with any further.

The above mentioned factors of the prehistory of DEM were pointed out by us as a pathogenic cause in 1942.

In their experiments in 1935 Rivers and Schwendtker were able to produce encephalomyelitis with the characteristics of a diffuse encephalomyelitis in monkeys by numerous injections of heterologous cerebro-spinal tissue. Already at that time, we were impressed by the similarity between their pathological findings and those observed in human encephalomyelitis. The same applies to the experiments of Ferraro and Jervis (1940) who succeeded in producing a diffuse encephalomyelitis in monkeys by numerous injections of brain suspension. Particularly pathogenically important appeared to us that after anti-rabic vaccinations neurological complications in the form of a disseminated encephalomyelitis occurred which were until then without an etiological explanation. We interpreted it as a manifestation of an immunopathological (=allergic) reaction.

"... In the clinical as well as in the anatomical course of a DEM numerous factors can be verified which are equivalent to allergic-hyperergic processes. Observations from the human pathology of vaccinations provide important support to this interpretation in so far as the postvaccinal paralysis as a consequence of the vaccinations (against rabies, tetanus, typhoid) that clinically and anatomically show a picture of an encephalomyelitis, should be explained as an effect of an antigenic-antibody reaction. There are many reasons why a majority of all the encephalomyelitis are a consequence of an antigenic-antibody reaction directed against the central nervous system (Neuro-

allergy). To explain the sensitivity of the neural tissue a decisive importance should be ascribed to the inoculation of protein substances (preventive vaccinations) as well as certain infections. The neural hyperergic process is not only elicited by specific irritations (relapsing and chronic infections) but also by unspecific factors such as climatic influences, hormonal crises, vegetative disturbances etc.)...". Quoted from the Monograph issued in 1942.

We do know today that the CNS in a similar way as other organs may become a shock organ in allergic reactions. The hypothesis of neuroallergy as the pathogenic principle for the genesis of MS has been well substantiated by numerous experimental findings obtained by Ferraro and Jarvis (1940), J. M. Morgan (1946), Kabat, Wolf and Bezer (1947), Koprowski (1948) Alvord (1949), Good (1950) Lumsden (1951). On interpreting his experimental studies, Ferraro in 1944 developed the theory of an "infectious-allergic" or "toxic-allergic" pathogenesis of the disseminated encephalomyelitis, considering, as we do, the MS as a consequence of an allergic reaction of the CNS.

Our team (G. Kersting and E. Pette, 1957) did also succeed in producing an acute DEM in guinea pigs, rabbits, and monkeys by repeated parenteral injections of an emulsion containing heterologous as well as homologous brain- and spinal tissues plus Freund's adjuvants. It is not yet solved whether the encephalitogenic factor is a pure protein or a proteolipid or a mixture of small quantities of protein with highly active lipids.

Comparison of Experimental Encephalomyelitis with MS

When comparing the experimental and the clinical findings in encephalomyelitis, the symptoms observed in the monkeys are found to be similar to those in MS patients: nystagmus, ocular mobility defects, amaurosis, mono- hemi- and para paresis and also disturbances of the sensibility. The severity of the clinical picture and the process of the disease in the animals varied in different cases. Besides a syndrome regressing the

CNS, we observe morbid forms leading to rapid death accompanied by severe paralysis. Even histologically, the situation was found analogous to a great extent. Preferably the white matter of brain and spinal cord, particularly the optic system and the vicinity of the spaces containing cerebrospinal fluid were attacked by the process of encephalomyelitis. The pleomorphism of this process is considerable different not only with different animals but even with the same one. Sometimes, this process is more diffuse in a kind of a diffuse (perivenous) encephalomyelitis (EM), sometimes more focal in a kind of a disseminated EM. The myelin sheaths are always far more damaged than the axons.

The most numerous plaques in the human MS are in contrast to the minor formation of plaques in monkeys. This is leading to the assumption that MS is a specific disease of Man. This is further supported by the fact that up to now no spontaneous MS has even been observed in animals. Therefore, experiments with animals should always be considered as a model only.

As the EM frequently appears following an acute infection or a vaccination, we have called it "Nachkrankheit". In this sense, the disseminated EM cases after an antirabic vaccination described by Uchimura, Shiraki and Haruhara in 1956 represent so to say a human experiment. Another case of antirabic postvaccinal EM described by E. Jones in 1957 showed histological alterations which were not discernable from those of MS. The same applies to an observation by Jellinger and Seitelberger. In this case, a fifty-one year old man was given 7 times a parenteral injection of an emulsion of brain tissue in the course of a treatment with living cells. The patient developed an acute MS which was verified anatomo-pathologically.

Frequently, a careful analysis of the anamnesis shows a close connection between the exogenous and the endogenous factors, particularly the hormonal factors. By the extensive studies of Kurland, it became obvious that also other factors play an important part and are especially responsible for the variable frequency of MS in different countries. In this connection, attention should be drawn to the studies of Schalten-

brand and Associates and to the Monograph of Georgi and Associates.

It is known that a stimulus is required to evoke the effect of an antigenic-antibody reaction on a determined tissue (Haurowitz). This stimulus may be provided in many ways. So the Freund adjuvant should be assigned the significance of a stimulating factor. Also certain viruses, bacteria, bacterial toxins, vaccinations and heterologous sera can be considered as stimulants. We attribute to them a decisive importance in the provocation of an EM. A repeated injection of an emulsion of brain and spinal cord in animals will not produce this EM by itself. Even here, an activator is required. This hypothesis is supported by: 1. Rivers and Schwentker (1935) had injected small pox virus in monkeys intracerebrally, killing them three days later and inoculating their brain in healthy monkeys subcutaneously. Some of these monkeys developed EM. 2. Ferraro and Jervis (1940), that is to say before the introductions of Freund's adjuvants, had injected their monkeys with an emulsion of brain 29 to 103 times during a period of 112 to 400 days before they developed EM. Certainly, we are not wrong in supposing that during their long stay in the cages a secondary infection had been produced that played the part of the activator. The best proof for the accurateness of our assumption is the appearance of EM following numerous antirabic vaccinations. It is known that this vaccine is a mixture of the emulsion spinal cord and attenuated rabic virus. If we include MS in the group of diseases which occur after certain viral infections (measles, chicken pox, scarlet fever, mumps, influenza), after vaccinations of various types and after infections of serum, we feel ourselves justified since in MS patients single exacerbations often appear after catarrhal and other viral infections. Recently, communications have increased to the effect that either the beginning or an exacerbation of MS may also appear after an antirabic vaccination. (Rosenhagen, Daemme, Nikolitsch, Palfey and Merei, Müller and Seitz).

The finding of virus in the central nervous system (measles and small pox virus) in the case of a para- or a postvaccinal EM

may not be interpreted as a proof for the assumption of a viral etiology of the EM, since we know from our own investigations that a virus, especially the small pox virus is demonstrable in the blood and also in the CNS for various weeks without any morbid manifestation. In the case of a viral infection most of the viruses are rendered inoffensive by neutralizing antibodies, the remaining viruses being phagocyted by the cells of the reticulo endothelial system (leucocytes, macrophages, monocytes, lymphocytes). It would be worthwhile discussing whether the virus during the latent stage of its stay inside the organism might not represent a stimulating factor for the production of an EM. Certain differences in the histological substrate between the postvaccinal and the parainfectious EM certainly are due to the difference in the activators (de Vries).

Discussion

Based on clinical and pathological experiences we have considered the antigenic-antibody reaction in the CNS as a fundamental pathogenic principle for the production of EM without being able to supply a proof neither in vitro nor in vivo. We, then, excluded the possibility of attributing the selective lesion of the myelin sheath to a multiplication of viruses within cells of the CNS. At that time, we termed the EM clinically as "Nachkrankheit", which appears after a latent period (after certain virus infections, vaccinations etc.).

An important step in advance in the analysis of the pathogenesis was the recognition won in recent years that the myelin sheath with its lipoprotein structure represents ultrastructurally an invagination of the cellular surface of the glial and of the Schwann cells (Geren, F. O. Schmitt, Robertson). Due to this it should be subject to the same biological laws as the glial cellular membrane. It might be concluded that a structural component of the cellular membrane or of the myelin sheath may be an antigen. This antigen combines specific antibodies formed in the organism whereby the antibody adheres to the membrane and by the

effect of the complement produces a lesion or even destruction of the myelin sheath.

Another proof for the thesis of the neuroallergy is rendered by findings in vitro experiments by Bornstein and Appel (1961), Appel, Bornstein, Seegel and Murray (1961) and myself (1961). The American authors were able to first produce a tumefaction of the neuroglia and of the myelin sheaths in the explanation of cerebellar tissue of just born rats by adding specific immun sera from rabbits. Thereupon a selective demyelination in explanation was observed. We, ourselves, have found alterations of the cellular membranes as well as of the myelinic nerve fibres in tissue cultures of Schwann cells which have been seeded with Schwann cell anti-immun-sera with or without adding complement. Under the fluorescent microscope the antibodies marked with fluoresceine were adhered to the cell surface membrane. When adding complement these antibodies could be seen in the cellular plasma. This view is supported by studies of the H. Green and B. Goldberg Group. These authors (1959) and particularly in their recently published work (Easton, H. Green and B. Goldberg, 1962) on Immunocytolysis, have shown that after the adsorption of the antibody to the cellular surface under the cooperation of the complement, a superficial lesion is produced in the cellular membrane which leads to an osmotic coloidal lysis. Relying on these findings and my own, made on the neuroglia cell, essential importance should be ascribed to the complement system in respect to the primary lesion of the membranes of the neuroglia cells, including the myelin sheath in connection with an antigenic-antibody reaction on the neuroglia cell.

It seems worthwhile to mention the results of experiments by H. Fischer and J. Haupt (1961). These authors discovered that during the complement fixation to the antigenic-antibody complex a cytolytic substance was produced simultaneously with the

loss of the lytic activity of the complement. They identified this substance by paper chromatography as lysolecithin. It has not been clarified yet whether the lysolecithin is formed during the cytolytic process directly on the cellular membrane accumulating focally on the cellular surface (O. Westphal). With Fischer and Associates' hypothesis that lysolecithin is one of the substances that is produced in an accelerated and ever-increasing way during an allergic and anaphylactic reaction, the investigations on the destruction of the myelin sheaths by lysolecithin (A. Weil, 1930, Morrison and Zamecznik, 1950, Birkmayer and Neumayer, 1957, Webster, 1957) once again have gained importance. So, it does seem to be permissible to ascribe a role to the mechanism of immunocytolytic processes in the pathological course of the demyelinating diseases of the nervous system.

Important for the discussion of our problem is the finding concerning the behaviour of the blood vessels in a state of hypersensitivity in which alterations in the permeability of the capillary walls are produced. In this way, antibodies and complement (B. Waksman) may enter the CNS. The previous disease, not always clinically evident, represents the provoking agent. An infection with determined viruses of a somewhat large size, or a vaccination or an injection of homologous or heterologous sera or bacterial toxins may also act as the provoking agent.

We would like to apply the discussed pathogenic mechanism of the demyelination in the EM also for the explanation for the pathogenesis of certain polyneuritic diseases. A demyelination in plaques, in the nerve roots and spinal ganglia is also produced in these cases while the axis cylinders remain intact and the Schwann cells show a very intense proliferation. These forms of polyneuritis may proceed in waves similar as in MS.

SUMMARY

An explanation is given why DEM cannot be the consequence of a primary viral infection. The viral infections fundamental-

ly differ in clinical and anatomic-pathological aspects from the DEM.

The disseminated and diffuse DEM have

the same mechanism of genesis. The hypothesis that the DEM including the acute MS is the expression of an antigenic-antibody reaction in the sense of a neuroallergy, was developed in 1942 based on the dynamics of the picture and the pathologic substrate.

The DEM is a "Nachkrankheit" whose genesis is based on a sensibilisation of certain cells of the CNS. The process will be set off by a stimulating factor that may be multigenetic. The stimulating factor is of importance for both the diffuse or disseminated form of EM.

The DEM of multiple sclerosis character, following an antirabic vaccination, as well as experiments with animals, support the hypothesis of a neuroallergic nature of MS.

According to observations with the electronic microscope the myelin sheath is an exvagination of the membranes of the glial and Schwann cells.

It seems possible that the myelin sheath, in a way analogous to the glial cell membrane, may be damaged in a certain manner by the action of the lysolecithin which is produced in an antigenic-antibody complex with the help of the complement.

RESUMEN

Se explica el porqué no pueda considerarse la encefalomiелitis como la consecuencia de una infección virósica primitiva. Las infecciones virósicas tienen diferencias clínicas y anátomo-patológicas con la encefalomiелitis.

Las encefalomiелitis difusas y diseminadas tienen el mismo mecanismo de producción.

La hipótesis de que la encefalomiелitis, en la cual se incluye la esclerosis múltiple, es la expresión de una reacción antígeno-anticuerpo configurando una neuroalergia, fue desarrollada en 1942 teniendo como base la dinámica del cuadro clínico y el substratum anátomo-patológico.

Las encefalomiелitis se desarrollan como "post enfermedades"; en su génesis están precedidas por una sensibilidad de algunas células del sistema nervioso central. El proceso es desencadenado por un factor esti-

mulante. Este factor estimulante es importante para la forma del proceso, si él es difuso o diseminado.

La encefalomiелitis que toma el carácter de una esclerosis múltiple a continuación de una vacunación antirrábica, confirma lo mismo que la experimentación animal, la hipótesis de que la esclerosis en placas es de naturaleza neuroalérgica.

Estudiada con el microscopio electrónico se observa que la vaina de mielina se origina de las membranas de las células gliales y de Schwann.

Parece posible que la vaina de mielina, en la misma forma que la membrana de la célula glial, puede ser dañada de cierta manera por la acción de la lisolecitina, la cual es producida en un complejo antígeno-anticuerpo causado por la acción del complemento sobre el anticuerpo.

R É S U M É

On s'explique le fait qu'on ne puisse pas considérer l'encéphalomyélite comme la conséquence d'une infection vireuse primitive. Les infections vireuses présentent des différences cliniques et anatomo-pathologiques avec l'encéphalomyélite.

Les encéphalomyélites diffuses et disséminées possèdent le même mécanisme de production. L'hypothèse que l'encéphalomyélite, dans laquelle on inclue la sclérose multiple,

est l'expression d'une réaction antigène anticorps figurant une neuroallergie, a été développée en 1942 en ayant comme base la dynamique du cadre clinique et le substratum anatomo-pathologique.

Les encéphalomyélites se développent comme des "post maladies" et dans leur genèse elles sont précédées par une sensibilité de quelques cellules du système nerveux central. Le procès est déchaîné par un

facteur stimulant. Ce facteur stimulant est important pour la forme du procès, s'il est diffus ou bien disséminé.

L'encéphalomyélite qui prend la forme d'une sclérose multiple à la suite d'un vaccin anti-rabique, confirme de même que l'expérimentation animale, l'hypothèse que la sclérose en plaques est de nature neuroallergique.

Etudiée au microscope électronique, on

observe que la gaine de myéline a son origine dans les membranes des cellules gliales et de Schwann.

Il semble possible que la gaine de myéline, ainsi que la membrane de la cellule gliale, puisse être endommagée d'une certaine façon par l'action de la lyssolécitine, laquelle est produite par un complexe antigène anticorps fatigué par l'action du complément sur l'anticorps.

ZUSAMMENFASSUNG

Es wird aufgezeigt, warum Entmarkungs-encephalomyelitiden (EEM) nicht Folge einer primären viralen Infektion sein können. Virale Infektionen unterscheiden sich klinisch und pathologisch-anatomisch grundsätzlich von den EEM.

Diffuse und disseminierte EEM haben den gleichen Entstehungsmechanismus.

Die Hypothese, dass die EEM einschliesslich der akuten MS Ausdruck einer Antigen-Antikörper-Reaktion im Sinne einer Neuroallergie seien, wurde 1942 auf Grund der Dynamik des klinischen Bildes und des pathologisch-anatomischen Substrates entwickelt.

Die EEM sind "Nachkrankheiten", deren Entstehung eine Sensibilisierung bestimmter Zellen des ZNS zur Voraussetzung hat. Der Prozess wird durch einen Reizfaktor zur

Auslösung gebracht, dieser kann multigenetisch sein. Für die Prozessgestaltung, ob diffus oder disseminiert, ist der Reizfaktor von Bedeutung.

Die EEM vom Charakter einer MS im Gefolge einer Lyssa-Schutzimpfung stützt in gleicher Weise wie das Tierexperiment die Auffassung, dass die MS neuroallergisch bedingt ist.

Elektronenoptisch ist die Markscheide eine Ausstülpung von Gliazell— bzw. Schwann'schen Zellmembranen.

Es erscheint möglich, dass die Markscheide analog der Gliazellmembran durch Einwirkung von Lysolecithin, das bei einem Antigen-Antikörper-Komplex durch Komplement auf dem Antikörper entsteht, in bestimmter Weise geschädigt wird.

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Biochemical Studies of the Composition of Cerebrospinal Fluid in Multiple Sclerosis

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The cerebrospinal fluid was at one time seriously considered to be a dialysate of plasma (Merritt & Fremont-Smith⁽⁹⁹⁾). Modern studies of its chemical composition have shown however that the distribution of a number of solutes between the cerebrospinal fluid and plasma is so different from what one would expect of a distribution between plasma and its dialysate, that the existence of secretory activity must be invoked to explain the chemical composition of the cerebrospinal fluid.

In other words, a study of the individual components of the cerebrospinal fluid will provide information both on the fluid and its environment.

The question occurring to anyone working with these problems is whether deviations from the values found in a normal material can be ascribed any diagnostic significance. There are numerous factors which determine the answer to this question, so an important point is to decide the limits which must be drawn to distinguish normal from deviant values.

It should be stressed primarily that every pathological change in the cerebrospinal fluid, perhaps in particular any displacement in the amount of protein, even though quite small, indicates clearly the presence of an organic disease in the actual central nervous system, or in the surrounding membranes, and this in itself is an important piece of information.

It should be emphasized that a diagnosis cannot usually be made on the basis of a single variation from normal. It might even

be claimed with justification that such a diagnosis would be impossible, provided cases involving the presence of bacteria or tumour cells are excepted. It would likewise seem quite incorrect to make a *definite* diagnosis on the basis of changes in the cell count, of a slightly increased amount of protein, or of displacement in the albumin/globulin ratio.

The basis for a diagnosis is not present until a record is available of numerous changes in the composition of the cerebrospinal fluid, and even under these circumstances there are only a few groups of diseases which can be diagnosed exclusively in this manner.

The findings in studies of the cerebrospinal fluid must be combined with the clinical findings, general biochemical investigations and roentgenological observations.

The investigations which follow were undertaken to find methods of diagnosing multiple sclerosis, or of providing support for a tentative diagnosis of the disease, and to find methods which would help in elucidating the nature of its progressive destructive activity in the central nervous system.

I

Cerebrospinal fluid electrolytes

Since *Mestrezat's*^(100, 101) investigations, there has been increased interest in the distribution of the various electrolytes in ce-

rebrospinal fluid and their relationship to the electrolytes in the blood.

The electrolytes of the cerebrospinal fluid have been studied thoroughly in the normal organism, but incompletely in various disease states. Changes in the concentration of the cerebrospinal fluid electrolytes are followed by profound body-changes as a whole^{(10, 16, 29,}

33, 39, 48, 62, 65, 67, 82, 88, 103, 109, 123, 135, 140, 141, 144, 164).

Sodium ions

The concentration in cerebrospinal fluid appears to be between 134 and 152 mEq/l, or individually between 3 and 5 per cent higher than in serum.

TABLE 1

Some of the normal values for sodium in the cerebrospinal fluid.		
Bailey (1931)	131-132 mEq/l	
Shohl (1939)	151	—
Harrison (1947)	141	—
Sundermann & Böemer (1949)	135-153	—
Shaw & Holley (1951)	134-152	—
Mannery (1952)	141	—

The sodium ion concentration in patients with multiple sclerosis has been determined only a few times, as no major investigation has been devoted to this topic, the patient material having been included in the various studies of neurological disorders⁽¹¹³⁾.

Author's investigations

Method: Flame photometry using the Beckmann DU spectrophotometer and Kipp's spectrophotometer.

Results: Table 2.

The results found indicate that there are no statistically significant variations within the patient groups examined. The results of the sodium level in cerebrospinal fluid confirm those of *Mond*⁽¹⁰²⁾ among others, as he finds a normal value of 146,5 (139-156) mEq/l, and in the patients with multiple sclerosis a mean value of 147 (144-151) mEq/l. The present investigation found 145 (132-157) mEq/l for multiple sclerosis.

TABLE 2

The concentration of sodium ion in cerebrospinal fluid in "normal" and pathological conditions			
	<i>N</i>	<i>Mean</i>	<i>Stand. dev.</i>
"Controls"	50	146.51	6.63
Multiple sclerosis	127	145.20	7.15
Observation for multiple sclerosis	53	141.94	8.04
Neurological disorders	646	146.14	9.08
Epilepsy	572	143.12	9.12
Psychiatric disorders	310	144.49	6.37

Potassium ions

Determination of potassium ion has involved some difficulty, both the results obtained and the methods employed having varied in the course of the last three decades. In table 3, a selection of the results obtained are set out for a so-called normal material, together with the very few data

available for patients with multiple sclerosis. As the table shows, the investigations on the potassium content of cerebrospinal fluid have given rather heterogeneous results, but most recent figures suggest that the mean value of 2.88 mEq/l may be reckoned with. This value corresponds to about 60 per cent of the amount normally found in serum⁽⁶¹⁾.

TABLE 3

Some of the values for potassium ions in the cerebrospinal fluid

	<i>Normal</i>	<i>Multiple sclerosis</i>
Pincus & Cramer (1923)	3.86	
Eisler (1928)	3.38	
Leipold (1928)	3.47	
Leulier et al. (1928)	3.14	
Sary et al. (1929)		2.97
Duliere (1931)	2.85	
Lierle & Sage (1931)	3.27	
Ballif et al. (1932)	2.62-4.62	
Merritt & Smith (1937)	3.38	
Honeymann & Zwemer (1938)	3.40 (2.85-3.74)	3.51 (3.27-3.75)
Harrison (1942)	2.50	
Helmworth (1947)	2.43	
Shaw & Holley (1951)	2.88	
Mannery (1952)	2.50	
Mond (1952)	2.74 (2.43-3.02)	2.81 (2.74-2.89)
Cooper et al. (1955)	2.96	
Sarteschi et al. (1955)		(2.56-3.06)
Rouen (1956)	2-4	

Author's investigations

Methods: Flame photometry using the Beckmann DU spectrophotometer and Kipp's spectrophotometer. *Results:* Table 4.

TABLE 4

The concentration of potassium ion in cerebrospinal fluid (mEq/l) in "normal" and pathological conditions

	<i>N</i>	<i>Mean</i>	<i>Stand. dev.</i>
"Controls"	50	2.77	0.48
Multiple sclerosis	127	2.86	0.54
Observation for multiple sclerosis	53	2.76	0.33
Neurological disorders	639	2.82	0.61
Epilepsy	556	2.87	0.58
Psychiatric disorders	298	2.79	0.49

In a previous study⁽¹¹³⁾, a few deviations from normal value were demonstrated, based on the literature of patients with epilepsy and psychiatric disorders, including among others hypermobility psychosis. The normal values for the potassium concentration in cerebrospinal fluid were obtained as mentioned from patients suffering from various medical diseases without neurological complications or anaemia. The values for the patients with multiple sclerosis were 1.6-4.1 mEq/l (mean 2.86) and the normal values were 1.7-3.8 mEq/l (mean 2.77).

Magnesium ions

The methods for determining the concentration of magnesium have been very diverse, and the literature gives a very wide range of values determined by various authors⁽¹⁵⁴⁾. In spite of the pronounced disagreement as to method all investigators appear to agree that the amount of magnesium in cerebrospinal fluid is normally greater than in serum, and the proportion is usually quoted as lying around 1.26 (1.09-1.40)^(12, 34, 35, 40, 45, 68, 99, 140, 141, 146).

TABLE 5

Some of the normal values for magnesium ions (mg %) in the cerebrospinal fluid

	<i>Normal</i>	<i>Multiple sclerosis</i>
Mestrezat (1909)	3.0	
Barrio (1923)	1.4-3.1	
Haurowitz (1923)	2.3	
Cohn et al. (1923/24)	3.28	
Massaza (1927)	0.5-2.5	
Eisler (1928)	1.15 (1.02-1.30)	
Stary et al. (1929)		2.81
Merritt (1938)	3.0 (1.0-3.5)	
Roeder & Rehm (1942)	1.02-1.30	
Rouen (1956)	1.00-1.30	

Author's investigations

Method: The determination of magnesium was made by Kunkel's method⁽⁸⁵⁾.

Results: Table 6.

TABLE 6

	<i>N</i>	<i>Mean</i>	<i>Stand. dev.</i>
"Controls"	50	2.38	0.33
Multiple sclerosis	65	2.04	0.26
Observation for multiple sclerosis ...	7	2.14	0.18
Neurological disorders	467	2.41	0.41
Epilepsy	425	2.37	0.37
Psychiatric disorders	280	2.43	0.34

Previously some results were given⁽¹¹³⁾ for the content of magnesium in serum: normal, mean 1.81 (1.46-2.15) and patients

with multiple sclerosis, mean 2.18 (1.40-2.90). The value also lies distinctly above the mean of 1.9 mg pr. 100 ml obtained

on the basis of the results in the literature. With regard to the concentration of magnesium in cerebrospinal fluid, the value obtained from an indifferent patient group was 2.38 (1.5-2.7) mg pr. 100 ml and for patients with multiple sclerosis 2.04 (1.4-2.5). The difference in means is not statistically significant and can hardly be ascribed any weight in view of the limited material. There have been a number of investigations on the proportion between the magnesium content of the cerebrospinal fluid and serum, and on the basis of the literature this ratio may be taken as varying between 1.09 and 1.40, being on the average 1.26. This ratio is generally reduced in patients with multiple sclerosis, being on the average of 0.93.

In previous paper⁽¹¹³⁾, a similar ratio was found in patients with epilepsy, and out of 252 patients with epilepsy about 25 per cent had a ratio of magnesium in cerebrospinal fluid to magnesium in blood of 0.96-1.09, i. e. below the lowest normal li-

mit, while at the same time a series of 105 psychiatric patients included only three with values below 1.09.

Phosphorus (inorganic)

In the form of phosphate, phosphorus is one of the major and most important constituents of the tissues of the central nervous system.

Its determination in cerebrospinal fluid might therefore be a diagnostic aid in multiple sclerosis.

A few authors^(34, 65) quote the amount of inorganic phosphorus in cerebrospinal fluid as being 50 per cent of the corresponding serum values, while numerous authors^(140, 141) maintain that the cerebrospinal fluid contains at most 40 per cent of the phosphorus content of the blood.

The amount of inorganic phosphorus reported in so-called normal subjects, as quoted in the literature, varies between 0.8 and 2.1 mg pr. 100 ml, but this must be

TABLE 7

Some of the values for phosphorus ions in the cerebrospinal fluid

	<i>Normal</i>	<i>Multiple sclerosis</i>
Apelt & Schumm (1908)	1.93	
DeBuck (1908)	4.87	
Donath (1908)	2.39	
Barrio (1923)	1.5-2.7	
Pincus et al. (1923)	1.23 (0.8-1.8)	
Cohn (1923/24)	1.64	
Shih-Hao (1924)	1.41-1.44	
Hamilton (1925)	1.6-4.0	
Wilcox et al. (1925)	1.7 (1.2-2.1)	
Scholberg et al. (1926)	1.27-1.60	
Berendt et al. (1926)	1.15-2.90	
Standorf et al. (1926)	1.27-1.68	
Sary (1929)		1.13
Lierle & Sage (1931/32)	1.65 (1.2-2.6)	
Fremont-Smith (1931)	1.7 (1.5-1.9)	
Merritt & Baur (1931)	1.53 (1.25-2.10)	
Merritt & Fremont-Smith (1937)	1.5 (1.2-2.1)	
Cohen et al. (1938/39)	1.4 (1.2-2.1)	
Roeder & Rehm (1942)	1.5-2.7	
Odessky et al. (1953)	1.37 (0.9-2.1)	
Rouen (1956)	1.0-1.85	

accepted with considerable reserve, as the diagnoses found in this "normal-material" include idiocy, hydrocephalus, agenesis etc. The most extensive and also best review of normal material is that of *Odessky et al.* ⁽¹⁰⁸⁾. This covers 170 individuals, 165 of whom had phosphorus between 0.8 and 2.0

mg pr. 100 ml, and only five of whom had values above 2.0 mg pr. 100 ml.

Author's investigations

Methods: King's method.

Results: Table 8.

TABLE 8

	<i>N</i>	<i>Mean</i>	<i>Stand. dev.</i>
"Controls"	50	1.54	0.54
Multiple sclerosis	59	1.57	0.31
Observation for multiple sclerosis	7	1.59	0.21
Neurological disorders	451	1.56	0.43
Epilepsy	412	1.79	0.57
Psychiatric disorders	278	1.55	0.62

In the cerebrospinal fluid, the values in patients with various medical diseases ("Controls") lie between 0.9-2.9 mg pr. 100 ml corresponding well with *Odessky's* normal material ⁽¹⁰⁸⁾. The mean values in the

groups examined lie within the limits quoted in the literature as normal values. However, the ratio between phosphate values in cerebrospinal fluid and blood is quoted as lying between 0.45 and 0.55 under normal

TABLE 9

Some of the values for calciums ions in the cerebrospinal fluid		
	<i>Normal</i>	<i>Multiple sclerosis</i>
Mestrezat (1909)	3.4	
Pincus & Kramer (1923)	2.4 (2.2-2.5)	
Haurowitz (1923)	2.7	
Leicher (1922)	2.5	
Depisch (1923)	2.5 (2.0-3.0)	
Behrendt (1924)	2.5	
Brücke (1925)	2.3-3.1	
Hamilton (1925)	2.8 (2.2-3.3)	
Scholberg et al. (1926)	2.5 (2.3-2.6)	
Eisler (1928)	2.6 (2.45-2.82)	
Cantarow (1929)	2.26-2.75	
Merritt & Baur (1931)	2.50-2.62	
Cohen et al. (1938/39)	2.05-2.95	
Merritt & Fremonth-Smith (1938)	2.5 (2.25-2.75)	
Roeder & Rehm (1942)	2.2-3.4	
Mond (1952)	2.5 (2.2-3.0)	
Stutzmann (1952)	2.43 (2.36-2.55)	
Eichhorn (1954)	2.55-3.40	
Rouen (1956)	2.0-3.5	

conditions. In patients with epilepsy the limits are shown to be displaced to 0.40 and 0.60⁽⁶⁵⁾. In multiple sclerosis, values of 0.35 are occasionally seen, as can also be the case in meningitis, where extreme variations from 0.35 to 1.23 are found.

In the present material, 44 out of 59 multiple sclerosis patients examined showed a ratio of 0.29 to 0.40 between the phosphorus in cerebrospinal fluid and serum. The mean for the "control material" examined was 0.48 against a value of 0.37 for patients with multiple sclerosis.

Calcium ions

The relationship between calcium in serum and calcium in cerebrospinal fluid has been thoroughly investigated, and the literature agrees that the cerebrospinal fluid calcium content is 40 to 60 per cent of the serum calcium. This corresponds to the amount of diffusible calcium in the blood.

In asthma, meningitis and cerebrospinal syphilis, for example, the cerebrospinal fluid level is slightly raised, while small variations can be observed in schizophrenia (78, 113).

Author's investigations

Methods: Kramer & Tisdall.

Results: Table 10.

TABLE 10

The concentration of calcium ions in cerebrospinal fluid (mEq/l) in "normal" and pathological conditions

	<i>N</i>	<i>Mean</i>	<i>Stand. dev.</i>
"Controls"	50	2.59	0.25
Multiple sclerosis	124	2.53	0.25
Observation for multiple sclerosis	51	2.51	0.23
Neurological disorders	579	2.54	0.26
Epilepsy	521	2.58	0.24
Psychiatric disorders	267	2.54	0.26

The results shown in table 10 showed no variation beyond the normal limits.

Copper ions

The literature contains very scanty infor-

mation on the way the copper is distributed between serum and cerebrospinal fluid, just as there are only a few studies on the amount of copper in the cerebrospinal fluid.

TABLE 11

Some of the normal values for copper ions in the cerebrospinal fluid

Tompsett (1934)	32-67 /ug. %
Axtrup (1946)	14.5 —
Munch Petersen (1950)	6-20 —
Cartwright et al. (1954)	3.9 —
Rouen (1956)	15 —
Plum et al. (1960)	6-22 —

Author's investigations*Method:* Levine Nielsen modified Brendstrup.*Results:* Table 12.

TABLE 12			
The copper ion content in cerebrospinal fluid in pathological conditions (/ug %)			
	<i>N</i>	<i>Mean</i>	<i>Stand. dev.</i>
"Controls"	20	12.5	5.20
Multiple sclerosis	32	12.8	5.71
Neurological disorders	18	12.1	5.15
Epilepsy	42	12.6	5.63
Psychiatric disorders	16	12.4	5.37

Copper is often mentioned in relation to demyelinating diseases, but the present examinations are unable to show any difference between the different groups investigated as regards for total amounts of copper (further informations see *Plum*⁽¹¹⁷⁾).

Iron ions

Shifts in the iron content of cerebrospinal fluid are reported in the literature⁽⁹²⁾, for example in tuberculous meningitis and pernicious anaemia. For this reason, the cerebrospinal fluid iron content was determined in a number of our patients simultaneously with the serum determinations. The normal limits for iron in the cerebrospinal fluid are quoted as between 23 and 52 /ug pr 100 ml, while in tuberculous meningitis the values are quoted as between only 10 /ug and 15 /ug pr 100 ml and in pernicious anaemia a value of up to 74 /ug pr 100 ml is quoted.

Results

The cerebrospinal fluid in twenty patients admitted with the diagnosis of neurosis and who showed no signs of anaemia, gave an iron content between 27 and 56 /ug pr 100 ml. In 45 patients with multiple sclerosis the cerebrospinal fluid gave an iron content between 30 and 69 /ug pr 100 ml. No definite distinction between the two groups can be shown; nevertheless there

were some patients⁽⁸⁾ within the group of multiple sclerosis, who showed an iron content considerably above that of the normal group.

If this is considered in relation to the changes in the diameter of the erythrocytes as has been discussed (*Plum*⁽¹¹⁴⁾), it is natural to think of the corresponding displacement that can be observed in patients with pernicious anaemia, of course without attempting to draw any conclusion as to a mutual connection between these two groups of diseases.

Chlorine ions

Simultaneous analyses of blood and cerebrospinal fluid show that the concentration of chlorine ion in the cerebrospinal fluid normally lies at 10 to 25 per cent above the blood level.

The amount of chlorine ion in the cerebrospinal fluid appears to be closely related to the concentration in the blood, but also appears to depend on the amount of protein in the cerebrospinal fluid.

The figures quoted in the literature support the assumption that there is no diagnostic value in a determination of the ratio between chlorine ion concentration in serum and cerebrospinal fluid, as the latter also depends to a high degree on the permeability of the blood-cerebrospinal fluid barrier.

TABLE 13

Some of the values for chlorine ions (mEq/l) in the cerebrospinal fluid

	<i>Normal</i>	<i>Multiple sclerosis</i>
Mestrezat (1912)	127	
Haurowitz (1923)	123	
Pincus & Kramer (1923)	126 (124-129)	
Nowicka (1924)	126	
Hamilton (1925)	118-128	
Fremonth-Smith & Dailey (1926)	126-130	
Becker (1927)	123-130	
Steiner & Beck (1927)	110-130	
Lickint (1928)	120-134	
Stary (1929)		125
Samson (1930)	124-130	
Merritt & Fremonth-Smith (1938)	126 (121-129)	
Roeder & Rehm (1942)	124-131	
Rouen (1956)	110-130	

Author's investigations*Method:* Schales & Schales.*Results:* Table 14.

TABLE 14

The chlorine ion content (mEq/l) in cerebrospinal fluid
in pathological conditions

	<i>N</i>	<i>Mean</i>	<i>Stand. dev.</i>
"Controls"	50	122.67	6.32
Multiple sclerosis	126	122.12	4.56
Observation for multiple sclerosis	52	122.13	5.05
Neurological disorders	644	121.09	6.79
Epilepsy	565	124.58	6.38
Psychiatric disorders	300	123.42	5.49

The values found both for normal subjects and patient material all lie within a normal range of variations, so that it cannot be stated with certainty whether there is any displacement in the individual groups examined.

It has been claimed in the literature⁽⁶¹⁾ that in the case of cerebrospinal fluid a reduced level of inorganic phosphate is reflected in slightly elevated values of chlorine ion. The present investigations have

been unable to confirm this, as a normal chlorine ion content has always been found, in spite of the inorganic phosphorus often having been reduced in amount.

Cerebrospinal fluid electrolytes*Discussion:*

Studies of the occurrence of electrolytes in the cerebrospinal fluid in cases of multiple sclerosis, compared with normal controls and pathological cases, show only small

variations, and even though it may be reported that variations from the normal values exist in case of the ions studied, in no case did these variations deviate significantly from normal.

Among the ions which were studied and which only occur in small amounts, it may be mentioned the iron in the cerebrospinal fluid. The mean is found to correspond to the value found in the control group, but the standard deviation is much greater, and the highest values reach those found in pernicious anaemia. This is of interest when viewed together with the changes in the peripheral blood (*Plum*⁽¹¹⁴⁾), without it being permissible to deduce that there is any direct relation between pernicious anaemia and multiple sclerosis.

The total amount of copper seems to be quite the same as in the normal controls, but in this field further studies are continuing.

II

The protein content of the cerebrospinal fluid

The concentration of protein in the cerebrospinal fluid has been the subject of innumerable studies, in view of the clinical and diagnostic significance attributed to this determination. The figures quoted for the total amount of protein have varied considerably, even for determinations of the

normal values. It has been difficult to decide the question of normal values, but on the basis of the very comprehensive literature on the subject, it appears reasonable to put the limit between 15 and 50 mg per cent for a normal adult up to the age of 50 years. Above this age, the upper limit appears to rise somewhat.

On the whole, the total protein in the cerebrospinal fluid in patients with multiple sclerosis lies within the normal range. As the literature and the results given in this paper show, the extreme deviations are rarely observed, but at the same time it is obvious that the finding of normal total protein in the cerebrospinal fluid does not permit the exclusion of this diagnosis.

The disagreement on the question of the total protein in multiple sclerosis is strongly reflected in the literature. While most authors consider that the deviations are small, there are a few who claim that over 50 per cent of the patients show quite high deviations in the protein values. These authors also believe that major deviations in the total protein can be observed, depending on the duration of the disease and on its phase. This association could not be demonstrated in the present material. Analysis of the cerebrospinal fluid in patients with multiple sclerosis frequently shows that even though the total protein is within the normal limits, the ratio between globulin and albumin is usually slightly raised, the globulin being most frequently increased, but the ratio never exceeds 1.00.

TABLE 15

Determinations of total protein, albumin and globulin in the cerebrospinal fluid in a number of different diseases

	N	Total protein	Stand. dev.	Albumin	Stand. dev.	Globulin	Stand. dev.
"Controls"	50	39.88	12.42	12.34	9.14	12.62	4.94
Multiple sclerosis	128	51.15	15.09	35.13	10.59	16.86	5.67
Observation for multiple sclerosis	53	47.04	19.78	33.42	13.17	13.58	6.43
Neurological disorders	646	42.93	11.88	28.96	12.72	13.24	5.88
Epilepsy	572	40.72	12.57	26.67	14.58	13.22	6.68
Psychiatric disorders	310	39.67	15.10	27.12	12.60	12.78	5.20

The older methods used for determining the total amount of protein made it possible at the same time to divide this group into two groups: albumin and globulin. The ratio of globulin to albumin is normally quoted as lying between 0.15 and 0.45, that is a very wide range. Our technical aids nowadays are well developed and by using electrophoretic separations we are now able to divide the proteins into several groups. Even more delicate methods are available such as immunoelectrophoretic separation (*Clausen*⁽³²⁾), and the latter may perhaps provide an answer to whether the proteins in the cerebrospinal fluid are able to throw new light on the study of multiple sclerosis.

A series of investigations has been made using normal electrophoresis (see table 16). After the first investigations, it appeared reasonable to assume that the distribution of the proteins in cerebrospinal fluid corresponds to that in serum^(74, 75, 165), but later investigations showed quite clearly that this is not the case. The relative albumin content in the cerebrospinal fluid is approxi-

mately identical with that of serum^(57, 58, 59, 132, 147). With respect to the globulin fraction, it is frequently observed in the cerebrospinal fluid, as in serum, that alpha-globulin can be split into two fractions, α_1 and α_2 ; the beta-globulin fraction in cerebrospinal fluid appears to be greater than in serum^(6, 57, 58, 59, 132, 145, 114). A small peak is often observed in the normal cerebrospinal fluid in close association with the beta-fraction; this is described as the tau-fraction, or alternatively a division into β_1 and β_2 . The gamma-fraction in the normal cerebrospinal fluid is found to be well-defined, but less so than the corresponding fraction in serum^(27, 57, 58, 59, 132). At times, the gamma-fraction can be found as a double-peaked fraction; this is then described as γ_1 and γ_2 .

Innumerable studies exist on the nature of the cerebrospinal fluid in multiple sclerosis, even though individual investigators have usually only carried out quite limited numbers of investigations. If an attempt is made to estimate the displacement within the individual proteins fractions on the

TABLE 16

Reports by various authors of the percentage normal distribution of the different protein fractions in the cerebrospinal fluid

	Albumin		Globulin		beta (1 + 2)	gamma
	fract. X	albumin	alpha (1)	alpha (2)		
Kabat (1942)	5.2	67.3	5.1		20.4	7.2
Labhart (1951)		57-76		23-43		
Schneider-Wallenius (1951)		56.5	9.8		15.8	18.0
Esser (1952)	1.2	56.1	4.7	7.5	24.1	6.4
Bücher (1952)	4.4	49.7	15.4		19.5	11.0
Ewerbeck (1952)		62.6	5.4	6.0	11.1	14.5
Bauer (1952)		59.4	13.4		7.7	9.4
Rossi (1953)		54.6-65.2	10.0-15.6		15.0-23.0	5.6-14.0
Gries (1953)		55.6	5.8	8.4	17.1	13.1
Sandrici (1954)	3	57	5.9	9.6	12.2	15.4
Wagenhofer (1954)		52.3	12.3		18.8	9.5
Roboz (1954)		57.3	6.1	11.0	9.2	16.5
Kutzim (1954)		56.5	4.5	8.0	22.0	8.9
Knapp (1956)		50.3	7.4	10.5	14.8	17.4
Ta Naka (1956)		52.8	7.3		15.8	23.6
Belanger (1958)	2.0-4.8	52.8-64.3	3.1-7.9	3.9-10.7	9.3-17.8	6.2-12.8

basis of the literature as a whole, it is clearly seen that there is an increased content of globulin and within this fraction considerable displacements are found^(73, 74, 75, 163, 114). As a rule these displacements favour the gamma-globulin fraction^(73, 74, 129, 130). It should be stressed that an increase in the gamma-globulin fraction, such as is seen in about 65 per cent of cases of multiple sclerosis, is an aid to diagnosis, but is not pathognomonic.

It is reported in the literature that "the highest incidence of cerebrospinal fluid gamma-globulin elevations occurs in cases

of multiple sclerosis in which there have been multiple attacks, multiple lesions and marked functional disability. No relationship exists between the time of onset, duration of occurrence of new symptoms in multiple sclerosis and the elevations in cerebrospinal fluid gamma globulin"^(129, 167).

As mentioned, however, immuno-electrophoretic examinations are able to give many more fractions, and as far as is known, in cases of multiple sclerosis at least two more fractions are to be found in the cerebrospinal fluid than in serum (*Clausen*⁽³²⁾).

TABLE 17

The protein distribution in the cerebrospinal fluid in multiple sclerosis as reported in the literature

	Albumin	Globulin alpha (1) alpha (2)		beta	gamma
Kabat (1942)	45.3-73.9	5.5-6.0		9.3-22.9	9.6-33.4
Labhart (1951)	58.9	9.0	8.5	5.5	18.5
Roboz (1954)	9.2-53.8	3.7-10.6	1.9-13.9	6.6-28.0	21.1-28.1
Knapp (1955)	53.1	11.5	8.2	9.8	17.4
Dowzenko (1956)	53-62	7-12		10-11	21-24
Smith (1956)	46.7-48.1	0.2-4.8	5.6-7.5	9.2-14.9	24.9-38.2

Author's investigations

Methods:

Electrophoresis: The cerebrospinal fluid is concentrated by using an ultra-pressure filter. Original material 10 ml, final volume approximately 0.2 ml. Whatmann paper I;

3.5 volt pr cm., veronal buffer pH 8.6 0.05 mol. Running 5 hours. Staining Amido black, reading: Analytrol: Sphingo.

Total Protein: Lowry method (cf. *Lous*⁽⁹¹⁾).

Results: see table 18.

TABLE 18

The percentage distribution of the globulin fractions in the cerebrospinal fluid

	N	alpha (1)	stand. dev.	alpha (2)	stand. dev.	beta	stand. dev.	gamma	stand. dev.
"Controls"	50	3.12	1.07	5.76	1.42	13.03	1.36	9.59	1.97
Multiple sclerosis	125	3.60	1.15	5.98	1.31	8.77	1.44	14.65	2.82
Observation for multiple sclerosis	53	3.28	0.93	5.68	1.28	9.22	1.52	11.28	2.44
Neurological disorders	610	3.16	1.22	6.12	1.59	9.96	1.72	11.76	2.27
Epilepsy	561	3.49	1.37	6.25	1.36	10.16	2.08	11.90	2.63
Psychiatric disorders	302	3.20	1.24	5.82	1.51	11.27	1.92	11.71	2.56

The values in the tables indicate that the findings confirm previously reported deviations with respect to the distribution of the various protein fractions in the cerebrospinal fluid in multiple sclerosis.

III

Lipids and Lipoproteins in the Cerebrospinal Fluid

The lipids, among which are included *inter alia* the fats, the phospholipids, the

cerebrosides and cholesterol, appear normally only in small quantities in the fluid. In several neurological diseases, however, specially in those accompanied by tissue degeneration, the content may be higher.

Only a very few investigations on the field of lipids in cerebrospinal fluid are mentioned in the literature, and the historical review by Tourtellotte^(155, 156) is excellent. The same author in 1959 gave a summary of the different values to be found (see table 19).

TABLE 19

The concentration of various lipid fractions in normal cerebrospinal fluid		
<i>Lipid</i>	<i>Selected authors</i>	<i>Tourtellotte</i>
Observed total phospholipid ...	0.6	0.370
Cephalins	0.3 (Plasmalogens)	0.090 (total)
Lecithin	not done	0.168
Sphingomyelin	not done	0.087
Cerebroside	3-700	0.059
Total Cholesterol	0.1-0.5	0.415
Free	none	0.109
Observed total lipid	0.5-3.7	1.254
Calculated neutral fat (unaccounted for lipids)	not available	0.409

All figures in mg per 100 ml of cerebrospinal fluid.

The methods and the material in the different papers in the literature are often so different that it is quite impossible to make up a really good normal value scheme, and in the present paper only a few values will be given. For anyone specially interested in the problems, the papers by *Tourtellotte*^(155, 156) and *Poser*⁽¹¹⁹⁾ should be read.

Author's investigations

In spite of the uncertain results of the technique, our single determination analyses on a scattered patient material show that out of 52 patients with multiple sclerosis 43 were positive on testing for neutral fat by *Swahn's* method⁽¹⁴⁹⁾, while only 4 out of 28 so-called normal patients gave a slight positive reaction. Out of 102 patients with

epilepsy 63 gave a positive reaction and finally out of 32 patients with psychoses and neuroses 6 patients gave a positive reaction.

On analysing for the presence of phospholipids, these could be demonstrated in both normal and pathological cases (see table 20) but it must be admitted that double analyses gave a large standard deviation.

No examinations have been carried out on cephalins, lecithin, and cerebroside. These examinations have just been started, but up to now we cannot say anything about the results, although they seem to confirm those given by *Tourtellotte*.

Cholesterol. The analyses are carried out by the method given by *Poser*⁽¹¹⁹⁾ and some more details and historical aspects are given by *Plum*⁽¹¹⁵⁾.

TABLE 20

Shows the fluctuation in the cholesterol content of the cerebrospinal fluid found by Poser & co-workers. (a) only positive with respect to free cholesterol in two out of 17 cases; (b) only positive reaction in seven out of 14 cases and (c) positive reaction in 15 out of 19 cases.

	N	Total cholesterol		Free cholesterol	
		range of values mean		range of values mean	
Control	25	0	-0.29 (0.11)	0	
Infectious diseases of the central nervous system	38	0.05-4.6 (0.84)		0 -2.6 (0.41)	
Neoplasms	11	0 -5.6 (1.4)		0 -2.2 (0.43)	
Multiple sclerosis:					
Inactive	17	0 -0.40 (0.17)		0 -0.06 (0.01)	(a)
Active (?)	14	0.05-0.46 (0.28)		0 -0.16 (0.07)	(b)
Active	19	0.05-0.65 (0.33)		0 -0.50 (0.15)	(c)
Amyotrophic lateral sclerosis	8	0.05-0.59 (0.37)		0 -0.50 (0.11)	

Examination of the cerebrospinal fluid from 76 patients with multiple sclerosis was divided into two parts according to the phase of the disease: a group of patients in whom the disease was in the active phase, and a group in whom the disease was in the inactive phase. The total cholesterol values in the patients whose disease was in the inactive phase did not differ from values found in the material of patients with diverse neurological diseases. Examining the values for cholesterol in patients with the disease in the active phase a clear increase was found, namely 0.42 against 0.15 in the "control group".

Multiple sclerosis is a disease in which laboratory, diagnostic and prognostic criteria are still lacking. On this front, therefore, every advance, be it ever so small, must arouse some attention. It would seem as if the ratio between free and esterified cholesterol in the cerebrospinal fluid is

always somewhat increased in this disease, and clearly during its active phase.

Lipoproteins

Opinions have varied as to lipid metabolism in patients with multiple sclerosis. For example, *Swank*^(150, 151, 152) maintained that a fundamental disturbance in lipid metabolism was involved, and advised a low-fat diet in the treatment of multiple sclerosis. Other authors maintain that only very slight variations in the lipid metabolism could be demonstrated in these patients: for example in the cholesterol, phospholipid and lipoprotein^(18, 31, 130). The experiments and theories of these investigators have had their origin in efforts to find typical myelin-degeneration products in the cerebrospinal fluid. This involves considerable difficulties, however, as the exact chemical composition of myelin, which is a lipopro-

TABLE 21

Shows the fluctuation in the cholesterol content of cerebrospinal fluid in different pathological cases.

	N	Cholesterol (total)				Cholesterol (free)			
		mean	max.	min.	stand. dev.	mean	max.	min.	stand. dev.
"Normal group"	32	0.15	0.45	0	0.11	0	(0)*	0	0
Multiple sclerosis (active phase)	44	0.42	0.80	0.09	0.20	0.21	0.38	0	0.12
Multiple sclerosis (inactive phase)	15	0.22	0.33	0	0.12	0.09	0.19	0	0.08
Various neurological diseases	72	0.24	0.60	0	0.16	0.09	0.29	0	0.10
Epilepsy	100	0.24	0.64	0.09	0.09	0.09	0.25	0	0.07
Various psychiatric diseases	25	0.18	0.42	0	0.12	0	(0)*	0	0

* Some of the samples showed weak reaction but quite outside the measurable range.

tein, is still unknown. In view of the established fact that there is a breakdown of myelin in multiple sclerosis, the present study has also attempted to compare the findings from electrophoresis of the concentrated cerebrospinal fluid, with the findings from other neurological diseases, as well as purely medical diseases.

Aird⁽³⁾ studied a number of normal cerebrospinal fluids by ultracentrifugation, but could not demonstrate the presence of lipoprotein in large amounts. Badium (1953), on the other hand, using concentrated cerebrospinal fluid, was able to demonstrate the presence of lipoprotein in normal subjects, and was furthermore able to demonstrate that this was split into two fractions, the one corresponding to alpha lipoprotein in serum.

Numerous reports in the older literature also show that lipids can be demonstrated in the cerebrospinal fluid in pathological conditions.

The groups involved are fatty acids^(83, 112) cholesterol⁽¹¹²⁾ and phospholipids⁽⁶⁰⁾. It must be stressed however that there is a great disagreement between the amounts of lipids found in serum and in the cerebro-

spinal fluid⁽¹¹²⁾.

The present studies were carried out parallel with those on lipoproteins in serum (Plum & Fog⁽¹¹⁴⁾). The latter investigations showed practically no variation from our findings in normal subjects and in patients with other neurological diseases, and as the findings correspond fully with observations by previous authors^(3, 130, 150, 152) the question of the serum lipoproteins will not be gone into further. On the other hand, the investigations on the lipoproteins in the cerebrospinal fluid appeared of great interest, even though it must be stressed that the findings are still not explained, but on the contrary have made it necessary to commence a fresh series of studies.

The technique employed was the same as in the determination of the amount of protein: Concentration by means of ultrapressure filters. The electrophoresis was carried out as described by Plum & Fog⁽¹¹⁴⁾, the staining was done by Durrum's method^(50, 51). The readings were made on a Zeiss extinction recorder II and later in Sphincro Analytrol. The material comprises 52 patients with multiple sclerosis, 75 patients with epilepsy, 25 patients with psychiatric

disorders, 52 with neurological disorders and a "control group" containing 20 numbers. In evaluating the results (table 22) a method of grading was chosen such as employed by *Smith*⁽¹⁴⁰⁾. The so-called normal distribution curve frequently shows a uniform distribution with some small peaks, or a distribution with the main peak corresponding to α_1 -globulin. Finally, it should not be overlooked that a completely negative finding, i. e. absence of staining of the lipids, must also be considered as a normal picture.

Numerous high peaks on the curve, an irregular distribution, is probably the most frequent deviation. Here the lipoprotein is found distributed throughout the entire electrophoretic field, and this picture is observed in patients who are in an active progressive phase of multiple sclerosis. This curve shape is also seen in epilepsy, in those cases where numerous fits are experienced and frequent "absences".

Finally there is the third and most interesting shape, observed in 10 cases of epilepsy, 10 cases of multiple sclerosis, in two cases of psychiatric disorders, in 4 cases of neurological disorders and in only one case in the controls — the typical albumin peak. No adequate explanation can be given for this factor, but it seems reasonable to assume that a special form of lipoprotein is involved, possibly a special break-down product of myelin.

The question of the occurrence of lipoprotein is in general of great interest. Is the very irregular distribution of this substance the result of the presence of several compounds, various complexes of lipid and protein, or have possible enzymatic processes affected the linkage between these two compounds in question?

These are questions which so far must remain unanswered, but the answer to them might lead to a deeper understanding of the etiology of multiple sclerosis.

TABLE 22

Summarized results showing the variations in the content of lipoprotein in the cerebrospinal fluid determined by electrophoresis

	Multiple sclerosis	Epilepsy	Psychiatric disorders	Neurological disorders	Controls
Number of single determinations	52	75	25	52	20
Normal lipoprotein curve	10	56	20	39	15
Numerous high peaks on the curve	32	9	3	9	4
Typical "albumin" peak	10	10	2	4	1

IV

The cholinesterase activity of cerebrospinal fluid

In 1930, *Plattner & Hinter*⁽¹¹¹⁾ succeeded in demonstrating cholinesterase activity in the cerebrospinal fluid. This observation could not be confirmed during the next

few years^(63, 142, 143, 162). In 1937, *Altenburger* succeeded in confirming *Plattner's* findings, although the amount of cholinesterase in the cerebrospinal fluid was found to be only 1/250 of the content in the blood, while *Plattner* found an amount of 1/20. *Bender*⁽¹⁷⁾ found an activity in the cerebrospinal fluid corresponding to about one to two per cent of the activity in the blood. *Al-*

tenburger's findings were subsequently confirmed by several investigators^(19, 20, 64, 110), but the amount was quoted as being around 1/200 of the activity in the blood.

In the cerebrospinal fluid, the specific cholinesterase dominates, in contrast to the case in plasma, where only the unspecified

cholinesterase is found. The literature gives only very few reports on variations in the cholinesterase activity in the cerebrospinal fluid; among the most important should be mentioned those of *Tower*⁽¹⁵⁷⁾ and *Jefferson*⁽⁷¹⁾. Further should be mentioned the investigations of *Pope et al.*⁽¹¹⁸⁾ and *Svensmark*⁽¹⁴⁸⁾.

TABLE 23

The cholinesterase activity of the cerebrospinal fluid according to Jefferson (1954)

Substrate	Multiple sclerosis n = 14	Not multiple sclerosis n = 36
Acetyl-betamethyl choline	mean 16.7	mean 16.9
Benzoyl-choline	mean 11.8	mean 12.2
Rate of hydrolysis in cu.mmCO ₂ per ml CSF per hr.		

TABLE 24

The cholinesterase content of cerebrospinal fluid according to Svensmark (1958)

	N	/uM/ml/hr
"Normal"	12	0.39 ± 0.04
Epilepsy	10	0.45 ± 0.04
Multiple sclerosis:		
in remission	4	0.22 ± 0.06
in progress	20	0.29 ± 0.02

Author's investigations

For results see table 25.

Cfr about the clinical examination, *Plum & Fog*(1960).

TABLE 25

The value of cholinesterase activity in the cerebrospinal fluid in normal and pathological conditions

	N	Mean	Stand dev.	/uM/ml/hr.
Controls	48	8.89	1.72	0.39 ± 0.07
Multiple sclerosis	123	5.17	1.34	0.23 ± 0.06
Observation for multiple sclerosis	53	6.91	1.53	0.31 ± 0.07
Neurological disorders .	533	8.52	1.79	0.38 ± 0.08
Epilepsy	420	9.92	2.09	0.44 ± 0.09
Psychiatric disorders ...	285	8.76	1.67	0.39 ± 0.07

The results show that in cases of multiple sclerosis a low activity is to be found, but low acetylcholinesterase activity can hardly be regarded as a specific sign in multiple sclerosis. The material included one patient with suspected amyotrophic lateral sclerosis and this patient shows the lowest value found. But taken as a whole, a decrease in the acetylcholinesterase activity can be taken as one of the laboratory findings which may be mentioned in the clinical chemistry of multiple sclerosis.

Glutamic oxalacetic transaminase in cerebrospinal fluid

Demyelinating lesions in the central nervous system have been known to develop in the course of such disorders as hepatic diseases, uremia, eclampsia and porphyria, and particularly in the terminal metabolic disturbance accompanying these disorders. Various workers have investigated the development of demyelinating lesions of the

central nervous system in disorders other than those of the nervous system, in the search for clues as to the pathogenesis of the demyelinating lesions of multiple sclerosis. There is thus a certain relationship between the function of the liver and the central nervous system, and as the determinations of serum glutamic oxalacetic transaminase (SGOT) is used in clinical medicine, for example in the study of liver disease, raised values being found in obstructive jaundice, infections and homologous serum hepatitis, it was natural to include this determination in the experimental investigations.

For the results found in serum see *Plum & Fog*⁽¹¹⁴⁾.

Author's investigations

Methods: Instructions in Sigma Chemical Company's Technical Bulletin no. 505, using the original chemicals supplied by the firm.

Results: see table.

TABLE 26

Variation in SGOT in cerebrospinal fluid in normal and pathological conditions

	<i>N</i>	<i>Mean</i>	<i>Stand. dev.</i>
"Controls"	50	3.10	1.67
Multiple sclerosis	63	3.13	1.52
Observation for multiple sclerosis	52	3.06	1.58
Neurological disorders	276	3.12	1.67
Epilepsy	327	3.24	1.83
Psychiatric disorders	238	3.18	1.74

No definite difference can be demonstrated between the values found for cerebrospinal fluid, the normal values lying between 1.9 with a mean of 3.10, and between 1.8 in patients with multiple sclerosis, with a mean of 3.13.

The occurrence of neuraminic acid in the cerebrospinal fluid

In recent years, clinical chemistry has been deeply engaged in a study of neuraminic acid and sialic acid.

Many different lipids are found in the central nervous system, but among these, cerebroside and ganglioside are the only ones containing carbohydrate radicals. When hydrolysed, the cerebroside gives mainly galactose, whereas the ganglioside also gives a complex aminoacid-carbohydrate compound, often called neuraminic acid.

Blix⁽²¹⁾ isolated the substance in 1936, and named it sialic acid, having prepared it from the submaxillary gland. *Klenk*⁽⁷⁹⁾ in the same year described a compound which appeared to be identical with *Blix's*

sialic acid, but which he named neuraminic acid. The discussion on the identity of sialic acid and neuraminic acid has been very protracted, and is hardly terminated yet. The names are frequently employed at random, although sialic acid is the designation of choice in the Anglo-american literature, while in the German, French and some other literature the designation neuraminic acid is used^(22, 149, 159).

Only a few determinations of neuraminic

acid in the cerebrospinal fluid have been made, most often as a stage in the determination of mucoprotein and similar complex compounds.

Roboz et al.⁽¹³¹⁾ quote the amount of neuraminic acid determined by Bial's reagent subject as 0.24 ± 0.09 mg per 100 ml, and in a series of neurological diseases not grouped further, values from 0.30 to 0.78 mg per 100 ml.

Author's investigations

Method: Böhm et al.⁽²⁸⁾.

Results: see table 27.

TABLE 27

The variation in the content of "neuraminic" acid in the cerebrospinal fluid			
	<i>N</i>	<i>Mean</i>	<i>Stand. dev.</i>
"Controls"	48	0.25	0.07
Multiple sclerosis	123	0.37	0.08
Observation for multiple sclerosis	52	0.32	0.09
Neurological disorders	456	0.26	0.08
Epilepsy	375	0.28	0.09
Psychiatric disorders	268	0.25	0.10

In agreement with the findings of *Roboz et al.*⁽¹³¹⁾, the cerebrospinal fluid neuraminic acid values found by the examinations given in this paper show a slight rise in cases of multiple sclerosis compared to the normal material.

However, this rise does not appear to be significant either. *Klenk*⁽⁸²⁾ has demonstrated a rise in the neuraminic acid in the ce-

rebrospinal cortex in a case of amaurotic idiocy, and *Cummings*⁽⁴³⁾ reports that a like increase is observed in all "demyelinating conditions". *Hansen, Plum & Olsen*⁽⁶¹⁾ also found an increase in a case of leucodystrophia. Such conditions can undoubtedly contribute to that rise in neuraminic acid found in the cerebrospinal fluid, but they do not in any way explain the slight reduction in the amount in the serum.

S U M M A R Y

A previous study described a number of parallel examinations of serum and cerebrospinal fluid in multiple sclerosis. These investigations, part of a more extensive series of studies, are compared in the present paper with a series of results from the literature, as the material has grown consider-

ably since publication in 1959 (*Plum & Fog*⁽¹¹⁴⁾), and it is now possible with certainty to state which series of investigations requires more detailed analysis and revision.

Reviewing the most important ions, it would appear that the determinations of the values for Na, K, Ca, phosphorus and

chlorine show deviations which are typical for multiple sclerosis. In the case of iron, there seems to be a slight increase; such an increase has hitherto been found only in patients with pernicious anaemia. This observation is interesting, for as mentioned by Plum & Fog⁽¹¹⁴⁾, certain morphological changes can be found in the blood picture of patients with multiple sclerosis, changes which are identical with those also observed in pernicious anaemia, although these observations are not to be interpreted as attempting to point to an etiological relationship between the two disease groups.

While normal amounts of copper are found in cerebrospinal fluid and in serum, the serum copper shows an abnormal distribution with regard to the proteins, and these studies have led to further studies of the cerebrospinal fluid in this connection.

The behaviour of the proteins under ordinary electrophoresis confirms previous observations, and immuno-electrophoresis might provide the possibility of a finer separation, which might reveal further pathological states in the proteins of the cerebrospinal fluid in multiple sclerosis.

The behaviour of the lipids has been analyzed. However, the separate groups have so far been studied only to a limited degree, so that nothing can be said as to possible shifts in values. One single group has been closely studied, however, namely cholesterol; here it is seen clearly that there is a pronounced increase in the amount of total cholesterol in the cerebrospinal fluid of patients with multiple sclerosis; furthermore it has been possible to show the presence of free cholesterol, which has never been possible in the normal material used.

Determined by electrophoresis, the lipoproteins seem to show a distribution which recalls that of the proteins, and which deviates very much from the normal findings. No explanation can be given at the moment for the individual pathological deviations.

Enzyme studies: While determinations of oxalacetic acid transaminase showed no deviations from normal, a clearly reduced function was found in the case of cholinesterase. The few observations in the literature on the cholinesterase questions in multiple sclerosis are confirmed by the results given in this paper, a reduced amount of "true" cholinesterase being found. It cannot be stated whether a more extensive material would decide that the distinction was significant, but a true reduction in the cholinesterase content of the cerebrospinal fluid is involved, a reduction which is not reflected in the blood stream.

Neuraminic acid: the slight increase of neuraminic acid found in multiple sclerosis cannot be explained as yet. No relationship appears to exist between the increase in amount and the phase of the disease.

As stated, the results presented here are only a supplement to the previous studies, but at the same time form a basis for further biochemical examination of the cerebrospinal fluid, in cooperation with Danish colleagues who are studying the problem from other points of view, for example neurochemical and histochemical studies, as the values found lead to the view that the localization of the individual groups of compounds in the CNS itself, is of great significance for explaining the changes in the fluids surrounding the CNS.

RESUMEN

En un estudio anterior fueron expuestos una serie de exámenes realizados paralelamente en el suero y el líquido céfalo raquídeo de pacientes afectados de Esclerosis Múltiple. Estas investigaciones que forman parte de estudios más extensos, son comparadas en este trabajo con otras existentes en la literatura. El material se acrecentó

considerablemente desde la publicación en 1959 (Plum y Fog)⁽¹¹⁴⁾ y ahora es posible establecer con certeza cuáles investigaciones requieren una revisión y análisis más detallado.

Considerando los iones más importantes, se vería que las determinaciones de los valores para N, K, Ca, fósforo y cloro, mues-

tran desviaciones que son típicas de la Esclerosis Múltiple. El hierro parece estar levemente aumentado; tal aumento ha sido hallado hasta ahora en pacientes con anemia perniciosa. Esta observación es interesante, puesto que como lo han mencionado Plum y Fog⁽¹¹⁴⁾, ciertos cambios morfológicos que pueden ser hallados en el cuadro sanguíneo de pacientes con Esclerosis Múltiple, son idénticos a los que también se observaron en la anemia perniciosa. Esto sin embargo no debe ser interpretado como un intento de señalar una relación etiológica entre las dos enfermedades.

Aunque el cobre se encuentra en cantidades normales en el líquido céfalo raquídeo y en el suero, en este último muestra una distribución anormal con respecto a las proteínas. Esto condujo a realizar estudios del líquido céfalo raquídeo con el fin de comprobar si en él ocurría lo mismo.

El comportamiento de las proteínas bajo electroforesis ordinaria confirma observaciones previas y la inmuno-electroforesis puede darnos la posibilidad de una separación más fina, lo cual puede revelar ulteriormente estados patológicos en las proteínas del líquido céfalo raquídeo en la Esclerosis Múltiple.

Se analizó el comportamiento de los lípidos. Los estudios de los grupos separados han sido hasta ahora realizados en un grado limitado, de modo que nada puede decirse en relación con posibles desviaciones en los valores. Sólo un grupo fue bien estudiado: el del colesterol; se ha visto que hay un aumento pronunciado en la cantidad del colesterol total en el líquido céfalo raquídeo de pacientes con Esclerosis Múltiple; ulteriormente fue posible mostrar

la presencia de colesterol libre, lo cual nunca se observó en el líquido normal.

Las determinaciones por electroforesis, de las lipoproteínas parecen mostrar una distribución que recuerda la de las proteínas, la cual se desvía mucho de los hallazgos normales. Hasta el momento no pueden darse explicaciones para estas desviaciones patológicas.

Estudios de las enzimas. — Las determinaciones de la transaminasa del ácido glutámico oxalacético no mostró anomalías. Para la colinesterasa se encontró una función claramente reducida. Las pocas observaciones en la literatura acerca de la colinesterasa en la Esclerosis Múltiple, indican que fue encontrada en cantidad reducida, lo cual se confirma por los resultados publicados en este trabajo.

La reducción en el contenido de colinesterasa del líquido céfalo raquídeo, no está reflejada en la sangre.

Ácido Neuramínico. — Aún no puede ser explicado el ligero aumento del ácido neuramínico encontrado en la Esclerosis Múltiple. No parece existir relación entre este aumento y la fase de la enfermedad.

Los resultados presentados aquí, son suplementarios a estudios previos, pero a la vez forman una base para exámenes bioquímicos ulteriores del líquido céfalo raquídeo, en cooperación con colegas daneses que estudian el problema de otros puntos de vista, por ejemplo estudios neuro e histoquímicos. Los valores encontrados hacen ver que la localización de los grupos de compuestos en el mismo Sistema Nervioso Central es de gran significación para explicar los cambios en los fluidos que lo rodean.

R É S U M É

Dans une étude antérieure une série d'examen furent exposés, réalisés parallèlement dans le sérum et le liquide céphalo rachidien de patients affectés de Sclérose Multiple. Ces investigations qui forment partie d'études plus étendus, sont comparées dans ce travail à d'autres existant dans la littérature. Le matériel a considérablement augmenté depuis la publication en

1959 (Plum et Fog)⁽¹¹⁴⁾ et il est maintenant possible d'établir avec certitude les investigations qui ont besoin d'une révision et d'une analyse plus détaillée.

En considérant les ions les plus importants, on verrait que les déterminations des valeurs pour le N, K, Ca, phosphore et chlore, présentent des déviations typiques à la Sclérose Multiple. Le fer paraît être lé-

gèrement augmenté; une telle augmentation a été trouvée jusqu'ici chez des malades avec une anémie perniciose. Cette observation est intéressante, car comme Plum et Fog⁽¹¹⁴⁾ l'on mentionné, certains changements morphologiques qui peuvent être trouvés dans le cadre sanguin de patients souffrant de Sclérose Multiple, sont identiques à ceux qui furent observés aussi dans l'anémie perniciose. Ceci ne doit pas cependant être interprété comme un essai de signaler une relation étiologique entre les deux maladies.

Malgré qu'on trouve le cuivre dans des quantités normales dans le liquide céphalo rachidien et dans le sérum, dans ce dernier il présente une distribution anormale vis-à-vis des protéines. Ceci mena à réaliser des études du liquide céphalo rachidien dans le but de constater si dans celui-ci on observait la même chose.

Le comportement des protéines sous l'électrophorese peut nous donner la possibilité d'une séparation plus fine, ce qui peut mener à révéler plus tard des états pathologiques dans les protéines du liquide céphalo rachidien dans la Sclérose Multiple.

On a analysé le comportement des lipides. Les études des groupes séparés ont été réalisées jusqu'ici à un degré limité, de façon qu'on ne peut rien dire en rapport avec de possibles déviations des valeurs. Un seul groupe fut bien étudié, celui du cholestérol; on a vu qu'il y a une augmentation prononcée dans la quantité du cholestérol total dans le liquide céphalo rachidien de malades affectés de Sclérose Multiple; plus tard il fut possible de montrer la présence de cholestérol libre, ce qui ne s'était jamais observé dans le liquide normal.

Les déterminations par électrophore des lipoprotéines semblent montrer une distribution qui rappelle celle des protéines, laquelle est assez éloignée de celles qu'on trouve normalement. Jusqu'ici on ne peut pas donner d'explications pour ces déviations pathologiques.

Etudes des enzymes. — Les déterminations de la transaminase de l'acide glutamique oxalacétique n'ont pas accusé des anomalies. Pour la colinestérase on a trouvé une fonction clairement réduite. Les quelques observations dans la littérature au sujet de la colinestérase dans la Sclérose Multiple indiquent que celle-ci fut trouvée en quantité réduite, ce qui se confirme par les résultats publiés dans ce travail.

La réduction dans le contenu de colinestérase du liquide céphalo rachidien, n'est pas reflétée dans le sang.

Acide Neuraminique. — On ne peut pas encore expliquer la légère augmentation de l'acide neuraminique trouvé dans la Sclérose Multiple. Il ne semble pas exister de relation entre cette augmentation et la phase de la maladie.

Les résultats présentés ici sont supplémentaires à des études préalables, mais ils forment à la fois une base pour des examens biochimiques ultérieurs du liquide céphalo rachidien, en coopération avec des collègues danois qui étudient le problème sous d'autres points de vue, comme par exemple des études neuro et histochimiques. Les valeurs trouvées démontrent que la localisation des groupes de composés dans le Système Nerveux Central même est d'une grande signification pour expliquer les variations dans les fluides qui l'entourent.

ZUSAMMENFASSUNG

In einer vorhergehenden Arbeit wurden eine Anzahl von parallelen Untersuchungen im Blutserum und in der Spinalflüssigkeit bei Multipler Sklerose (M.S.) beschrieben. Diese Untersuchungen, als Teil einer umfassenderen Forschungsserie werden in dieser Arbeit mit einer Anzahl von Ergebnissen aus der Literatur verglichen, da das Material seit der Veröffentlichung im

Jahre 1959 (Plum & Fog)⁽¹¹⁴⁾, beträchtlich angewachsen ist. Und nun ist es möglich, mit Sicherheit festzustellen, welche der Forschungsserien einer mehr ins Einzelne gehenden Analyse und Revision bedürfen.

Bezüglich der wichtigsten Ionen scheinen die Bestimmungen der Werte für Natrium, Kalium, Calcium, Phosphor und Chlor Abweichungen aufzuweisen, die ty-

pisch fuer M.S. sind. Beim Eisen scheint eine leichte Erhoehung zu bestehen; solche Erhoehung ist bis jetzt nur bei Patienten mit pernizioeser Anaemie gefunden worden. Diese Beobachtung ist interessant, weil, wie schon Plum und Fog⁽¹¹⁴⁾ erwaeht haben, gewisse morphologische Veraenderungen im Blutbild von Patienten mit M.S. gefunden werden koennen, die denen bei der pernizioesen Anaemia beobachteten identisch sind, obwohl solche Beobachtungen nicht in dem Sinne ausgelegt werden sollen, dass man versucht auf eine aetiologische Beziehung zwischen diesen beiden Krankheiten hinzuweisen.

Waehrend der Kupferspiegel in der Spinalfluessigkeit normal ist, zeigt er im Blutserum eine anormale Verteilung bezueglich der Proteine; und diese Untersuchungen haben zu weiteren Untersuchungen der Spinalfluessigkeit in diesem Zusammenhang gefuehrt.

Das Verhalten der Proteine bei der gewoehnlichen Elektrophorese bestaetigt fruhere Beobachtungen, und die Immuno—Elektrophorese koennte die Moeglichkeit einer noch feineren Separierung bieten, die weitere pathologische Veraenderungen der Proteine in der Spinalfluessigkeit bei M.S. enthuelen koennte.

Es ist das Verhalten der Lipaide analysiert worden. Aber die verschiedenen Gruppen sind bisher nur in beschaenkteter Masse studiert worden, sodass nichts ueber eventuelle Veraenderungen ihrer Werte gesagt werden kann. Immerhin ist eine einzige Gruppe gruendlich studiert worden, naemlich das Cholesterol; hier beobachtet man deutlich eine starke Vermehrung des totalen Cholesterols in der Spinalfluessigkeit bei Patienten mit M.S. Es ist ueberdies moeglich gewesen, die Anwesenheit von freiem Cholesterol nachzuweisen, was nie bei normalem Material moeglich gewesen war.

Nach ihrer elektrophoretischen Bestimmung scheinen die Lipoproteine eine Ver-

teilung aufzuweisen, welche an die der Proteine erinnert und stark von der normalen Werten abweicht. Bis jetzt kann noch keine Erklaerung fuer die einzelnen pathologischen Abweichungen gegeben werden.

Enzymuntersuchungen. — Waehrend die Bestimmungen der Glutaminoxallessigsaeuretransaminase keine Abweichungen vom Normalen aufwiesen, fand man eine deutlich verminderte Funktion bei der Cholinesterase. Die wenigen Beobachtungen in der Literatur ueber das Cholinesteraseproblem bei der M.S. werden durch die in dieser Arbeit angegebenen Resultate bestaetigt, wobei eine verminderte Quantitaet der "wirklichen Cholinesterase" gefunden worden war. Es kann nicht festgestellt werden, ob ein reichlicheres Material entschieden haette, ob der Unterschied signifikant war; aber eine wirkliche Verminderung des Cholinesterasegehaltes der Spinalfluessigkeit ist vorhanden, die sich im Blutstrom nicht widerspiegelt.

Neuraminsaeure. — Die bei der M.S. gefundene leichte Vermehrung der Neuraminsaeure kann bis jetzt noch nicht erklart werden. Es scheint keine Beziehung zwischen der Erhoehung der Werte und der Krankheitsphase zu bestehen.

Wie schon erwaeht, sind die hier angefuhrten Resultate nur eine Vervollstaendigung vorhergehender Studien, aber zur gleichen Zeit sind sie die Base fuer weitere biochemische Untersuchungen der Spinalfluessigkeit zusammen mit den daenischen Kollegen, welche das Problem von anderen Gesichtspunkten aus studieren, z.B. bei neurochemischen und histochemischen Untersuchungen, da die gefundenen Werte zu der Ansicht fuehren, dass die Lokalisierung der verschiedenen Gruppen von Verbindungen im Zentralnervensystem selbst von grosser Wichtigkeit fuer die Erklaerung der Veraenderungen in den das zentrale Nervensystem umspielenden Fluessigkeiten ist.

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Aspects Cliniques et Evolutifs de la Sclérose en Plaques

Étude statistique en 145 cas.

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Depuis les premières descriptions de Charcot, de multiples travaux où l'on rencontre tous les grands noms des Ecoles Neurologiques ont édifié le tableau clinique de la sclérose en plaques (S.E.P.), ont précisé sa symptomatologie et ses aspects anatomo-cliniques en même temps que ses limites nosographiques. Le rapport de GUILLAIN à la Vème. Réunion Neurologique Internationale de Paris en 1924 a tracé de la maladie un tableau clinique qu'ont à peine retouché les travaux des années suivantes, alors que les incertitudes qu'il exprimait quant aux mécanismes étiologiques qui la régissent, persistent, comme restent imparfaites les méthodes biologiques de diagnostic.

Différentes études statistiques récentes portant sur de vastes groupes de malades, différentes études portant sur certains points particuliers ont apporté quelques précisions sans modifier profondément la description clinique de la S.E.P.

L'étude dont nous donnons les résultats n'apportera aucune notion hétérodoxe. Il est même assez remarquable que ces chiffres s'accordent pour la plupart avec ceux des statistiques récentes publiées dans d'autres pays. La confrontation des chiffres ne pourra pas ne pas être utile, rapportée aux notions qui se dégagent des études récentes de l'épidémiologie de la S.E.P. et de l'étude de sa répartition géographique.

Notre travail porte sur 145 malades examinés ou réexaminés au cours de ces

cinq dernières années. Le chiffre n'est pas considérable, mais nos observations ont toutefois l'avantage de former un groupe parfaitement homogène. Tous nos malades —hospitalisés pour la plupart pour de courtes périodes de mise en observation— sont régulièrement suivis à la consultation externe. Nous les avons tous personnellement examinés et les mêmes critères diagnostiques ont été appliqués à chacun d'eux.

Pour cette étude statistique nous n'avons retenu que les cas pour lesquels le diagnostic de S.E.P. apparaît certain.

Parfois, dès le début de la maladie, dès la première poussée, le tableau clinique peut être suffisamment riche, les signes suffisamment disséminés pour que le diagnostic puisse être établi avec sûreté. Certains débuts monosymptomatiques sont eux-mêmes très évocateurs mais même si la formule du L.C.R. est caractéristique, c'est seulement la suite évolutive qui donnera la certitude —et parfois à très longue échéance.

Toutes les observations de ce type qui n'avaient pas encore reçu la sanction de l'évolution ont donc été rejetées —même si le diagnostic apparaissait très vraisemblable.

L'étude de ces 145 observations a permis de dégager un certain nombre de notions cliniques que nous exposerons succinctement, nous réservant de nous attarder sur quelques problèmes séméiologiques, évolutifs et pronostiques qui, depuis des années, ont retenu notre attention.

Notions Etiologiques.

Suivant le *sexe* les cas se répartissent ainsi:

<i>Femmes</i>	<i>Hommes</i>
88	57
soit 60,7 %	39,3 %

Cette prédominance des cas féminins est inhabituelle et dans la plupart des statistiques les sexes se répartissent d'une façon à peu près égale les cas de S.E.P. ABB et SCHALTENBRANDT indiquent 51,3 % de femmes (58 % dans une première statistique) alors que d'autres auteurs donnent une proportion inverse 50 % d'hommes (WECKSLER) et 57 % (WILSON).

TABLEAU 1

AGE DE DÉBUT DE LA S.E.P.			
— Avant 10 ans	1	(7 ans)	} 15 = 10,4 % } 101 = 69,6 %
— De 10 à 14 ans	3	} 12 ans } 13 ans } 14 ans	
— De 15 à 19	11		
— 20 - 24	31		
— 25 - 29	35	} 86 = 59,2 %	} 44 = 30,4 %
— 30 - 34	20		
— 35 - 39	15		
— 40 - 44	13		
— 45 - 49	9		
— 50 - 54	5		
— 55 - 59	2		

Quant à l'âge de début, les données numériques du tableau 1, sont conformes à toutes celles publiées, qui indiquent sans conteste que la S.E.P. est une *maladie de l'adulte jeune*.

Dans 101 cas, la maladie débute avant l'âge de 35 ans —soit dans près de 70 %— et dans 86 cas entre 20 et 35 ans, soit dans près de 60 % des cas.

Le début dans l'enfance —avant l'âge de 15 ans— est rare mais il n'est pas réellement exceptionnel puisque nous en comptons 4 cas —avec des âges de début respectivement à 14, 13 et 12 ans; enfin à 7 ans. En publiant en 1954 cette observation exceptionnelle à la Société Française de Neurologie, nous avons insisté alors sur la

nécessité d'exiger chez l'enfant, plus encore que chez l'adulte, des critères diagnostiques et évolutifs très exacts. Et nous disions que, même si la maladie de SCHILDER pouvait être considérée comme la forme de l'enfant de la S.E.P., il importait de ne retenir sous le nom de S.E.P. que les formes identiques, par leur allure clinique et évolutive, à celles de l'adulte. C'est à ces exigences que répondent les 3 autres cas dont le début entre 10 et 15 ans est déjà plus banal.

Les formes à début tardif sont moins rares et il est remarquable que les chiffres de début entre 40 et 45 ans soient supérieurs à ceux de 15 à 20 ans et que de 50 à 60 ans, on trouve encore 7 cas.

On peut schématiser ces résultats en indiquant que:

- 60 % environ des cas débutent entre 20 et 35 ans;
- 10 % environ avant 20 ans;
- 30 % environ après 35 ans.

Incidence Familiale.

Diverses observations publiées au cours de ces dernières années de cas familiaux de S.E.P. ont fait discuter l'existence possible d'un facteur génétique.

Disons seulement que dans nos 145 cas nous comptons 2 cas familiaux (soit 1,4 %) :

- une femme dont la mère était morte à la Salpêtrière de S.E.P. (renseignements succincts);
- une jeune fille, suivie depuis 8 ans, dont 1 frère, de deux années son aîné, est atteint depuis un an d'une S.E.P.

Symptomatologie.

Le tableau 2 indique, par ordre de fréquence, les signes ou symptômes révélés dans les diverses observations sans qu'il soit tenu compte de leur caractère transitoire

TABLEAU 2

SYMPTOMES ET SIGNES PAR ORDRE DE FRÉQUENCE

— <i>Troubles de la sensibilité:</i>	116 cas = 80 %
dysesthésies	98
troubles objectifs de la sensibilité superficielle ou profonde	53
décharges électriques à la flexion de la tête	29
astéréognosie	20
— <i>Signes pyramidaux:</i>	111 cas = 76,5 %
paraplégie (quelle que soit sa gravité)	79 = 54,5 %
quadriplégie spasmodique	4
hémiplegie	20
signes pyramidaux discrets (par exemple un signe de Babinski isolé)	12
monoplégie	5
syndrome de Brown-Séquard	5
syndrome de myélite transverse aiguë	4
— <i>Signes cérébelleux:</i>	61 = 42 %
— <i>Névrite optique</i>	58 = 39,5 %
— <i>Nystagmus</i>	57 = 39 %
— <i>Sensation vertigineuse de type labyrinthique</i>	28 = 19 %
— <i>Ophtalmoplégie</i>	45 = 31 %
— <i>Abolition de certains réflexes tendineux</i>	22 = 15 %
— <i>Amyotrophies</i>	3 = 2,1 %
— <i>Paralysie faciale périphérique</i>	15 = 10,3 %
— <i>Hémispasme facial</i>	6 = 4,2 %
— <i>Troubles psychiques majeurs</i>	10 = 6,9 %
— <i>Grands tremblements complexes</i>	8 = 5,5 %
— <i>Céphalées</i>	8 = 5,5 %
— <i>Douleurs du trijumeau</i>	3 = 2,1 %
— <i>Epilepsie</i>	3 = 2,1 %
— <i>Agueusie</i>	2
— <i>Syndrome de Wallenberg</i>	1
— <i>Rigidité parkinsonienne</i>	1
— <i>Aphasie</i>	1

—cas le plus fréquent dans les premiers stades évolutifs— ou de leur caractère définitif.

Il n'est pas tenu compte non plus de leur association et cette étude analytique n'a pour but que d'indiquer les manifestations dans leur ordre de fréquence sans vouloir faire la synthèse des différents tableaux cliniques que peut réaliser leur groupement.

Ces chiffres indiquent tout d'abord la fréquence des troubles de la sensibilité, des troubles pyramidaux, des troubles cérébelleux, de la névrite optique et du nystagmus, des ophtalmoplégies enfin, après lesquelles les pourcentages des autres signes cliniques baissent de façon considérable.

L'association en proportion diverse de cas différents signes est immédiatement évocatrice du diagnostic de S.E.P. dont elle constitue le tableau clinique habituel. Nous ne reprendrons pas cette séméiologie tout à fait classique, nous attardant seulement sur quelques particularités ou sur certains points controversés.

Tremblements.

Notre statistique en fait apparaître un chiffre étonnamment bas si l'on songe aux descriptions classiques de la S.E.P.

En fait, nous n'avons pas retenu les discrets tremblements (geste irrégulièrement accompli plutôt que tremblement) qui appartiennent au syndrome cérébelleux. Le chiffre de 8 que nous indiquons, ne représente que les grands tremblements, dénommés habituellement *tremblements intentionnels*, tremblements complexes qui associent une composante cinétique —élément du syndrome cérébelleux— et une *composante d'attitude*, plus ou moins régulière, parfois considérable. On connaît l'importance de ces grandes dyskinésies, disparaissant au repos complet, se manifestant à la moindre tentative de mouvement et entraînant parfois, par un simple geste de la main, une gesticulation du corps tout entier.

Les décharges électriques, limitées au rachis ou parcourant en éclair le rachis et les membres inférieurs, parfois les quatre membres, apparaissant à la flexion de la tête ont été décrites d'abord par PIERRE MARIE, puis par BABINSKI dans les traumatismes de

la nuque. En 1923, elles sont signalées dans les cas de S.E.P. par J. LHERMITTE et sont dès lors considérées comme un signe important pour le diagnostic de S.E.P. Elles existent dans 19 de nos observations.

Nous l'avons dit, toutes les observations figurant dans cette statistique n'ont été retenues que si la symptomatologie ou l'évolution permettaient d'en affirmer le diagnostic. Cette exigence a été particulièrement rigoureuse dans les cas de décharges électriques dont la constatation, loin de conduire à un diagnostic de facilité de S.E.P., doit au contraire orienter vers l'hypothèse d'une lésion cervicale ou d'une tumeur intra-rachidienne. Dans plusieurs cas malgré un L.C.R. normal —ou altéré dans le sens de la S.E.P.— et malgré des épreuves manométriques parfaitement normales nous avons jugé nécessaire —en raison même de ces décharges électriques— de faire un contrôle lipiodolé avant de nous en tenir au diagnostic de sclérose multiple.

Paralysie Faciale.

C'est une manifestation relativement fréquente puisqu'elle a été observée chez 15 malades. Une fois elle a été récidivante et trois fois à bascule ce qui fait pour ces quinze malades un total de 19 paralysies faciales.

Il s'agit dans tout les cas d'une paralysie faciale périphérique, complète, à installation brutale ou rapide (en quelques jours).

—Elle est presque toujours *régressive*

- 14 fois (chez 11 malades dont 3 avec paralysie faciale à bascule) la régression a été complète ou presque, ne laissant subsister que de très discrètes séquelles, dans des délais allant de 8 jours à 4 mois.
- 3 fois seulement, la paralysie faciale a laissé d'importantes séquelles définitives et s'est compliquée d'un hémispasme post-paralytique.

—Elle est presque toujours *associée* à d'autres atteintes neurologiques et, avec une fréquence remarquable à celle d'un *autre nerf crânien, homolatéral* ou bilatéral: 10 fois avec une ophtalmoplégie externe (VI, III, IV); 2 fois avec une névrite optique; 1 fois avec une atteinte du trijumeau et 1 fois du VIII.

Deux fois seulement la paralysie faciale a résumé toute la symptomatologie d'une poussée évolutive en survenant isolément en cours d'évolution.

—Elle est le plus souvent un signe *précoce* au cours de l'évolution de la S.E.P.: 4 fois le signe inaugural et 3 fois appartenant au groupement symptomatique de la première poussée évolutive.

L'hémispasme facial, a été observé six fois.

—Trois fois, il s'agissait d'un *hémispasme post-paralytique* associé à un déficit résiduel définitif.

—Dans trois autres cas, *l'hémispasme a été primitif*; sans déficit moteur associé, ou très discret; et les trois fois il a été de courte durée: 8 jours, 15 jours; 1 mois.

Une seule fois, nous avons examiné le malade pendant le cours de l'évolution.

Les secousses qui occupaient le territoire du VII droit tout entier et de façon égale pour tous les muscles, n'avaient ni la répartition élective, ni le rythme en salves de "l'hémispasme essentiel". Elles étaient permanentes, régulières, et *ce rythme régulier en faisait un véritable tremblement*.

Un de nos autres cas a été observé il y a une dizaine d'années par M. TOURNAY qui dans son compte-rendu, décrit des faits analogues, et parle de tremblement.

Algies Faciales.

De nombreuses publications ont signalé l'existence possible dans la S.E.P. de syndrômes douloureux du trijumeau —soit à type "de névralgie essentielle", habituellement de longue durée; soit à type "*d'algies atypiques*".

C'est sous ce dernier type que se présentent les trois cas que nous avons observés:

—occupant deux fois un territoire partiel (maxillaire supérieur et maxillaire inférieur); et une fois totalité du territoire du trijumeau;

—évoluant 2 fois par crises de quelques heures se répétant au cours d'épisodes de quelques jours; et une fois sous forme d'une douleur continue, relativement modérée pendant une période de huit jours.

Céphalées.

Le chiffre de 8 —représentant 5,5 % du total— montre une discordance frappante avec les chiffres donnés par ABB et SCHALTENBRANDT de 32,5 % qui fait de la céphalée un des symptômes les plus fréquents de la maladie.

Cette discordance ne peut venir que de l'interprétation donnée à un symptôme aussi banal et aussi fréquent en dehors même de toute affection organique du système nerveux.

Nous n'avons retenu que les cas:

—où la céphalée, intermittente ou continue, était nettement définie (ce qui élimine les cas fréquents où une gêne vaguement douloureuse orbitaire et périorbitaire accompagne l'apparition d'une névrite optique)

—où elle apparaissait comme un phénomène récent chez un malade qui en avait été jusque-là exempt, accompagnant ou précédant —de quelques jours ou de quelques semaines— les signes neurologiques d'une poussée évolutive; se répétant parfois, dans les mêmes conditions à chaque nouvelle poussée.

Trois fois la céphalée a représenté le phénomène inaugural de la maladie.

Troubles Psychiques Majeurs.

On a reconnu depuis longtemps —depuis toujours— un comportement fréquent chez les malades atteints de S.E.P., fait souvent d'une exagération de l'émotivité avec un certain puérilisme, mais surtout d'une euphorie, d'un optimisme, d'une méconnaissance de la gravité de leur affection contrastant avec l'importance des troubles moteurs qui font souvent de ces malades des grabataires et avec le caractère récidivant et progressif de l'évolution.

Les troubles psychiques *majeurs*, par contre, sont rares et nous ne les avons relevés que dans 10 observations, soit 6,9 %.

De leur étude détaillée, se détache nettement la notion de deux groupes de faits qui se partagent à égalité ces dix observations:

—un groupe de 5 cas où l'on observe des troubles psychiques variables, régressifs

ou procédant par poussées, s'améliorant indépendamment ou non des autres manifestations neurologiques. Il s'agit d'états dépressifs successifs, de bouffées délirantes, d'épisodes confusionnels. Il s'agit donc d'un groupe très hétérogène et pour chacun de ces 5 cas, il est impossible de ne pas tenir compte du terrain préalable névrotique ou psychotique.

- Un autre groupe de 5 cas est remarquable par contre par son homogénéité. Ces cinq cas appartiennent tous à des formes graves à symptomatologie complexe, ils apparaissent à une époque tardive de l'évolution —entre 8 et 21 ans après le début, sauf pour un cas, mortel en deux ans. Ils sont caractérisés par une *détérioration intellectuelle progressive*, avec comme phénomènes plus particuliers infantilisme et perte du sens des convenances.

Epilepsie.

C'est une éventualité peu fréquente mais qu'on observe parfois soit précocement, précédant ou accompagnant les premières manifestations neurologiques, soit tardivement au cours de l'évolution.

Nous l'avons observée dans trois cas, sous la forme habituelle des épilepsies de la S.E.P. c'est-à-dire sous forme d'*épilepsie focale*.

- dans un cas, chez un homme de 22 ans, la première crise est survenue un mois après un épisode régressif de névrite optique et deux ans après deux épisodes vertigineux de quelques jours. Crise convulsive précédée d'un épisode anarthrique avec, à l'E.E.G. une dysrythmie temporale gauche à discret potentiel épileptogène.
- dans le deuxième cas, les premières crises surviennent à l'âge de 32 ans, neuf ans après un premier épisode évolutif: crises convulsives débutant par l'hémicorps droit, suivies d'une aphasia post-critique de courte durée. Sur plusieurs E.E.G. successifs: courtes bouffées de pointes ondes dégradées temporales gauches, diffusant à l'hyperpnée. Cinq ans plus tard apparition par poussées successives d'un grand tremble-

ment, d'une paralysie oculo-motrice, de signes pyramidaux. Pendant toute cette période, aucune crise convulsive.

Douze ans après la première crise, état de mal de vingt-quatre heures ayant débuté par une crise clonique limitée à l'hémicorps droit. Aggravation rapidement progressive du tremblement. Apparition d'un hémisyndrome parkinsonien gauche; d'une détérioration intellectuelle progressive. Mort deux mois plus tard.

- dans le troisième cas, la responsabilité de la maladie démyélinisante est discutable quoique ni l'anamnèse ni aucune des investigations pratiquées (artériographie, encéphalographie gazeuse) n'aient pu mettre en évidence une autre étiologie. Les premières crises sont survenues à l'âge de 12 ans: crises convulsives précédées d'une rotation de la tête. Les E.E.G. montrent des bouffées d'ondes lentes antérieures droites, se généralisant à l'hyperpnée.

Ce n'est que huit ans après la première crise qu'apparaissent les signes neurologiques par poussées successives: nystagmus complexe, grand syndrome cérébelleux, ophtalmoplégie, troubles psychiques, qui font du malade un grabataire pendant plusieurs mois. Puis amélioration remarquable avec, comme seule séquelle, un discret nystagmus. Crises convulsives rares (une par an). Même dans ce troisième cas, une coïncidence est peu probable et il nous semble légitime de retenir cette observation.

Ces trois cas représentent 2,14 % du total. Chiffre qui se place nettement au-dessus du chiffre moyenne de l'éventualité de l'épilepsie pour la population totale, qu'on évalue à 0,50 %.

Il est inférieur à la plupart des chiffres publiés pour la S.E.P. —chiffres qui vont jusqu'à 10,8 % (FUGLSANG - FREDERIKSEN, 1952). Dans certaines statistiques, ils sont cependant plus faibles que les nôtres: BERGER (1905): 1,4; ABB et SCHALTENBRANDT: 1,8; LHERMITTE (Congrès de Rome 1961): 1,3.

Le chiffre moyen calculé par DRAKE et MACRAL (Neurology, septembre 1961) sur

le total des statistiques publiées est de 4,1 %.

Amyotrophie et Abolition des Reflexes Tendineux.

La survenue d'amyotrophies au cours de la S.E.P. est certainement une éventualité rare. Quoique CHARCOT, dès ses premières descriptions, ait parlé de "formes latérales amyotrophiques" de la S.E.P., les observations anatomo-cliniques en sont restées exceptionnelles depuis la thèse de LEJONNE (Paris 1903) qui contient cinq observations dont trois avec contrôle anatomique.

Nous avons observé des amyotrophies systématisées dans 3 cas —les trois fois chez des hommes:

- après 16 ans d'évolution d'une S.E.P. à évolution classique ayant débuté à l'âge de 44 ans, apparition d'une amyotrophie progressive de la main gauche à type *Aran-Duchenne*, avec abolition du réflexe tricipital et du réflexe des fléchisseurs des doigts;

- début à l'âge de 32 ans, évolution par poussées successives partiellement régressives (troubles de l'équilibre, signes pyramidaux, diplopie, névrite optique). Onze ans plus tard, constitution progressive d'une *paralysie élective des muscles de la loge antéro-externe*, complète à gauche, incomplète à droite avec amyotrophie profonde. Abolition des deux achilléens.

Aux membres supérieurs, très discrète *amyotrophie thénarienne gauche* avec abolition des réflexes tendineux à l'exception du bicipital.

- forme chronique d'emblée (début à 32 ans) à symptomatologie classique, qui après 15 ans d'évolution fait du malade un grabataire: paraplégie spasmodique, grand tremblement, nystagmus, névrite optique bilatérale, détérioration intellectuelle. Il s'y ajoute une *amyotrophie des deux membres supérieurs* à prédominance distale telle qu'on l'observe dans la maladie de Charcot-Marie-Tooth. Abolition de tous les réflexes tendineux des deux membres supérieurs sauf bicipital et stylo-radial gauches.

Dans chacune de ces observations, nous

avons été surpris par la discrétion des signes électriques, contrastant avec la profondeur et l'ancienneté des atrophies musculaires. La même remarque avait été faite par GUILLAIN et par LEJONNE. L'E.M.G. confirme les résultats de l'examen électrique classique en montrant des altérations le plus souvent discrètes, à type de tracé intermédiaire, notablement variables d'un muscle à l'autre.

Dans aucun cas nous n'avons noté de fibrillations.

Dans aucun cas nous n'avons non plus noté de troubles systématisés de la sensibilité —argument clinique en faveur de la lésion des cornes antérieures signalée dans les quelques protocoles anatomiques rapportés.

Dans ce trois cas, l'amyotrophie apparaît comme une particularité du tableau clinique, qui —par ailleurs— est parfaitement classique par sa symptomatologie et son évolution —grave dans les trois cas, sinon du point de vue vital, du moins du point de vue fonctionnel.

Dans chacune de ces trois observations, l'amyotrophie n'est survenue que tardivement au cours de l'évolution; et le tableau clinique n'a pu, en aucun cas, prêter à confusion ou à discussion avec la sclérose latérale amyotrophique. A la lumière de ces trois cas, très comparables à ceux rapportés par LEJONNE, il nous semble difficile de partager entièrement les conclusions de cet auteur et de parler avec lui d'une forme amyotrophique de la S.E.P. Il est plus juste de dire qu'il s'agit de formes *avec* amyotrophies.

A côté de ce cas d'amyotrophie systématisée —qui comporte l'abolition des réflexes tendineux des amyotrophiques et des territoires voisins— nous avons observé *l'abolition isolée d'un ou plusieurs réflexes tendineux*, dans 19 cas.

Cette constatation vaut qu'on s'y arrête, car l'abolition des réflexes dans la S.E.P., loin d'être classique, est toujours suspecte. Nous appliquerons à ce signe la même remarque qu'aux décharges électriques. L'abolition, même isolée, d'un réflexe tendineux d'un membre supérieur avec une paraplégie spasmodique sous-jacente oriente d'emblée vers le diagnostic d'une lésion cervicale:

tumeur ou myélopathie par cervicarthrose. A plusieurs reprises, en l'absence de signes liquidiens de compression, nous avons fait —et même refait— une myélographie lipiodolée.

Sur l'ensemble des 19 cas, 5 fois seulement les réflexes des membres inférieurs étaient abolis (rotuliens et achilléens droits et gauches, 2 fois; rotulien et achilléen gauche, 1 fois; achilléens droit et gauche, 1 fois; rotulien droit, 1 fois).

Dans 16 autres cas, seuls étaient intéressés les membres supérieurs:

—8 fois, un seul réflexe: tricipital 3 fois; stylo-radial: 2 fois; bicipital: 1 fois; flexion des doigts: 2 fois.

—8 fois, plusieurs réflexes sont abolis, soit d'un seul côté, soit des deux côtés.

Dans tous ces cas, il n'y a pas d'amyotrophie ni de déficit moteur systématisé dans le territoire radiculaire correspondant.

7 fois nous avons constaté des troubles discrets de la sensibilité objective, à type d'hypoesthésie superficielle limitée à la partie distale du territoire radiculaire.

4 fois, l'abolition du réflexe a été transitoire et le signe, constaté lors d'une poussée évolutive, a disparu en même temps que s'amélioraient les autres manifestations.

2 fois, l'abolition d'un réflexe a été récidivante.

Les autres fois elle a été définitive.

Signes Exceptionnels.

Nous ne les avons notés qu'à titre de curiosité.

Les atteintes du X, ne serait-ce que sous forme d'abolition du réflexe du voile du palais sont fréquentes. Nous ne les avons pas chiffrées car faute d'être nommément signalées dans toutes les observations, le chiffre risquait d'être inexact.

Une fois nous avons observé un *syndrome de Wallenberg* à début brutal dont la symptomatologie était complète, et, dans les premiers jours, tout à fait pure. La régression rapide des troubles bulbaires et l'apparition de dysesthésies des deux membres inférieurs, les résultats de l'examen du L.C.R. ont permis de faire le diagnostic de S.E.P. qu'a confirmé l'évolution.

Une fois on a observé une *rigidité d'un hémicorps de type parkinsonien* d'appari-

tion tardive, dans une forme grave (déjà signalée: deuxième cas d'épilepsie).

Dans une autre observation que n'a pas été retenue en raison d'atypies séméiologiques mais pour laquelle le diagnostic de S.E.P. est très vraisemblable il existait un syndrome parkinsonien avec faciès figé, hypersalivation, palilalie et une discrète akinésie.

Pour terminer cette étude séméiologique nous indiquerons (tableau 3) quelle a été la *première manifestation de la maladie*.

TABLEAU 3

MANIFESTATION NEUROLOGIQUE PREMIÈRE EN DATE

(Les signes sont indiqués par ordre de fréquence, sans qu'il soit tenu compte du fait qu'ils sont groupés ou isolés).

—Troubles de la marche (déficitaires ou spastiques)		35
—Dysthésies	28	}
—Décharges électriques	4	
—Baisse de l'acuité visuelle (névrite optique)		32
—Sensations vertigineuses ou troubles de l'équilibre		30
—Diplopie		20
—Maladresse d'un membre supérieur ou des deux		17
—Paralysie faciale périphérique		6
—Troubles de la sensibilité objective		4
—Céphalées		4
—Hémiplégie		3
—Troubles sphinctériens		2
—Crise épileptique		2
—Tableau d'encéphalite subaigue		1
—Syndrome de Wallenberg		1

Certains de ces chiffres, rapportés aux chiffres globaux du tableau 2 sont remarquables:

—Les troubles subjectifs de la sensibilité —essentiellement les *dysesthésies*— n'ouvrent la scène clinique que dans un cas sur cinq environ, chiffre peu élevé comparativement à la fréquence globale des troubles de la sensibilité au cours de l'évolution.

Par contre *la névrite optique* —dont le chiffre total relativement bas, est de 58 —est 30 fois la manifestation inaugurale. C'est-à-dire que dans plus d'un cas sur 5 de S.E.P., c'est la névrite optique qui en est le premier signe.

C'est un chiffre très voisin que donne MC ALPINE, avec cette seule différence que dans sa statistique la névrite optique arrive en première ligne, suivie des dysesthésies, puis des troubles de la marche.

Une remarque analogue à celle que nous avons faite à propos de la névrite optique, peut s'appliquer aux *ophtalmoplégies*: sur un total de 44 cas, l'ophtalmoplégie (VI, III ou IV) est 17 fois le signe inaugural.

Liquide Céphalo-rachidien (L.C.R.).

Nous nous limiterons à quelques rares remarques concernant la formule du L.C.R., un article de ce volume étant consacré aux données biochimiques.

L'examen standard du L.C.R. pratiqué chez 122 malades, a comporté au minimum:

- Etude de la cytologie; albumine; réactions colloïdales. Pour celles-ci nous avons toujours utilisé la réaction du Benjoin colloïdal de Guillain.
- Réactions spécifiques (Wassermann et Nelson); disons, pour n'y plus revenir, que —dans tous les cas— les réactions syphilitiques ont été négatives.

Les résultats ont été classés en trois catégories:

—L.C.R. normal:

- 1 ou 2 lymphocytes par mmc.
- 0,25 $\pm$ 0,05 d'albumine par l.
- Benjoin précipitant dans les tubes 7 et 8 —et parfois un tube voisin (00000 02200 00000).

—Formule classique:

Nous avons considéré comme formule classique —et caractéristique— celle comportant:

- une albuminorrhachie normale ou un peu élevée (jusqu'à 0,50)
- une cytologie normale ou un peu élevée (jusqu'à 5 ou 10 leucocytes par mmc.)
- un Benjoin élargi:
 - soit précipitant dans les 5 ou 6 tubes médians;

—soit précipitant dans les 10 premiers tubes - (type paralysie générale);

—soit à double plateau: tubes 3 ou 3 et 4; et les 4 ou 5 tubes médians (00120 02222 000000).

—Altérations non caractéristiques:

Ce sont des L.C.R. anormaux:

- avec une albuminorrhachie plus ou moins importante, le plus souvent aux environs de 0,40 ou 0,50;
- une lymphocytose modérée de 5 à 20;
- et un benjoin normal ou abnormal.

(Deux fois nous avons observé une formule de dissociation albumino-cytologique avec: albumine lg. et 5 lymphocytes).

Les résultats se répartissent de la façon suivante:

T A B L E A U 4

—L.C.R. normal	32	26,3 %	} 73,7 %
—Formule classique	35	28,7 %	
—Altérations non caractéristiques	55	45 %	

On voit donc que, dans plus d'un quart des cas le L.C.R. est strictement normal —ce qui implique qu'une formule normale du L.C.R. ne peut, en aucun cas, infirmer un diagnostic clinique de S.E.P.

Dans moins d'un tiers des cas, on constate une "formule caractéristique". Ceci ne veut pas dire qu'une telle formule soit capable, à elle seule, d'affirmer un diagnostic de S.E.P. Elle ne peut être considérée que comme un argument important, indissociable de la clinique et non spécifique.

Dans 45 % des cas, le liquide est altéré, sans que ces altérations puissent être une aide déterminante au diagnostic dans un sens positif ou négatif.

Il n'existe aucun parallélisme entre la gravité évolutive de la maladie et la formule du L.C.R. qui, en aucun cas, ne nous a semblé avoir de signification pronostique.

Il y a quelques années nous avons entrepris une étude du L.C.R. des S.E.P. par la méthode courante de *l'électrophorèse sur papier*. Ce que nous attendions de cette méthode, alors nouvelle, était d'y trouver une épreuve aux résultats suffisamment constants pour qu'elle puisse être un élé-

ment fidèle du diagnostic. Elle n'a pas répondu à cette attente et nous en avons abandonné l'étude.

Accidents de la Ponction Lominaire.

Deux fois nous avons observé une poussée évolutive sévère à la suite immédiate d'une ponction lominaire.

—Une fois chez une jeune fille de 20 ans, dans les heures suivant une ponction lominaire pratiquée au cours d'une poussée évolutive sans gravité particulière, nous avons assisté à une exagération considérable des troubles antérieurs, cérébelleux et pyramidaux.

—Une autre fois, un syndrome de myélite transverse s'est constitué brutalement à la suite immédiate d'une deuxième injection intra-rachidienne d'Hydrocortisone chez un malade présentant une paraplégie spasmodique ancienne, sans poussée récente.

Il est difficile de ne pas retenir la responsabilité de la ponction lominaire dans ces deux cas et d'y voir une simple coïncidence. Quoique le second cas soit très comparable aux deux exemples cités par GUILLAIN dans son rapport, il faut remarquer qu'il ne s'est pas agi d'une simple ponction lominaire —mais de l'injection intra-rachidienne de Cortisone.

De tels exemples restant l'exception ils ne sauraient interdire la ponction lominaire qui, dans de nombreux cas, reste une investigation diagnostique indispensable. Nous pensons être en accord sur ce point avec la grande majorité des Neurologistes.

Formes Evolutives.

Il est devenu classique de distinguer trois grandes formes évolutives:

T A B L E A U 5

	Nombre:
—S.E.P. <i>aigue</i>	2 = 1,5 %
—Forme <i>commune</i>	
à poussées successives	114 }
et régressives	+16 }
—Forme <i>chronique</i>	
<i>d'emblée</i>	13 = 9 %
	145

Cette distinction n'est, en fait, que très schématique et nous montrerons la fréquence des modalités de passages entre ces trois grandes formes.

1° S.E.P. Aigue.

Son identité histologique avec la S.E.P. commune est reconnue (MARBURG 1904) avec cette seule différence, que les plaques de démyélinisation sont des "plaques jeunes" dont l'évolution cicatricielle a été interrompue par la mort.

COURNAUD (1930) et GÉRAUD (1932) leur reconnaissent deux caractères essentiels: la dissémination des lésions et la rapidité d'évolution.

—La poussée aigue mortelle peut être la poussée initiale et représenter à elle seule toute la maladie.

(Ce fut le cas d'une de nos malades, âgée de 34 ans, chez qui apparurent presque en même temps un syndrome cérébelleux, un nystagmus et des troubles pyramidaux, dont l'aggravation très rapide constitua en quelques jours un tableau de myélite transverse avec abolition complète de la motricité et de la sensibilité de la partie inférieure du corps et entraîna la mort après une évolution de dix-huit jours {L.C.R.: albumine 0,55; 70 leucocytes; B.W. négatif; Benjoin: 00000/02210/00000}).

—Mais cette poussée aigue —qu'elle soit médullaire, cérébrale ou disséminée— peut succéder à des poussées antérieures d'apparence banale et rompant brusquement leur rythme évolutif, entraîner la mort en quelques semaines.

Dans la seconde observation, un syndrome de myélite transverse, installée en une dizaine de jours évolue vers la mort en six mois. Le seul antécédent était une première poussée régressive faite de dysesthésies des membres inférieurs survenue trois ans auparavant.

—Certaines de ces formes malgré un début dramatique peuvent cependant rétrocéder en ne laissant même que des séquelles relativement peu importantes.

C'est ainsi que la poussée aigue à type de myélite transverse que nous avons signalée plus haut, apparue à la suite d'une injection intrarachidienne d'Hydrocortisone a rétrocédé après une période critique de plusieurs semaines, ne laissant guère per-

sister trois mois après sont début que les troubles qui existaient antérieurement.

Une autre cas se présentait avec tous les caractères de la S.E.P. aigue à forme disséminée.

Femme de 26 ans: début par petits troubles de l'équilibre, régressifs. Quinze jours plus tard, dysesthésies de l'hémicorps droit, puis petit syndrome pyramidal bilatéral. Quinze jours plus tard apparition brutale d'une paralysie et d'une anesthésie complètes des membres inférieurs avec ophtalmoplégie et névrite optique bilatérale. (L.C.R.: albumine 0,40 — 20 leucocytes — B.W. négatif; Benjoin: 01210 22200 00000).

En trois mois, on assiste à la régression presque complète de ces troubles qui ne laissent derrière eux, qu'un discret syndrome pyramidal limité au membre inférieur gauche. Depuis 1954, date de cette première poussée aigue, il y a eu quatre poussées évolutives, peu intenses et toutes régressives.

Ces observations — aussi bien celles de poussées aiguës venant brusquement achever une évolution jusqu'alors banale que celles de poussées aiguës initiales tournant court — indiquent bien qu'il n'existe aucune limite absolue entre S.E.P. aigue et forme commune.

2° Forme Commune.

Cette forme à poussées successives et régressives dont l'évolution s'étale sur de nombreuses années est la forme de beaucoup la plus fréquente de la S.E.P. et sa forme la plus caractéristique.

Nous comptons 114 observations qui comportent au moins deux poussées évolutives. Et le tableau 6 indique les délais entre la première et la deuxième poussée.

Dans plus de la moitié des cas la seconde poussée évolutive survient dans un délai inférieur à deux ans et dans un peu moins d'un cinquième des cas ce délai est supérieur à 5 ans.

Calculée sur ces chiffres, la durée moyenne de délai entre la première et la deuxième poussée est approximativement de *trois ans* et ce chiffre indique assez fidèlement le rythme évolutif de la plupart des formes communes de S.E.P.

A partir de la deuxième poussée le rythme

est variable, les poussées ultérieures étant souvent plus rapprochées: mais par-

T A B L E A U 6

INTERVALLE ENTRE LA 1ère. ET LA 2ème. POUSSÉE ÉVOLUTIVE

—moins de six mois	20	
—six mois à un an	27	
—1 à 2 ans	20	
—2 à 5 ans	25	
—plus de 5 ans	13	
—plus de 10 ans	9	(avec comme chiffres extrêmes 16 et 17 ans).

fois très éloignées (dans un cas, poussées aux âges de 13 ans, 23, 26, 28, 50).

Les poussées se succèdent suivant deux grandes *modalités évolutives*:

—Soit qu'elles atteignent toujours les mêmes appareils: nerf optique, nerfs oculomoteurs, faisceau pyramidal, voies cérébelleuses —avec des poussées successives en quelque sorte stéréotypées. Chaque poussée régresse plus ou moins complètement mais laisse finalement des séquelles, aggravées à chaque nouvel épisode.

—Soit que chaque poussée atteigne plusieurs appareils chaque fois différents les uns des autres, avec cette diffusion très évocatrice de la S.E.P.

Au bout d'un temps plus ou moins long —dont nous indiquerons plus loin les délais moyens— on aboutit au stade de lésions irréversibles et l'évolution se fait alors fréquemment sur le mode chronique: aggravation progressive sans poussées manifestes —à moins qu'une poussée aigue, dont nous avons vu la possibilité —rare d'ailleurs— vienne couper brusquement le mode évolutif.

De part et d'autre de cette évolution moyenne, deux types évolutifs s'observent parfois:

—*Poussées subinivantes*, observées dans deux cas, où l'on voit apparaître successivement et à un rythme très rapide de multi-

ples manifestations. Chaque fois remarquablement régressives.

—*Evolution à étapes éloignées* dont une de nos observations donne un exemple remarquable:

- Début à 28 ans par une amaurose de l'oeil gauche qui régresse en huit jours.
- 2ème. poussée à 33 ans, nouvelle amaurose de l'oeil gauche, régressive qui laissera une vision réduite à 5/10^e; petit syndrome pyramidal gauche qui ne laissera que des réflexes un peu plus vifs.
- 3ème. poussée à 53 ans: amaurose complète de l'oeil gauche partiellement régressive (2/10^e).

Ce sont ces *formes à étapes évolutives éloignées* qui représentent une bonne partie de ce que MAC ALPINE a très justement appelé les *S.E.P. bénignes*. C'est presque toujours le cas des formes dans lesquelles existe un long délai entre la première et la deuxième poussée

Dans 16 de nos observations, il n'y a eu jusqu'à la date de ce travail, qu'une seule poussée (dont la symptomatologie a été suffisamment démonstrative pour que le cas soit retenu).

Dans 14 cas, le délai d'observation est inférieur à trois ans.

Les deux autres cas, observés avec un recul de 7 ans et de 14 ans, posent le problème des *formes abortives*. Problème insoluble car on ne peut assigner aucune limite de temps, aucun délai après lequel on serait en droit de conclure. Nous avons vu que la seconde poussée peut être séparée de la première par un délai de 17 ans. Rien ne permet de dire qu'il ne puisse être plus long encore.

Si ces formes ne peuvent être considérées comme des formes abortives, au moins sont-elles des formes bénignes.

Forme Chronique D'Emblée.

Observée dans 13 cas, soit 8,95 % —chiffre très voisin de celui donné par MAC ALPINE d'environ 10 %.

C'est le mode évolutif qu'on considère comme habituel aux S.E.P. à début tardif et, de nos 13 cas, 9 c'est-à-dire, près des 3/4, commencent effectivement après l'âge de 35 ans (tableau 7).

Mais cette affirmation n'est que partiellement exacte puisque sur 44 cas à début tardif (après 35 ans), 9 seulement sont à forme chronique d'emblée; et 2 seulement, sur les 7 cas ayant débuté après 50 ans.

T A B L E A U 7

AGES DE DÉBUT DES FORMES CHRONIQUE D'EMBLÉE

26 ans	1 cas	}	4
27 ans	1 cas		
32 ans	2 cas		
36 ans	3 cas	}	9
38 ans	2 cas		
39 ans	1 cas		
46 ans	1 cas		
51 ans	1 cas		
57 ans	1 cas		

C'est une forme habituellement grave:

—Deux morts, après, respectivement, 3 ans et 4 ans d'évolution (alors que le chiffre total de morts pour l'ensemble des cas est de 9).

—Grande infirmité apparue après 2 ans d'évolution: 1 fois;

grande infirmité apparue après 3 ans d'évolution: 1 fois.

grande infirmité apparue après 10 ans d'évolution: 3 fois.

—Dans un cas suivi seulement depuis trois ans, existe une infirmité déjà importante.

Ce caractère de gravité s'il est le plus fréquent n'est pas absolu et pour 3 cas, on note une infirmité légère, permettant une vie sociale sensiblement normale:

—deux fois après 5 ans d'évolution;

—une fois après 10 ans d'évolution;

—une fois après 20 ans d'évolution (il s'agit réellement ici d'une forme bénigne).

Durée D'Evolution. Pronostic Vital et Pronostic Fonctionnel.

Les durées d'observation de nos différents malades sont très variables. Dans plus du

tiers des cas la durée de la maladie n'excède pas quelques années et cette évolution est trop brève pour qu'on puisse retenir de tels cas dans une étude pronostique — à l'exception des formes graves évoluant vers la mort en quelques années, dont nous comptons six cas sur un total de 9 décès pour l'ensemble de nos malades.

Nous avons retenu trois étapes évolutives: 5 ans; 10 ans; au-delà de 15 ans — les malades des deux derniers groupes figurant aux étapes antérieures pour l'état où ils se trouvaient alors.

—1er. groupe:

- moyenne de 5 ans d'évolution (de 4 à 7 ans): 85
 - mort avant 5 ans d'évolution: 6
- } 91

—2ème. groupe:

- moyenne de 10 ans d'évolution (entre 8 et 15 ans): 48

—3ème. groupe:

- Plus de 15 ans d'évolution: 16

Les chiffres des formes bénignes, des formes graves et des morts, avec leur pourcentage respectif pour chaque groupe sont donnés par le tableau 8.

TABLEAU 8

		1er. groupe: 5 ans 91	2ème. groupe: 10 ans 48	3ème. groupe: 15 ans 16
I	—Troubles mineurs	43 = 47,25 %	16 = 33,3 %	4 = 25 %
	—Petite infirmité (permettant une vie sociale sensiblement normale)	28 = 31,1 %	14 = 29,2 %	7 = 43,75 %
		} 78,35 %	} 62,5 %	} 68,75 %
II	—Infirmité grave	11 = 12,1 %	10 = 20,8 %	2 = 12,5 %
	—Etat grabataire	3 = 2,95 %	6 = 12,5 %	2 = 12,5 %
		} 15,05 %	} 33,3 %	} 25 %
III	Mort	6 = 6,6 %	2 = 4,2 %	1 = 6,25 %

De l'étude de ces chiffres, quelques conclusions se dégagent:

- les formes mortelles sont, dans la majorité des cas (6 fois sur 9) graves d'emblée et rapidement évolutives;
- les malades qui ont franchi la cinquième année d'évolution ont peu de chances de mourir de leur S.E.P. dans les dix années suivantes;
- de ceux qui ont franchi la dixième année, 2 sur 3 ne sont atteints que d'une petite infirmité.
C'est dans cette période d'évolution entre 5 et 15 ans que l'on trouve le plus fort pourcentage de formes graves du point de vue fonctionnel.
- de ceux qui ont franchi la 15ème. année, 3 sur 4 ne sont atteints que d'une petite infirmité. Proportion encore plus faible

pour les évolutions exceptionnellement longues.

Dans 5 cas de plus de 25 ans d'évolution (25, 28, 29, 38 et 45 ans) un seul est devenu grabataire après 29 ans d'évolution; les 4 autres ne sont atteints que d'une petite infirmité.

Il faut toutefois remarquer que ce pourcentage très élevé de formes bénignes ne se rapporte qu'à des malades des consultations. Il ne tient pas compte des malades hospitalisés en service de chroniques dont les statistiques compteraient sans doute une quasi-totalité de grabataires.

Elements de Pronostic.

De l'étude des formes graves nous pouvons dégager certains éléments qui, en dépit de la fantaisie évolutive de la S.E.P., permettent d'établir un pronostic d'avenir

dès les premières étapes de la maladie.

1^o — L'incidence pronostique de l'âge de début est une notion controversée et plusieurs fois débattue.

Sur 29 cas ayant débuté après 40 ans, on compte:

- 10 d'évolution trop brève pour être retenue
- 9 cas graves: { 3 mortels
6 infirmités graves après 5 ans d'évolution
- 10 cas bénins

Si l'on rapporte ces chiffres aux pourcentages globaux de cas mortels, de cas graves et de cas bénins, on doit retenir une *indiscutable gravité de ces formes à début tardif, qui sont graves 1 fois sur 2 environ*.

2^o — L'intensité des premières manifestations, par leur gravité et leur diffusion, doit être retenue comme un élément de mauvais pronostic.

Dans 10 cas analogues (dont 6 à début tardif):

- 2 d'évolution trop brève pour être retenus
- 5 cas graves: { 3 mortels (1 S.E.P. aiguë; 2 ans; 3 ans)
2 états grabataires en 3 ans et 10 ans
- 3 cas seulement ont tourné court et ont eu une évolution ultérieure relativement bénigne

3^o — La rapidité du rythme évolutif joue un rôle évident en ce qui concerne les formes à étapes éloignées. Si la seconde pous-

sée survient après un délai de dix ans ou plus, on ne peut guère parler de forme grave —et l'étude des cas analogues montre que, passés de tels délais, la maladie ne transforme pas son allure évolutive.

L'inverse est vrai aussi pour les délais courts. C'est ainsi que dans les six cas ayant suffisamment de recul évolutif avec un délai de moins de six mois entre la première et la deuxième poussée on compte:

- 1 mort après deux ans d'évolution;
- 3 infirmités graves avant 5 ans;
- 2 restés bénins après 5 ans et 10 ans d'évolution,

soit un total de 2/3 de formes graves.

4^o — Les formes chroniques d'emblée —qui sont souvent des formes à début tardif— sont, nous l'avons vu, des formes habituellement graves (dans plus de 2/3 des cas).

—Le sexe ne conditionne aucune forme évolutive particulière.

Mais à ce sujet se pose la question de l'incidence aggravante de la grossesse. Rien dans l'étude de nos cas ne nous permet de prendre position sur ce problème controversé —et sans doute insoluble. Nous nous contenterons de verser au débat l'observation suivante: début à 13 ans; premier accouchement à 26 ans, suivi *trois mois* plus tard d'une poussée régressive; même chose pour le second accouchement; *rien au cours ou à la suite des cinq autres grossesses*; paraplégie spasmodique progressive ayant débuté à la ménopause.

RESUME

Etude de 145 observation de S.E.P. formant un groupe homogène.

Notions étiologiques

- 60 % des cas débutent entre 20 et 35 ans
- 10 % avant 20 ans
- 30 % après 35 ans
- deux cas familiaux (1,4 %)

Symptomatologie

Troubles de la sensibilité, signes pyramidaux, signes cérébelleux, névrite optique, signes vestibulaires sont les signes les plus

fréquents et leurs groupements constituent le tableau classique de la S.E.P. Certains signes plus rares sont étudiés plus particulièrement: paralysie faciale et mouvements anormaux de la face; algies faciales; céphalées; épilepsie (3 cas soit 2,14 %); amyotrophies (3 cas) et abolition de certains réflexes tendineux (19 cas).

Le L.C.R. est normal dans 1/4 des cas. Il ne possède une formule caractéristique (mais non spécifique) que dans moins d'un tiers des cas.

Formes évolutives

—S.E.P. aiguë	1,5 %
—Forme commune à poussées successives	89,5 %
—Forme chronique d'emblée	9 %

Le délai moyen entre la première et la deuxième poussée est de 2 à 3 ans. Les formes à *étapes évolutives éloignées* ne sont pas exceptionnelles; à leur propos, est évoqué le problème des *formes abortives*.

Pronostic

Le tableau indiquant la gravité rapportée à la durée d'évolution montre la fréquence des *formes bénignes* ou peu graves (avec le correctif qu'il s'agit de malades de consultation et non d'hospice).

Certains *indices de gravité* sont retenus: début tardif, intensité des premières manifestations, rapidité du rythme évolutif (6 sur 9 des formes mortelles ont évolué en moins de 5 ans), chronicité d'emblée.

SUMMARY

A study of 145 cases of multiple-sclerosis (which form a homogeneous group).

Etiological Facts:

- 60 % of the cases start between 20 and 35 year of age.
 - 10 % before 20.
 - 30 % after 35.
- Two (2) familial cases (1.4 %).

Symptomatology:

Somatic sensory disturbances, pyramidal signs, cerebellar signs, retro-bulbar neuritis, vestibular signs are the most frequent; and the combinations of these constitute the typical picture of multiple sclerosis.

Certain less frequent signs are studied more particularly: facial paralysis and abnormal movements of the face, facial pain, headache, epilepsy (3 cases, i.e. 2.14 %), muscular atrophy (3 cases) and the abolition of tendon reflexes (19 cases).

The cerebrospinal fluid is normal in 1/4 of the cases. It is characteristic (but not specific) in less than 1/3 of the cases.

Course of Disease:

- Acute multiple sclerosis 1.5 %
- Typical relapsing form 89.5 %
- Chronic progressive form (from the onset) 9 %

The average interval between the onset and first relapse is from two (2) to three (3) years. The form with *relapses occurring after long intervals* are not exceptional; in relation to these, the problem of *abortive forms* arises.

Prognosis:

The chart, indicating the gravity in relation to the duration of the course of the disease shows the frequency of *benign* (or less serious) *forms* (with this corrective factor: this study deals mainly with out-patients and not with institutionalized patients).

Certain *indications of gravity* are pointed out: onset at an advanced age, intensity of the first symptoms, rapid rhythm of development (6 out of 9 mortal cases developed in less than 5 years), chronic course from the onset.

ZUSAMMENFASSUNG

Bericht über eine homogene Gruppe von 145 Fällen von Multiple Sklerose.

Anamnese

- 60 % der Fälle beginnen zwischen 20 und 35 Jahren
- 10 % vor 20 Jahren

30 % nach 35 Jahren
Zwei erblich bedingte Fälle (1,4 %)

Symptomatologie

Reizstörungen, pyramidale Anzeichen, Kleinhirnstörungen, Sehnervreizung, vesti-

buläre Anzeichen kommen am häufigsten vor. Ihr gemeinsames Auftreten bildet das klassische Krankheitsbild des M.S. Seltener Anzeichen werden näher untersucht: Facialis-Lähmung und anormale Bewegungen der Gesichtsmuskulatur; Gesichtsschmerzen; Kopfschmerzen; Epilepsie (3 Fälle, d.h. 2,14%); Muskelatrophie (3 Fälle) und Verschwinden gewisser Sehnenreflexe (19 Fälle).

Der Liquor ist in 25 % der Fälle normal. In weniger als 30 % ist die Formel charakteristisch (aber nicht spezifisch).

Entwicklung

—Akuter M.S.	1,5 %
—Gewöhnliche Form mit wiederholten Schüben	89,5 %
—Sofort chronische Form	9 %

Die Zeitspanne zwischen dem ersten und zweiten Schub beträgt im Durchschnitt 2-3 Jahre. Fälle mit *ausgedehnten Entwicklungsschüben* sind nicht selten; dazu wird das Problem der *abortiven Formen* erwähnt.

Prognose

Eine Tabelle mit dem Schweregrad im Vergleich zur Entwicklungsdauer zeigt die Frequenz der *gutartigen* oder leichten Formen (allerdings handelt es sich hier um ambulante und nicht stationäre Patienten).

Einige Symptome bestätigen den *Schweregrad* der Krankheit: Verzögertes Auftreten der ersten Anzeichen, ihre Heftigkeit, rascher Entwicklungszyklus (6 von 9 Fällen mit tödlichen Ausgang verschlimmerten sich in weniger als 5 Jahren). Sofortiger Übergang in ein chronisches Stadium.

RESUMEN

Estudio de un grupo homogéneo de 145 casos de Esclerosis Múltiple.

Hechos etiológicos

El 60 % de los casos comienzan entre los 20 y 35 años.

El 10 % antes de los 20 años.

El 30 % después de los 35 años.

Se observaron dos casos familiares (1,4%).

Sintomatología

Lo más frecuentemente se comprueban disturbios somáticos sensoriales, signos piramidales, signos cerebelosos, neuritis retrobulbar, y signos vestibulares; la combinación de estos elementos constituye el cuadro típico de la esclerosis múltiple.

Se estudiaron en forma particular ciertos signos menos frecuentes: parálisis facial y movimientos anormales de la cara, dolor facial, cefalalgia, epilepsia (3 casos, o sea 2,14%), atrofia muscular (3 casos) y la abolición de reflejos tendinosos (19 casos).

El líquido cefaloraquídeo es normal en la cuarta parte de los casos. Es característico (pero no específico) en menos de la tercera parte de los casos.

Características evolutivas

Esclerosis múltiple aguda	1,5 %
Forma típica a empujes y remisiones	89,5 %
Forma crónica progresiva desde el comienzo	9 %

El intervalo entre el comienzo y el primer empuje es de 2 a 3 años.

No es excepcional que los intervalos entre los empujes sean muy prolongados; vinculado a este hecho está el problema de las formas abortivas.

Pronóstico

El cuadro en el cual se señala la relación de la gravedad a la duración del curso de la enfermedad, muestra la frecuencia de las formas benignas (o menos serias); con este elemento correctivo: que este estudio ha sido hecho principalmente con pacientes de consultorio externo y no con pacientes internados.

Se señalaron ciertos indicios de gravedad: comienzo a una edad avanzada; intensidad de los primeros síntomas; desarrollo rápido (6 de 9 casos mortales evolucionarán en menos de 5 años); curso crónico desde el comienzo.

Ophthalmologic Symptoms of Multiple Sclerosis

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Discussion of ophthalmologic symptoms of multiple sclerosis is subject to the same questionable proof as are other symptoms. It is difficult to make a definite diagnosis and one probably should not attempt to do so before accumulated evidence has substantiated the provisional conception. The symptoms are as scattered and as variable as the possible sites of the lesions producing them. In order to systematize this discussion, the chief ocular symptoms have been divided into two groups, visual and oculogyric. These ocular symptoms, one kind or another, are found as the initial affection in about 40% of the early cases,⁽¹⁾ and as time passes, the percentage increases until late in the course by far the majority of patients have acquired visual and oculogyric disturbances. These symptoms may be transient at first, appearing and culminating rather rapidly, to linger and disappear. These symptoms are often accompanied or followed by manifestation of involvement elsewhere in the nervous system. This multiplicity of lesions with the symptoms produced, their transiency and fluctuation are characteristic of the disease which appears usually in the 3rd and 4th decade of life, infrequently before or after.

There are certain areas confined to the central nervous system which seem to have a predelection for these demyelinating affections, and many of these areas are intimately concerned with visual and oculogyric functions as they contain nuclei and axons comprising these symptoms. The optic nerve and (Fig. 1) chiasma are particularly vulnerable as is the white matter surrounding the cerebral ventricles. The posterior horns of the lateral ventricles

which are incased to a great extent by the optic radiations are a favorite site for sclerotic plaques. (Fig. 5).

This predelection for white matter surrounding the cerebro-spinal fluid system is carried down into the brain stem and we find disturbances of eye movements by involvement of the white matter around the aqueduct of Sylvius (Fig. 3) and the fourth ventricle affecting many nuclei situated in the floor of these channels and also the tracts, particularly the medial longitudinal fasciculus and cerebellar peduncles, (Fig. 4) connecting these nuclei.

Visual Symptoms

Blurring, dimness or loss of vision may occur as the first symptom. The patient may complain of shimmering vision as though looking through heat waves or agitated water (oscillopsia). Visual disturbances will occur during the course of the disease in about half of the patients.

Probably the most frequent site of involvement is in the retrobulbar optic nerve, usually unilateral, occasional bilateral, especially in acute forms of demyelination of neuromyelitis optica (Devic's disease).⁽²⁾ A lesion in the optic nerve usually produces a central scotoma (or caeco-central, para or peri-central), with sudden impairment of vision. Involvement may occasionally extend to the periphery in one area. Retrobulbar soreness or pain, upon eye movement, is not complained of as much as in other types, probably because there is less inflammation and infiltration.

Examination of optic nerve sections demonstrate an acellular reaction with plaque formation (Fig. 1). Comparing



Fig. 1. — Section through optic nerve showing multiple sclerotic plaques.

these lesions with other types of retrobulbar neuritis, where cellular activity is prominent, (i.e., meningo-vascular syphilis), the contrast is quite striking. The lack of inflammatory cellular activity points to multiple sclerotic degeneration.

In these conditions there is, at first, no ophthalmoscopic evidence of visual change until the degeneration and destructive processes appear at the papilla when pallor and optic atrophy are in evidence.

The optic chiasma, a continuation and partial crossing of the visual axons is also a rather frequent sight of involvement. A lesion here will probably produce bilateral fields defects, and, depending upon location, will show scotomata or peripheral field loss.

Optic tract and lateral geniculate lesions appear to be very rare, or perhaps may be difficult to localize.

Before passing to the next neuron of the visual system, let us return to the eye. Usually, at first, ophthalmoscopic evidence of affection of the visual system producing dimness or loss of vision is lacking. Later the discs frequently appear pale, especially the temporal portion containing the central nerve fibers, and the retinal vessels appear somewhat attenuated. This pallor may be

the result of destruction of the myelin sheaths, which have been replaced by gliosis without implicating the function of the nerve fibers which they had ensheathed. The pallor observed may be due to pressure of these so-called glial plaques which have constricted the blood vessels; or it may be due to compensatory reduction of blood supply. In brief, we cannot determine, by the pallor of the optic discs in multiple sclerosis, the amount of vision present. Vision may be lost with normal appearing discs, it may be present with very pale discs.

OPTIC NEURITIS.

Multiple Sclerosis

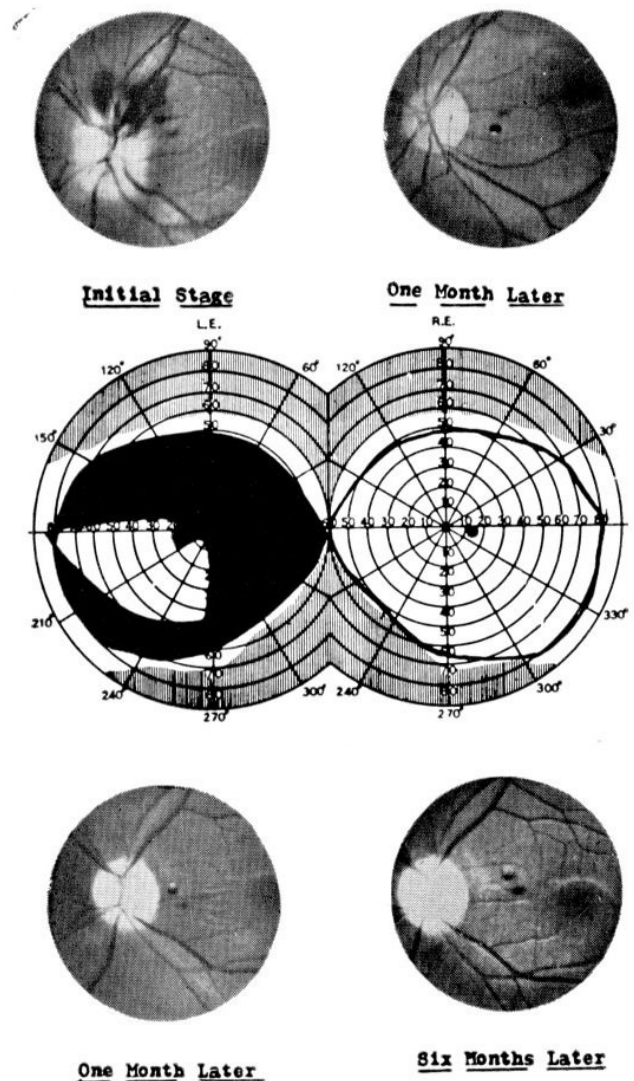


Fig. 2. — Optic neuritis (papillitis) in multiple sclerosis. a) Photographs showing cellular papillary swelling. b) Visual field loss - central with peripheral extension.

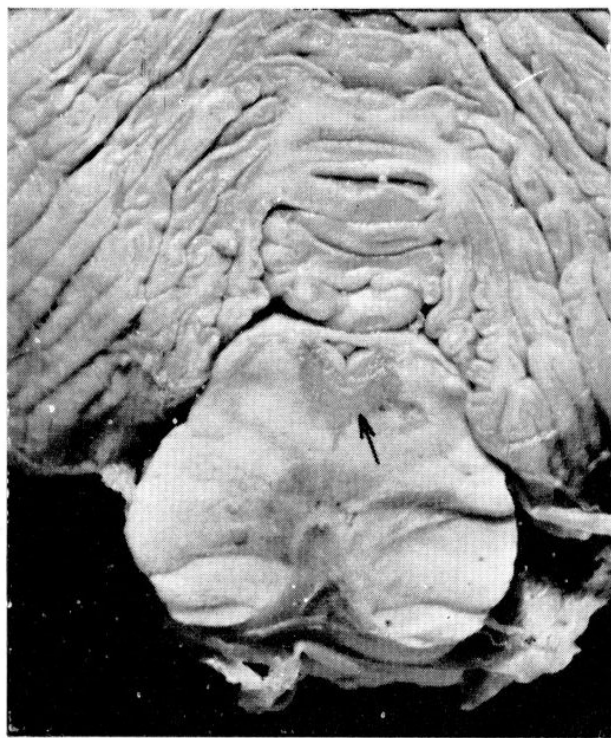


Fig. 3. — Plaque of multiple sclerosis surrounding aqueduct of Sylvius involving oculomotor nuclei and medial longitudinal fasciculus.

Seldom, one observes papillitis or optic neuritis with the discs showing edema with feathery edges and with venous engorgement and occasional hemorrhages in or adjacent to the disc. Inflammatory cellular infiltration of the papilla and adjacent retina and vitreous is minimal, or not present, which is in contradistinction to the cellular activity in other types of papillitis. This clear view of the disc may be of diagnostic significance in pointing to multiple sclerosis as the causative factor (Fig. 2).

Proceeding intra-cranially from the lateral geniculate body to the visual cortex we find rather frequent involvement of the optic radiations. Although multiple sclerosis chiefly affects the white matter surrounding the ventricles, its process, especially in acute or virulent forms, may extend into the gray, and thus directly affect the visual cortex. Cortical involvement at the occipital pole produces central visual loss, usually scotomata; farther forward in the calcarine area peripheral loss, which is usually seen as depressions in the peripheral field.

With cortical involvement, with the visual field loss, various types of aphasia may occur, and mental processes may be affected. I recall a patient completely blind with extensive lesions surrounding the posterior horn of the lateral ventricles, proven at autopsy, who persisted in attesting he was not blind, and constantly wrongly describing objects he could not see. When he attempted to walk, he bumped into furniture and walls. (Anton's Syndrome). Frequently in these patients, there is interference with the normal optokinetic responses.

Visual Field Studies

In order to determine the site of the lesions causing loss of visual acuity, visual field studies are of great importance. Multiple sclerotic implication of the visual fields may be found anywhere from the optic disc to the cerebral cortex, most frequently in the retrobulbar optic nerve and chiasma and next most frequently in the optic radiations. When charting fields, various sized spotters should be used to determine the activity of the process. In

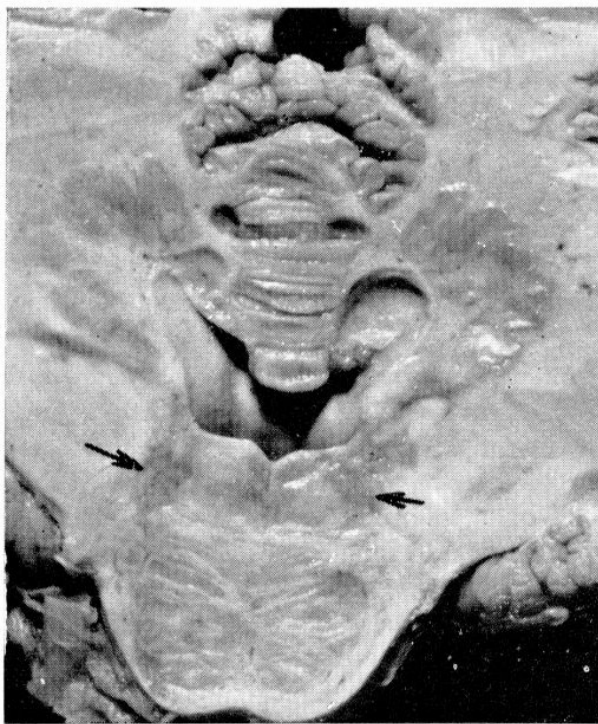


Fig. 4. — Plaque of multiple sclerosis involving vestibular nuclei and restiform body.

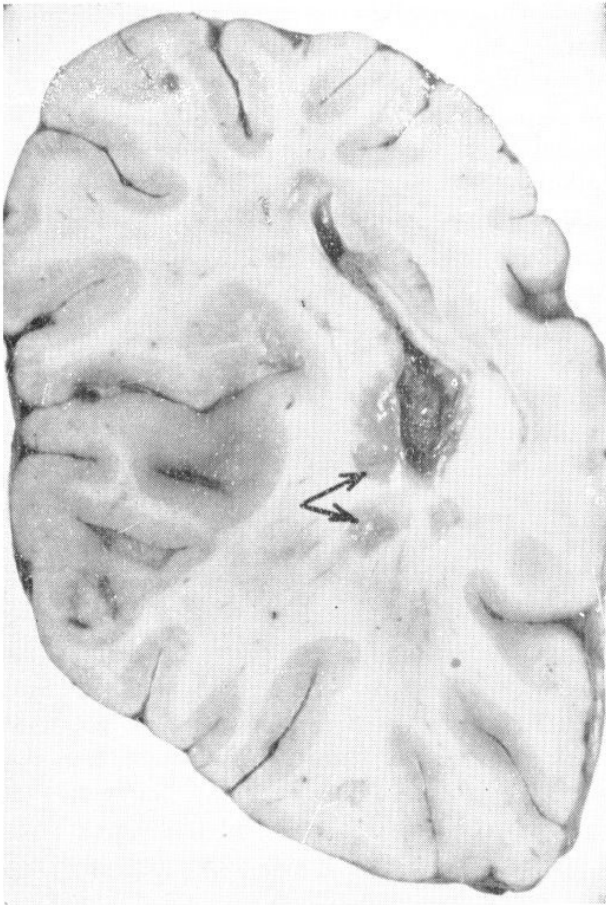


Fig. 5. — Plaque of multiple sclerosis in optic radiations in wall of posterior horn of lateral ventricle.

multiple sclerosis we find most frequently defects with sloping edges and great separation of the isopters indicating the presence of activity which is rather characteristic of the multiple sclerotic lesion.

Especially with retrobulbar lesions, the color spotters (red and green) are of little value, as very frequently in this condition, color blindness is present. The Ishihara, or other test for color blindness, is one of the procedures resorted to in the study of this condition. I do not believe these color tests are of great diagnostic importance as any type of retrobulbar involvement with loss of vision will affect color sensitivity.

With involvement of the papilla and retrobulbar optic nerve, central scotoma, possibly with peripheral extension, is found. The condition is usually unilateral. The field defect may be fluctuating in size and intensity and even in position before it finally disappears or, in the minority of cases, becomes stationary and permanent,

the isopters of various sizes becoming superimposed.

Rather similar involvement of the visual axons in the chiasma produces a variety of field defects which are of little diagnostic value but because of their positions in both fields are of considerable localizing importance. If there is involvement of the optic tract or lateral geniculate body homonomous field changes appear which are incongruous and, because of the compactness of the structures, rather extensive. Pupil changes may occur in tract lesions as the pupil fibers accompany those of vision.

The optic radiations are implicated most frequently in later stages of multiple sclerosis and in certain virulent types. Usually peripheral homonomous visual field loss is produced as contrasted to the more frequent central involvement when the visual cortex is affected. If the upper field shows loss, the lower radiations are involved in the temporal or occipital lobes. If the lower fields are affected, the lesion is in the upper radiations which may involve the lower posterior parietal and occipital lobes. Extensive, frequently bilateral, involvement is found in encephalitis perixialis

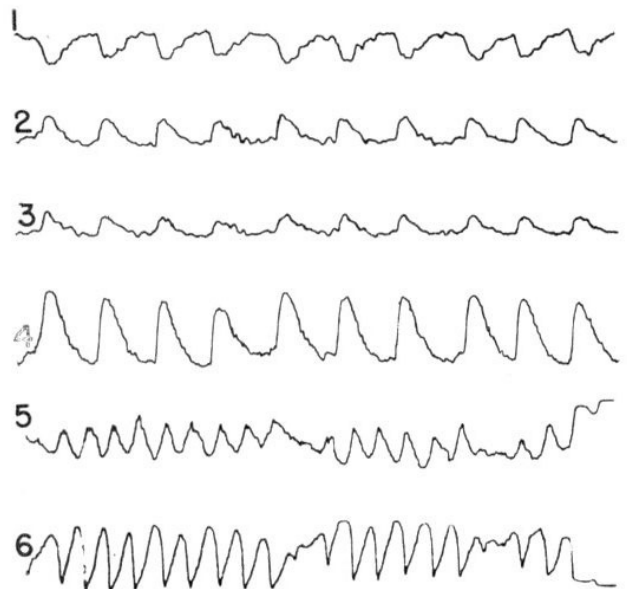


Fig. 6. — Ocular myograms demonstrating various types of reaction in: 1 and 2 spontaneous vestibular nystagmus in multiple sclerosis. 3 and 4 induced vestibular (caloric) and ocular (optokinetic) nystagmus. 5 and 6 spontaneous ocular nystagmus from early loss of central vision.

difusa of Schilder.⁽²⁾ In these cases, so-called cerebral blindness may be present, the patient not seeing, although there is no ophthalmoscopic evidence of visual disturbances, the pupil reflexes remaining intact.

The Oculogyric System

The oculogyric system is quite frequently the site of multiple sclerotic lesions. Although supranuclear involvement is rare, internuclear, nuclear and infranuclear disturbances occur in about one-third of those affected with multiple sclerosis sometime during the course of the disease. The subjective complaint is diplopia with nuclear and infranuclear lesions. Paresis or paralysis of a nerve, the abducens most frequently, the oculomotor, and rarely the trochlear is found. When the medial longitudinal fasciculus is involved, there is incoordination or disassociation of eye movements but not necessarily diplopia. There is no diplopia with supranuclear lesions when conjugate deviations are affected.

Studies of electromyography of the oculogyric system is revealing further information regarding the action of eye movements. Breinin⁽³⁾ is able to differentiate between supranuclear, internuclear, and infranuclear lesions, and thus locate the site producing motor disturbances. His work promises to be of great aid in detecting and localizing these lesions.

Pupil changes are not the rule in multiple sclerosis, although patients may develop a variety of pupillary affections, chiefly anisocoria. Argyll Robertson pupils, usually without myosis, have been cited.

Nystagmus of the vestibular-brain stem type occurs frequently, probably in half of the patients, during the course of the disease. Although ocular nystagmus, resulting from loss of central vision in infancy is not found, occasionally the visuo-tegmental or visuo-tectal tracts are implicated with loss of coordination of horizontal and vertical eye movements which are instigated by visual perception. In these cases disturbances of induced optokinetic responses occur. The usual nystagmus in multiple

sclerosis is produced from lesions in the vestibular-oculogyric internuclear systems, and may be horizontal, vertical or rotatory. Monocular nystagmus or jelly like nystagmus (oscillopsia) is considered suggestive of the disease.

The vestibular types of nystagmus may be differentiated from the ocular type as they tend to have a slow and fast phase, are usually less frequent and persist with closure of the eyes; whereas ocular nystagmus occurs in individuals with reduced central vision early in life. With ocular nystagmus the movements are more pendular with no slow and rapid phase, are more frequent, and disappear upon closure of the eyelids or lack of visual stimulus. (Fig. 6).

These affections may be associated with other brain stem and cerebellar disturbances so that vertigo, ataxia and implication of other tracks, systems, and nerves may be found.

One must not overlook involvement of several other structures producing ocular symptoms. Facial weakness or paralysis (Bell's palsy) involving closure of the eyelids, and trigeminal analgesia or parasthesia of the cornea and the anterior segment of the eye may be an early (outpost), or late manifestation of multiple sclerosis. It has been observed that sensory symptoms, which include visual, have a greater tendency to remit than do motor symptoms, which have a greater tendency to progress. Multiple are less favorable than solitary symptoms. It is quite obvious that one symptom is of doubtful significance.

We have seen that ophthalmology plays a primary and major role in multiple sclerosis. Eye symptoms were first noted and described over 100 years ago. Throughout the years since then, we have endeavored to make a diagnosis of multiple sclerosis on symptoms alone. We have found these manifestations are of no absolute diagnostic value as other lesions may produce the same symptoms. Not until the etiology is revealed, the greatest obstacle to our progress, can we definitely establish the diagnosis before autopsy confirms our suspicions.

SUMMARY

The chief ocular symptoms have been divided into two groups, visual and oculogyric.

Ocular symptoms, are found as the initial affection in about 40 % of the early cases. The optic nerve and chiasma are particularly vulnerable as is the white matter surrounding the cerebral ventricles. From the lateral geniculate body to the visual cortex we find rather frequent involvement of the optic radiations.

We find disturbances of eye movements by involvement of the white matter in the brain stem around the aqueduct of Sylvius and the fourth ventricle, affecting many nuclei and also the tracts, particularly the medial longitudinal fasciculus and cerebellar peduncles connecting these nuclei.

Examination of optic nerve sections demonstrate an acellular reaction with plaque formation. The lack of inflammatory cellular activity points to multiple sclerotic degeneration.

The optic chiasma is also a rather frequent sight of involvement.

Usually at first ophthalmoscopic evidence of affection of the visual system producing dimness or loss of vision is lacking. Later the discs frequently appear pale, especially the temporal portion containing the central nerve fibers.

We cannot determine, by the pallor of the optic discs in multiple sclerosis the amount of vision present.

Visual field studies are of great importance. With involvement of the papilla and retrobulbar optic nerve, central scotoma, possibly with peripheral extension is found. The condition is usually unilateral.

Involvement of the chiasma produces a variety of defects in both fields of considerable localizing importance.

The optic radiations are implicated most frequently in later stages of multiple sclerosis and in certain virulent types. Usually peripheral homonymous visual field less is produced as contrasted to the more frequent central involvement when the visual cortex is affected.

Although supranuclear involvement is rare, internuclear, nuclear and infranuclear disturbances occur in about one third of these affected with multiple sclerosis sometime during the course of the disease.

Studies of electromyography of the oculogyric system is revealing further information regarding the action of eye movements.

Nystagmus of the vestibular-brain stem type occurs frequently, probably in half of the patients, during the course of the disease. The usual nystagmus in multiplesclerosis is produced from lesions in the vestibular-oculogyric internuclear systems, and may be horizontal, vertical or rotatory.

It has been observed that sensory symptoms, which include visual, have a greater tendency to remit than do motor symptoms.

RESUMEN

Los principales síntomas oculares fueron agrupados en visuales y oculógiros.

Los síntomas oculares pueden existir al comienzo de la enfermedad en el 40% de los casos. El nervio óptico, el quiasma y la sustancia blanca que rodea los ventrículos cerebrales son particularmente vulnerables. Desde el cuerpo geniculado lateral a la corteza visual encontramos con cierta frecuencia lesiones de las radiaciones ópticas.

Los movimientos oculares están perturbados por haber lesiones en el tronco cerebral, en la sustancia blanca alrededor del acue-

ducto de Silvio y en el cuarto ventrículo, que afectan distintos núcleos y fibras, particularmente el haz longitudinal posterior y los pedúnculos cerebelosos que conectan los núcleos.

El examen de cortes del nervio óptico demuestra una reacción acelular con formación de placas. La falta de actividad celular de tipo inflamatorio indica el proceso degenerativo de la esclerosis múltiple. Las lesiones se observan también con frecuencia en el quiasma.

Por lo general en el comienzo no existe

en el examen oftalmoscópico evidencia de cambios anatómicos que expliquen defectos visuales. Posteriormente las papilas con frecuencia se ponen pálidas, especialmente en el sector temporal que confina las fibras centrales del nervio.

No es posible determinar, por la palidez papilar en la esclerosis múltiple, el grado de visión conservada. Los estudios del campo visual son de gran importancia. Por lesión de la papila y de la porción retrobulbar del nervio óptico, se encuentra escotoma central, posiblemente extendido a la periferia. El trastorno es habitualmente unilateral. La lesión quismática produce defectos en ambos campos visuales de gran importancia localizadora.

Las radiaciones ópticas se afectan en general en etapas tardías de la enfermedad y en ciertos tipos virulentos.

Habitualmente se produce una pérdida homónima periférica en el campo visual, lo

cual contrasta con la forma más frecuentemente central que se observa cuando la corteza visual está alterada.

En el curso de la enfermedad la tercera parte de los enfermos muestran síntomas de trastornos internucleares, nucleares o infranucleares. La lesión supranuclear es rara.

Con los estudios electromiográficos del sistema oculógiro se ha conseguido obtener nueva información con respecto a la acción de los movimientos oculares.

En la mitad de los pacientes aparece misagmus del tipo vestibular cerebral. El misagmus habitual en la esclerosis múltiple puede ser horizontal, vertical o rotatorio y es producido por lesiones en los sistemas internucleares vestibulo-oculógiros.

Se ha observado que los síntomas sensoriales, incluidos los visuales, tienen mayor tendencia a retroceder que los síntomas motores.

R É S U M É

Les principaux symptômes oculaires ont été groupés en visuels et oculistiques.

Les symptômes oculaires peuvent exister au début de la maladie pour le 40% des cas. Le nerf optique, le chiasma et la substance blanche qui entoure les ventricles cérébraux sont particulièrement vulnérables. Depuis le corps géniculé latéral jusqu'à l'écorce visuelle, nous rencontrons avec une certaine fréquence des lésions provoquées par les radiations optiques.

Les mouvements oculaires sont perturbés par des lésions dans le tronc cérébral, dans la substance blanche autour de l'aqueduc de Silvio et dans le quatrième ventricule, qui affectent différents noyaux et fibres, en particulier le faisceau longitudinal postérieur et les pédoncules cérébelleux qui connectent les noyaux.

L'examen de coupures du nerf optique démontre une réaction acellulaire avec une formation de plaques. Le manque d'activité cellulaire du type inflammatoire indique le procès dégénératif de la sclérose multiple. Les lésions s'observent fréquemment aussi dans le chiasma.

En général au début il n'existe pas dans l'examen oftalmoscopique une évidence de

changements anatomiques qui expliquent des défauts visuels. Plus tard les papilles deviennent souvent pâles, spécialement dans le secteur temporel qui confine les fibres centrales du nerf.

Il n'est pas possible de déterminer, d'après la pâleur des papilles dans la sclérose multiple, le degré de vision conservé. Les études du champ visuel sont d'une grande importance. Par une lésion de la papille et de la portion rétrobulbaire du nerf optique, on trouve le scotome central, probablement étendu jusqu'à la périphérie. Le trouble est en général unilatéral. La lésion chiasmatique produit des défauts d'une grande importance localisatrice dans les deux champs visuels.

Les radiations optiques s'affectent généralement dans des étapes tardives de la maladie et dans certains types virulents.

D'habitude il se produit une perte homonyme périphérique dans le champ visuel, ce qui contraste avec la forme plus fréquemment centrale qui s'observe quand l'écorce visuelle est altérée.

Au cours de la maladie un tiers des malades montrent des symptômes de troubles internucléaires, nucléaires et infranucléaires.

La lésion supranucléaire est plutôt rare.

Grâce aux études électromyographiques du système oculistique on a pu obtenir une nouvelle information quant à l'action des mouvements oculaires.

Chez la moitié des patients il y a une apparition de mistagmus du type vestibulaire cérébral. Le mistagmus habituel dans

la sclérose multiple peut être horizontal, vertical ou rotatif et il est provoqué par des lésions dans les systèmes internucléaires vestibulo-oculistiques.

On a observé que les symptômes sensoriels, y inclus les visuels, ont une plus grande tendance à revenir en arrière que les symptômes moteurs.

ZUSAMMENFASSUNG

Die hauptsächlichen Augensymptome werden in visuelle und Augenbewegungssymptome eingeteilt. Die Augensymptome können im Beginn der Krankheit bei 40% der Fälle vorhanden sein. Der Sehnerv, das Chiasma und die weisse Substanz, die die Hirnventrikel umgibt, sind besonders anfällig. Vom corpus geniculatum laterale bis zur Sehinde finden wir ziemlich häufig Laesionen in der Sehstrahlung.

Die Augenbewegungen sind gestört durch Laesionen im Hirnstamm, in der weissen Substanz um den Aqueductus Silvii und der vierten Ventrikel herum, wobei verschiedene Kerne und Fasern betroffen sind, insbesondere das Hintere Längsbündel und die Kleinhirnschenkel, die die Kerne unter sich in Verbindung setzen.

Das Studium der Schnitte des nervus opticus zeigt eine nichtzelluläre Reaktion mit der Bildung von Plaques. Die Abwesenheit einer zellulären Aktivität endgültigen Charakters weist auf den degenerativen Prozess bei der Multiplen Sklerose hin.

Laesionen des Chiasma werden auch sehr häufig beobachtet.

Im allgemeinen, im Beginne der Krankheit, gibt es keine ophthalmoskopischen Zeichen anatomischer Veränderungen, die die Sehstörungen erklären könnten. Später werden die Papillen häufig blass, besonders im temporalen Sektor, die die zentralen Fasern des Nerven enthält.

Durch die Abblässung der Papille bei der Multiplen Sklerose ist es nicht möglich, den Grad des erhaltenen Sehvermögens festzustellen. Die Prüfung der Sehfelder

ist von grosser Wichtigkeit. Durch die Laesion der Papille und des retrobulbären Teiles des Sehnerven ist das zentrale Skotom verursacht, welches unter Umständen bis zur Peripherie reicht.

Die Störung ist gewöhnlich einseitig. Eine Laesion im Chiasma erzeugt Defekte in beiden Sehfeldern, was für die Lokalisierung der Laesion von grosser Bedeutung ist.

Die Sehstrahlung wird für gewöhnlich in den Spätstadien oder bei gewissen virulenten Spielarten der Krankheit betroffen.

Im allgemeinen handelt es sich um einen homonymen peripheren Defekt der Sehfelder, was im Gegensatz zu häufigeren zentralen Form bei einer Affektion der Sehinde steht.

Im Verlauf der Erkrankung weisen ein Drittel der Patienten Symptome von internukleären, nukleären oder infranukleären Störungen auf. Die supranukleären Störungen sind selten.

Mit Hilfe elektromyographischer Untersuchungen der Augenbewegungsapparates hat man neue Aufklärung über die Aktivität der Augenbewegungen erhalten.

Bei der Hälfte der Patienten tritt ein Nystagmus vom zerebellarvestibulären Typ auf. Gewöhnlich ist der Nystagmus bei der Multiplen Sklerose horizontal, vertical oder kreisend; er ist durch Laesionen der internukleären vestibulo-oculären Systeme verursacht. Man hat beobachtet, dass die sensorialen Symptome, einschliesslich des Sehvermögens, eine grössere Neigung zur Rückbildung zeigen als die motorischen Symptome.

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Therapy in Multiple Sclerosis

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Treatment measures employed in multiple sclerosis consist of 1) measures directed at the primary disease process, i.e., at the lesions or their supposed cause (primary therapy); 2) measures counteracting the resulting dysfunctions and symptoms (symptomatic therapy); 3) measures against secondary complications (secondary therapy). To date therapeutic efforts in the second and third categories have been more helpful over the long range than those in the first category and still constitute the major portion of the physician's activities on behalf of the patient's welfare.

1. Primary Therapy

In the absence of knowledge of specific etiology and with only beginning comprehension even today of the possible modes of pathogenesis of the inflammatory demyelinated plaques of central nervous system white matter, efforts to achieve specific curative or preventive therapy have necessarily been empirical or based on presumptive concepts of causation. Over the past half-century numerous investigations of attempted specific therapy have been reported with favorable results. None has, however, withstood the test of time. Therapies which have largely fallen by the wayside will not be discussed, but allusions to them must be made because of continued sporadic use of some of these in different parts of the world.

Characteristics of the disease and associated problems hampering the evaluation of

treatment results have been 1) lack of a specific diagnostic test or even uniformly reliable diagnostic criteria for inclusion or exclusion of cases from clinical trials of therapy; 2) uncertainty over whether the disease is in reality a syndrome of multiple causation or a disorder of unitary etiology; 3) a chronic, highly irregular, unpredictable course often with exacerbations followed by spontaneous remissions unrelated to therapy, leading to grave difficulties in deciding whether improvement in a given subject is owing to therapy or merely coincidental; 4) the difficulties encountered in assessing the intensity of the disease process in order to provide reliable, quantitative measures of improvement or worsening; 5) the psychological peculiarities inherent in multiple sclerosis patients with euphoric and not uncommonly hysterical tendencies predisposing them to optimistic appraisal of the effects of almost any type of therapy; 6) the unlikelihood of therapeutic benefit from any measure on irreversible lesions where permanently destroyed nerve fibers have been replaced by gliosis, and the masking effect of such areas of sclerotic damage on the manifestations of fresh and potentially reversible lesions or on their response to therapy; 7) the difficulty of obtaining sufficiently large numbers of cases (several hundred) followed under carefully controlled conditions over a sufficiently long period (five to ten years) to satisfy the requirements of statistical validity.

As already indicated, critical evaluation

of many former and still used methods of primary therapy lies outside the scope of this paper and may be found in other reviews over the past decade^(1, 2, 3, 4, 5, 6, 7). It is sufficient to say that until quite recently, none of the favorably reported treatment attempts were characterized by the application of statistical principles in order to achieve reasonable scientific control of the trials of therapy and few are still advocated. These include 1) oral or parenteral use of liver extract or any of the specific vitamins, including B₁, B₁₂, and nicotinic acid and vitamin C; 2) dietary measures such as special vegetable and fruit juice preparations, high-fat diet, diets to counteract hypoglycemia, and the specific feeding of brain lipid material such as cerebroside; 3) geographic steps such as moving to a warmer climate; 4) sustained anti-coagulant therapy (with dicoumarol, heparin, and other agents); 5) parenteral histamine therapy; 6) other methods of vasodilatation, such as parenteral T E A C (tetraethylammonium-chloride), inhalation of amyl nitrite, flushing doses of nicotinic acid, alcohol, and CO₂ inhalation; 7) metabolically active substances such as adenosine triphosphate, adenosine-5-monophosphate (muscle adenylic acid), sodium succinate, pancreatic extract of heart muscle (Pancorphen); deproteinated pancreatic extract (Depropanex) and tolbutamide (Orinase); 8) anti-allergy measures such as skin or ophthalmic sensitivity tests to determine specific hypersensitivity followed by desensitization injections or food elimination diets; 9) transfusions; 10) anti-infectious agents such as antibiotics, chemotherapeutic agents, notably isonicotinic acid hydrazide (Isoniazid) and injections of vaccines allegedly specific against multiple sclerosis derived from encephalitic viral agents.

On the basis of 12 years' experience in a significantly large group of patients, considerable benefit has been alleged to accrue from the use of a rigorously restricted low-fat diet in subjects with multiple sclerosis⁽⁸⁾. The improvement is reported to consist of maintenance of an improved status of neuromuscular disability and a reduction in the frequency of relapses.

Reasonable scientific controls and the application of statistical principles enhance the value of this study.

For over a decade the value of corticotrophin (ACTH) and orally administered adrenal cortical hormones (cortisone and prednisone) in the treatment of multiple sclerosis has been disputed. These agents appear to have little place in sustained or long-term therapy⁽⁹⁾, but may exert an ameliorating effect, shortening the period of illness during acute exacerbations⁽¹⁰⁾. Theoretical considerations based on the suspected autoimmune (isoallergic) mechanism in the pathogenesis of lesions, the high incidence of raised gamma-globulin levels in the cerebrospinal fluid, the inflammatory character of the acute lesions and the known anti-inflammatory effect of these agents have lent scientific credence to their potential therapeutic value in multiple sclerosis. Unfortunately, many early reports of beneficial effects in multiple sclerosis from these substances were impressionistic and based on claims of more rapid defervescence of acute episodes than might occur spontaneously. Such evidence is notoriously unreliable because of great variability in the natural course of acute episodes. More recent investigations with somewhat better statistical control of the data have been reported^(13, 14) in an attempt to arrive at more reliable conclusions.

Evidence of dramatic therapeutic effect from these agents in human encephalomyelitis has been reported^(10, 11) but lack of controls prevents final conclusions as to whether these alterations represent responses to therapy or are coincidental. Nevertheless prevention or rapid subsidence of experimental "allergic" encephalomyelitis in animals with associated prevention or reduction of raised gamma-globulin content in the cerebrospinal fluid has provided further theoretical support for this approach to therapy.

At present, investigators who have applied some degree of scientific control in trials of steroid therapy for multiple sclerosis favor parenteral ACTH as a more effective agent than orally administered adrenocortical substance such as prednisone, whose

disadvantage lies also in the greater incidence of side-effects including post-therapy depression of adrenal function. ACTH has been administered by Miller⁽¹⁴⁾ for fresh attacks of neurologic dysfunctions whose duration was no longer than 14 days, and which have shown no signs of spontaneous regression during this period. The dosage plan consisted of the intramuscular injection of ACTH gel in amounts of 60 units twice daily for one week, reduced to 40 units twice daily for one week, followed by injections on alternate days of 60, 40, and 20 units in succession during the third and last week of therapy. Intravenous therapy was considered preferable for the acute episodes of multiple sclerosis by Wallace and Williams⁽¹⁰⁾ whose dosage plan consisted of 20 to 40 units of ACTH given daily in slow intravenous infusions for two to four weeks followed by the intramuscular injection of 20 units of ACTH gel given intramuscularly two to three times per week and tapering off to none over a variable period. Alexander and his co-workers who have quantitated their data in the therapy of multiple sclerosis with ACTH⁽¹³⁾ described the details of their dosage plan under three headings: 1) Intensive treatment phase. 2) The tapering-off phase. 3) The maintenance regimen (for rapidly progressive cases). Variable dosages and durations of treatment were employed in each of these regimens depending on the clinical course of the patients. The reader is referred to the monograph by Alexander, Berkeley, and Alexander⁽¹³⁾ (b) for details.

Personal experience and personal communication⁽¹⁵⁾ has revealed instances of spectacularly rapid recovery (within three to five days) from severe wide-spread neurologic dysfunction in acute episodes of multiple sclerosis associated with the use of massive oral doses of prednisone (200 mg. daily for one week, 100 mg. daily for one week, followed by progressive reduction in dosage at the rate of 10 mg. daily for one week and to none over the fourth week. All the necessary precautions to protect against the potentially serious side-effects were taken. Several injections of intramuscular ACTH were given after the course

of prednisone therapy, if evidence of adrenocortical hypofunction arose. It is not known, however, whether the dramatic changes in some of these patients were coincidental and related to other factors (e.g., hospitalization, rest, diminished anxiety, use of sedatives and ataraxics, etc.) or represent specific responses to steroid therapy.

2. Symptomatic Therapy

Until the benefits of any type of allegedly specific therapy can be more widely substantiated, symptomatic therapy will remain the most important aspect of the management of patients with multiple sclerosis. Such therapy is directed toward the amelioration of motor dysfunction, the alleviation of bladder and rectal dysfunction, minor help for visual disturbances, the improvement of pernicious emotional reactions and mood disorders, and the reduction of pain.

Motor dysfunction: The motor loss in multiple sclerosis consists of weakness, muscle wasting, loss of functional patterns, ataxia, intention tremor, impairment of fine skilled acts, spasticity, involuntary reflex spasms, and muscle contractures which restrict full range of motion at the joints. Techniques of physical therapy developed to counteract all these phenomena may in some cases be used to advantage. Physical therapy is of no value for the non-motor symptoms of multiple sclerosis (visual, speech, sensory, bladder, etc.) It is probably contraindicated in acute phases of the disease where rest would appear to favor reparative processes in the central nervous system. In those cases where a slow, steady downhill progression is evident, it may assist in slowing the rate of progressive motor incapacitation.

Its maximal usefulness appears to be in those patients who have residual motor disabilities but are in a relatively static phase of the disease. Here, active resistance exercises to improve power of limb and trunk muscles, daily passive stretching to counteract spasticity in order to delay inevitable contracture, and coordination exercises are helpful. Gait training, to improve efficiency and safety, and help in

learning new ways of achieving the innumerable daily acts of living are of special importance in increasing the independence of such patients.

Drugs to reduce spasticity and reflex spasms continue to be evaluated. Mephenesin (TOLSEROL) and curare are but little used for this purpose now. Chlorpromazine (THORAZINE) and meprobamate (EQUANIL, MILTOWN) have been shown to have slight muscle-relaxing properties on oral administration. The most recently developed synthetic oral skeletal-muscle relaxants, zoxazolamine (FLEXIN), methocarbamol (ROBAXIN), chlorthalidone (PARAFLEX), and carisoprodol (SOMA, RELAXIN), appear in some patients to have a fair effect in reducing spasticity and flexor spasms, but as yet no ideal agent for this purpose is available.

When spasticity is extremely severe, with hyperadduction and scissoring of the lower limbs or excessive involuntary flexion spasm, and with beginning deformity due to incipient contractures, the likelihood of regaining useful function of the lower limbs is remote. In such instances, as a measure of last resort for symptomatic help, surgical intervention is carried out. This may be selective alcohol block or surgical section of the sciatic or obturator nerves or, intraspinally, the lumbosacral nerve roots, to bring about permanent relaxation of lower limb muscles. Such procedures usually add greatly to the patient's comfort and alleviate nursing problems, though permanent paralysis of the denervated muscle groups must be accepted.

Bladder and rectal dysfunction: The lesser degrees of bladder dysfunction such as urgency, frequency and occasional mild incontinence may be effectively relieved through the use of anticholinergic drugs including the belladonna alkaloids, especially atropine, and the synthetic preparations such as propantheline (PROBANTHINE) and isopropamide (DARBIID). Though fecal incontinence is less common than urinary incontinence, these drugs similarly inhibit involuntary rectal overactivity. The more common rectal symptom of constipation has been effectively treated by use of an oral detergent, dioctyl sodium sulfosuc-

inate (DOXINATE, COLACE), and mild peristaltic stimulants such as senna derivatives (SENOKOT) or cascara. Another preparation sold commercially for the latter purpose is 1,8-dihydroxyanthraquinone (DORBANE). Many patients are able to establish quite regular bowel habits with spontaneous evacuations every second or third day through the help of these agents. In other patients regular bowel emptying is impossible save with the use of regularly given enemas, usually not more often than at two or three day intervals.

In patients with more advanced disease who have total loss of bladder control, an indwelling catheter is essential to counteract the damaging effects of chronic urinary retention. The catheter may be attached to a tidal drainage apparatus, providing rhythmic and somewhat more physiologic filling and emptying of the bladder, or simply to a dependent rubber drainage tube leading to a reservoir. Rubber urinals strapped to the thigh or leg are quite useful and practical for this purpose if the patient is ambulatory or in a wheel chair. Complications in relation to bladder disturbance are discussed later.

Visual disturbances: Patients frequently seek symptomatic help for visual disturbances. The impairment of visual acuity due to retrobulbar neuritis cannot be symptomatically helped and patients should be discouraged from seeking repeated refractions and changes of lenses. Diplopia, present as long as both eyes are open, may be eliminated by using a plastic eye shield alternately covering one eye or the other.

Mood and emotional disorders: Some patients with multiple sclerosis are euphoric and apparently in little emotional distress. Others, however seem perpetually irritable, dissatisfied, tense, apprehensive or depressed. Two aspects of psychotherapy have been stressed: 1) supportive ("morale building") and 2) corrective. The former implies a sympathetic, hopeful and encouraging attitude on the part of the physician and a willingness to help the patient cope with his incapacitation and life problems. Such therapy may be as helpful as some of the allegedly specific modes of therapy already referred to. Corrective therapy, more prop-

erly the function of the psychiatrist, aims at a deeper reorganization of the personality with the releasing of anxiety, hostility and resentment, and stimulation of emotional maturation and growth, in this way perhaps influencing the progress of the disease 16).

The long-term use of the newer ataractics or anti-depressants is justified if an ameliorating effect on the emotional disturbance can be demonstrated by trial of one of these agents. Drugs of the phenothiazine group such as chlorpromazine (THORAZINE) or of the monoamine oxidase inhibitor group such as nialamide (NIAMID) may lead to sustained improvement when anxiety on the one hand, or marked depressive features on the other, are prominent.

Pain: Though pain is an infrequent symptom in multiple sclerosis, the occasional occurrence of facial pain resembling trigeminal neuralgia demands help. High doses of orally administered nicotinic acid (100 to 200 mg. four times a day) seem in some instances to be associated with the relief of the paroxysms, but the response of this symptom to high doses of oral nicotinic acid or of parenteral vitamin B₁₂ has been quite inconsistent. Sodium diphenylhydantoin (DILANTIN) in the usual dosage (0.1 gm. three or four times a day), recently shown to be of value in tic douloureux, may be effective in paroxysmal facial pain in multiple sclerosis. Peripheral alcohol block of the involved trigeminal division as a temporary measure followed by eventual trigeminal root section has been resorted to when pain was persistent and recurrent.

3. Secondary Therapy (Treatment of Complications)

Urinary tract: The complications of bladder dysfunction are those of secondary infection, formation of bladder calculi, and obstruction of bladder drainage from encrustation of the catheter. Prevention of these complications may be assisted

through daily irrigation of the bladder with 180 to 240 cc. of 0.5 per cent acetic acid, liberal intake of liquids, substitution of clean sterile catheters at intervals, and the daily administration of an antacid such as colloidal aluminum gel, claimed to inhibit the excretion of phosphates in the urine. If there is no encrustation of the catheter and no evidence of acute infection, the catheter may be left in place indefinitely. Regular urinalysis to determine the degree of inevitable pyuria, and culture of the urine when there is systemic or local evidence of an acute flare-up of genitourinary tract infection should be carried out, followed by treatment with appropriate chemotherapeutic and antibiotic agents when indicated. These should never be given over a long period or used prophylactically.

Decubiti: When patients are chair-ridden or bedridden, decubitus ulcers sooner or later become a problem and should be treated by the usual conservative measures which will often lead to healing. These are avoidance of further pressure; application of wet dressings, antibiotic solutions or ointments; and after clearing of local infection, simply exposure to air or heat lamp followed by dry sterile dressings. Unless the patient is virtually moribund, surgical repair may be carried out, including debridement and grafting.

Pulmonary and terminal:

The complication of acute pulmonary infection is treated in the usual way. In patients with far-advanced multiple sclerosis, aspiration pneumonia or hypostatic pneumonia may be a terminal event regardless of therapy.

The elucidation of the cause of multiple sclerosis will no doubt eventually provide the best means for the development of rational therapy. Until then, the common sense of the physician, his kindness, patience and encouragement will remain major ingredients in the treatment of those afflicted.

SUMMARY

Therapy in multiple sclerosis consists of 1) measures directed at the primary disease

process; 2) those counteracting the resulting dysfunctions and symptoms; 3) measures

against secondary complications. Efforts to achieve specific curative or preventive therapy have necessarily been empirical or based on presumptive concepts of causation. Though many methods have been favorably reported, lack of scientific controls and lack of confirmation in the hands of others have caused most of these methods to fall by the wayside. These treatment attempts have consisted of liver injections, vitamins (B₁, B₁₂, C, nicotinic acid), vasodilatation (histamine, TEAC), anticoagulation, various diets, antiallergic (desensitization) treatment, metabolically active substances (ATP, succinate, tolbutamide), anti-infectious agents (antibiotics, isoniazide), and transfusions. Under current observation and with better scientific controls are still being reported favorable results from low fat diet, adrenal cortical steroids, and ACTH.

Until the benefits of any type of allegedly specific therapy can be more widely substantiated, symptomatic therapy will remain the most important aspect of management. Such therapy is directed toward motor dysfunction, alleviation of bladder and rectal dysfunction, visual disturbances, improvement of emotional and mood disorders, and the reduction of pain. Lastly, the treatment of the complications of multiple sclerosis are important. These consist of urinary tract infection and bladder calculi, decubiti, and pulmonary infection.

The elucidation of the cause of multiple sclerosis will no doubt eventually provide better means of rational therapy. Until then, the common sense of the physician, his kindness, patience and encouragement will remain major ingredients in the treatment of those afflicted.

RESUMEN

La terapéutica de la esclerosis múltiple consiste en: (1) medidas dirigidas a combatir la lesión; (2) contrarrestar los síntomas y trastornos funcionales que resultan de las mismas; (3) medidas contra las complicaciones secundarias. Los esfuerzos realizados para alcanzar una terapéutica específica preventiva o curativa han sido necesariamente empíricos o basados en presunciones con respecto a las causas. Aunque numerosos métodos han sido informados favorablemente, la falta de control científico y la falta de confirmación en otras manos, han hecho que la mayoría de estos métodos se hayan dejado de lado. Estas tentativas terapéuticas consistieron en inyecciones de hígado, vitaminas (B₁, B₁₂, C, ácido nicotínico), vasodilatación (histamina, TEAC), anticoagulantes, dietas variadas, antialérgicas (disensibilización), sustancias activas en el metabolismo (ATP, succinato, tolbutamida) agentes antiinfecciosos (antibióticos, isoniácida) y transfusiones. Bajo observación corriente y con mejores controles cien-

tíficos se mencionan todavía resultados favorables por dietas pobres en grasa, corticosteroides, y ACTH.

Hasta que se le de más fundamento a los beneficios que se obtienen de cualquiera de los tratamientos llamados específicos el tratamiento sintomático constituye lo más importante en el cuidado de estos pacientes.

Tal terapéutica está dirigida hacia la disfunción motora, alivio de la disfunción vesicular y rectal, trastornos visuales, mejora de los desórdenes emocionales y del humor, y reducción del dolor.

Por último es importante el tratamiento de las complicaciones de la esclerosis múltiple. Estas son la infección de las vías urinarias, los cálculos vesicales, las escaras y la infección pulmonar.

El hallazgo de la causa de la esclerosis múltiple dará lugar a una terapéutica más racional. Hasta entonces el sentido común del médico, su bondad, paciencia y estímulo, serán los mejores ingredientes en el tratamiento de aquellos afectados por la enfermedad.

RÉSUMÉ

La thérapeutique de la sclérose multiple consiste en: (1) des mesures destinées à

combattre la lésion; (2) contrarrestar les symptômes et les perturbations fonctionnelles.

lles qui résultent de celles-ci; (3) des mesures contre les complications secondaires. Les efforts réalisés pour atteindre une thérapeutique spécifique préventive ou curative ont été nécessairement empiriques ou bien basés sur des présomptions vis-à-vis des causes. Malgré que de nombreuses méthodes ont été favorablement informées, le manque de contrôle scientifique et le manque de confirmation en d'autres mains, ont fait que la plupart de ces méthodes aient été laissées de côté. Ces tentatives thérapeutiques ont consisté en des injections de foie, des vitamines (B₁, B₁₂, C, acide nicotinique), la vasodilatation (histamine, TEAC), des anticoagulants, des régimes variés, des antiallergiques (disensibilisation), des substances actives dans le métabolisme (ATP, succinate, tolbutamide), des agents anti-infectieux (antibiotiques, isoniazide) et des transfusions. Dans une observation courante et avec de meilleurs contrôles scientifiques on mentionne encore des résultats favorables par des régimes pauvres en graisses, en corticostéroïdes et en ACTH.

Jusqu'à ce que les bénéfices obtenus par n'importe lequel des traitements dits spécifiques aient un plus grand fondement, le traitement symptomatique constitue la partie la plus importante dans l'attention de ces patients.

Une telle thérapeutique est dirigée vers la disfonction motrice, le soulagement de la disfonction vésicale et rectale, les perturbations visuelles, une amélioration des troubles émotifs et de l'humeur, et une réduction de la douleur.

Finalement, le traitement des complications de la sclérose multiple est important. Celles-ci sont l'infection des voies urinaires, l'urcalithe, les escarres et l'infection pulmonaire.

La découverte de la cause de la sclérose multiple donnera lieu à une thérapeutique plus rationnelle. Jusque là le sens commun du médecin, sa bonté, sa patience et sa stimulation, seront les meilleurs moyens dans le traitement de ceux qui sont affectés par la maladie.

ZUSAMMENFASSUNG

Die Behandlung der multiplen Sklerose besteht aus Massnahmen 1) die auf den primären Krankheitsprozess abzielen; 2) solche die den resultierenden Funktionstörungen und Symptomen entgegenwirken; 3) Massnahmen gegen sekundäre Komplikationen. Unsere Bemühungen spezifische heilende oder vorbeugende Therapie zu erzielen waren notwendigerweise empirisch oder waren auf angenommenen Kausalbegriffen basiert. Obwohl verschiedene Methoden als erfolgreich berichtet worden sind, sind doch die meisten dieser Methoden unbeachtet geblieben aus Mangel an wissenschaftlicher Kontrolle und Bestätigung. Diese Behandlungsversuche bestanden aus Lebereinspritzungen, Vitaminen (B₁, B₁₂, C, Nikotinsäure), Blutgefässausdehnung (Histamin, TETC), Mittel gegen Blutgerinne, verschiedene Diäten, Behandlung gegen Allergien, metabolisch aktive Substanzen (ATP, Succinat, Tolbutamid), Infektionsgegenmittel, und Transfusionen.

Gegenwärtig und mit besseren wissenschaftlichen Kontrollen sind auch gute

Resultate mit fettfreien Diäten, Hormonen der Nebennierenrinde, und ACTH berichtet worden.

Bis die Vorteile von irgend einer angeblichen Spezifischen Behandlung besser bewiesen werden können, wird symptomatische Therapie der wichtigste Teil der Behandlung bleiben. Eine solche Therapie zielt auf die motorischen Störungen ab, auf die Erleichterung der Blasen- und Darmstörungen, der Sehstörungen, Gemütsstörungen, und Minderung der Schmerzen. Auch die Behandlung der Komplikationen der multiplen Sklerose ist wichtig. Diese bestehen aus Infektionen des Urinsystems, Blasensteinen, Decubiti und Lungeninfektionen.

Wenn einmal die Ursache der multiplen Sklerose erklärt sein wird dann werden ohne Zweifel bessere Wege für eine rationale Therapie gefunden werden. Bis dahin werden der Gesundenmenschenverstand des Arztes, seine Freundlichkeit, Geduld, und Ermutigung die Hauptfaktoren in der Behandlung bleiben.

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Disseminated Sclerosis in India*

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INTRODUCTION

It is an accepted fact that disseminated sclerosis is rarely seen in the tropics and subtropics. Thus Dean(7) found it rare in South Africa, and no death was reported from this cause among 500,000 inhabitants of Hawaii during the years 1951-1953(11).

There appears to be some correlation between the incidence of this disease and the latitudes and isotherms. Kurland et al (12) found it more frequent in the northern than in the southern parts of the United States, irrespective of race, occupation and social status.

Previous reports of the incidence of disseminated sclerosis in various parts of India include those of Singh et al(19), Laha and Johri(13) and Datta(6). The authors noted that disseminated sclerosis constituted 1.2 to 1.3 per cent of neurological admissions to their hospitals in Vellore (South India) and Gwalior (Central India) respectively.

Sathe(18) found that disseminated sclerosis constituted 0.8 per cent of all the paraplegias admitted to one Bombay teaching hospital and Desai(8) observed that the disease constituted 2.2 per cent of all paraplegias at another teaching hospital in Bombay.

The present study is an attempt to evaluate the incidence of disseminated sclerosis and neuromyelitis optica among patients admitted to the main teaching hospitals all over India during the years 1956-1960.

MATERIAL AND METHODS

The in-patient records of five large hos-

pitals from Bombay have been scrutinized for the years 1956-1960. Letters, with enclosed minimal acceptable criteria for the diagnosis of disseminated sclerosis, were sent to the heads of 41 medical centres all over India. Only 10 centres reported cases. Fifteen cases of disseminated sclerosis seen by one of us (E.P.B.) in private consulting practice have also been included in this series.

Only those cases were accepted where was a history of previous episodes of visual, motor, sensory or visceral disturbances, a remitting paraplegia, or a paraplegia with evidences of lesions at multiple levels of the neuraxis or of the optic nerves. Also included in this series were cases of primary retrobulbar neuritis of known aetiology and remitting brain stem lesions.

In every case appropriate neurological investigations had been carried out to exclude other neurological diseases commonly met with in this country.

RESULTS

In all, 151 cases have been provisionally accepted as disseminated sclerosis (including 17 cases of neuromyelitis optica). Another 155 cases which were diagnosed as disseminated sclerosis have not been included in this series for lack of sufficient data. Only 73 cases, about whom complete details were available, were considered for analysis.

Geographic Distribution

There seems to be a pretty even scatter of cases of disseminated sclerosis all over India with the exception of Bombay, Delhi and Madras.

* Part of this paper was read at World Congress of Neurology, at Rome (1961).

TABLE 1

**Geographic distribution of 151 cases with incidence
among neurological diseases.**

Investigator	Place	Latitude (°N) Approx.	Total No. of neuro- logical admissions	Disseminated sclerosis	
				Total No.	Per cent of neurological admissions
Present series	Bombay	19	16,064	45*	0.19
Singh B. ⁽²⁰⁾	Delhi	29	2,912	32	1.10
Arjundas G. ⁽²⁾	Madras	13	—	42	—
Akbar Ali ⁽¹⁾	Indore	23	—	10	—
Laha P. N. ⁽¹⁴⁾	Gwalior	26	—	8	—
Desai N. ⁽⁹⁾	Ahmedabad	23	—	3	—
Heilig R. ⁽¹⁰⁾	Jaipur	27	—	4	—
Chuttani P. N. ⁽⁵⁾	Amritsar	31	—	3	—
Basavaraj N. ⁽³⁾	Mysore	12	—	2	—
Vengsarkar S. G. ⁽²¹⁾	Pondicherry	12	—	2	—

* Including 15 cases seen in private consulting practice during the same five year period.

Delhi, situated in the northern part of India and with a much smaller number of neurological admissions, showed a greater incidence of disseminated sclerosis than Bombay and probably also Madras. This finding may not be of any significance in view of conflicting observations of other authors(19),(13),(6).

Age and Sex Incidence

The highest incidence of this disease was in the third and fourth decades (66.2 per cent), which is in accordance with figures from Western countries(22). The male to female ratio was 3:1 as against 1:1.5 to 2 observed by Western investigators(15).

Neuromyelitis optica and Disseminated Sclerosis

Of the total of 151 cases there were 17 (11.3 per cent) of neuromyelitis optica indicating that disseminated sclerosis is by far the commoner of the two diseases. However, cases with retrobulbar neuritis

alone (8 cases) have been regarded as variants of disseminated sclerosis.

Disseminated sclerosis and Motor Neurone Disease

During this five year period there were 47 cases of motor neurone disease as opposed to 30 cases of disseminated sclerosis in the Bombay Hospital series showing that the incidence of motor neurone disease is one and a half times greater than that of disseminated sclerosis. The former was selected for comparison as it is not a rare disease of the central nervous system encountered in India, and it allows of ready clinical diagnosis.

CLINICAL FINDINGS

First symptom

The commonest initial symptom was limb weakness, especially of the legs (41.0 per cent). Ocular symptoms occurred at the onset in 31.2 per cent and limb paraesthesiae in 13.2 per cent of cases.

TABLE 2

Initial symptom in 61 cases of disseminated sclerosis.

First symptom	Present series		Brain(4) Per cent
	No. of cases	Per cent	
Weakness of limb(s) involving	25	41.0	48.0
Both lower limbs	16	26.3	18.0
One lower limb	6	9.8	14.0
One upper and one lower limb	2	3.3	9.0
All four limbs	1	1.6	7.0
Ocular symptom(s)	19	31.2	28.0
Blurring of vision	12	19.7	24.0
Double vision	7	11.5	4.0
Paraesthesiae	8	13.2	11.0
Miscellaneous symptoms			
Vertigo	3	4.8	2.0
Epilepsy	1	1.6	1.0
Dysarthria	2	3.3	—
Sphincter disturbances	3	4.8	—

As is seen from Table 2 these findings correlate closely with those of Brain(4). One case presented with focal seizures affecting the left half of the face and left arm and leg.

CLINICAL FEATURES

Only 8 cases (16.7 per cent) did not show remission and 7 of these, showed features of multiple levels of involvement of the neuraxis.

TABLE 3

Salient clinical features in 53 cases of disseminated sclerosis.

Clinical features	Present series		Merritt(16) Per cent
	No. of cases	Per cent	
Symptoms:			
Blurring of vision	18	33.3	
Diplopia	18	33.3	21
Paraesthesiae	23	43.8	32
Limb weakness	46	84.0	54
Sphincter disturbances	17	32.9	7
Signs:			
Euphoria	5	9.1	34
Pallor of optic discs	19	33.8	32
Dysarthria	14	27.8	26
Nystagmus	21	38.9	68
Pyramidal signs	48	89.1	89
Posterior column signs	11	22.2	47
Cerebellar signs	26	49.8	43
Remission of one or more of above	45	83.3	

In the only case of progressive spastic paraplegia without remissions or evidences of dissemination of lesions, the diagnosis

of disseminated sclerosis was made because of the association of an intention tremor in the arms and spasticity in the legs.

CLINICAL TYPES

The classical or generalized type was by far the commonest (52.7 per cent). This included cases of paraplegia, with in addition, evidences of multiple lesions, such

as intention tremor, nystagmus or retrobulbar neuritis. In many cases there was a history of previous episodes of motor, sensory, sphincter or visual disturbances.

TABLE 4

Various clinical types in 61 cases of disseminated sclerosis.

N.o	Clinical types	Present series		Wilson (22) Per cent
		No. of cases	Per cent	
1	Classical or generalized	32	52.7	36.3
2	Cerebellar	8	13.1	4.8
3	Amaurotic or retrobulbar	8	13.1	10.9
4	Cerebral	6	9.6	3.6
5	Progressive spastic paraplegia	1	1.7	38.7
6	Brain stem	5	8.1	4.8
7	Acute disseminated sclerosis	1	1.7	—

The striking feature seen in Table 4 is the much less frequent occurrence of progressive spastic paraplegia in the present series (1.7 per cent) as compared with Wilson's (22) combined series (38.7 per cent). In a country where disseminated sclerosis is as rare as it is in India, this diagnosis is never made in a case of paraplegia unless other manifestations are present (when it becomes of the generalized type) or when remissions are present, when ipso facto it ceases to be of "the steadily progressive type".

What is also apparent is that the cerebellar, cerebral and brain stem types are much more frequently met with in India than in the West.

DISCUSSION

As was the experience of Okinaka et al (17) in Japan, we have found that disseminated sclerosis in this country presents pictures which are often atypical as compared with the disease as it occurs in Great

Britain and the United States. In two young females in this series a large number of symptoms with a paucity of physical signs, when seen initially, made us suspect a psychogenic origin of symptoms. In this country, young adults who present a mixed picture of pyramidal and cerebellar involvement are usually "labelled" as hereditary ataxia. In older individuals, a cerebellar degeneration is suspected (either primary or secondary to malignancy) rather than disseminated sclerosis. When cerebellar and pyramidal symptoms are of acute onset, an infective or toxic affection of the central nervous system is considered in preference to disseminated sclerosis. It is therefore only the most typical of cases with dissemination of lesions in both space and time which permit the diagnosis of disseminated sclerosis.

The question of remissions is also a vexing one. Very often a young individual gives a history of a short bout of fever followed by hemiparesis or paraparesis which becomes complete within 2 to 3 weeks and

then improves, the recovery being complete (according to the patient) within 2 to 3 months. Such patients often give a history of several such episodes with varying degrees of improvement, and by the time they are seen by a neurologist (for the first time) there is a well marked spastic paraplegia or hemiplegia with perhaps cerebellar signs in the arms. Are these cases to be regarded as disseminated sclerosis?

Then again there are seen in hospital and in private practice cases of retrobulbar neuritis without any demonstrable cause, occasionally these are accompanied by papillitis. Are all of these to be regarded as the amaurotic variety of disseminated sclerosis? There has been no follow-up of

the 8 cases of retrobulbar neuritis in the present series and it is not known if any of them has developed paraplegia.

Finally it must be borne in mind that the criteria of selection themselves modify the clinical picture to some extent, and that variations in regional incidence of the disease are not only an indication of absolute differences of frequency in these different areas but are also an index of the willingness of the population in seeking prompt medical advice and of the diagnostic bias of the medical personnel concerned. It is against this background that one must evaluate the frequency of visual disturbances and remissions, the rarity of progressive spastic paraplegia and the high incidence of the disease in males in the present series.

SUMMARY

Disseminated sclerosis is said to be infrequent in the tropics.

The present paper attempts a preliminary survey of the incidence of this disease among admissions to the larger hospitals all over India during the years 1956-1960.

In this combined Indian hospitals series there were 151 cases where the diagnosis of disseminated sclerosis could be made with reasonable certainty.

Among these 151 cases, in 17 a diagnosis of neuromyelitis optica was considered. This indicates the much greater frequency of disseminated sclerosis.

Disseminated sclerosis constituted 0.19% of 16,064 total neurological admissions in Bombay, while it formed 1.1% of 2,912 neurological cases in Delhi.

The age incidence of the present series is similar to that of western observers. However, the sex incidence indicates a much greater predilection for males.

In the present series the incidence of motor neurone disease in Bombay was two or three times greater than that of disseminated sclerosis in the years 1956-57-58, but in 1959 and 1960 the two diseases had an almost equal incidence.

The commonest clinical type was the classical or generalized form as is the case in the west. However, the cerebral, cerebellar and brain-stem forms are very much commoner in India, while the progressive spinal type is less frequently met with.

RESUMEN

Se afirma que la esclerosis diseminada es infrecuente en los trópicos.

En este trabajo se hace un estudio preliminar de la frecuencia de esta enfermedad analizando las admisiones en los grandes hospitales de la India durante el período 1956-1960.

En las series obtenidas en los hospitales de la India se encontraron 151 casos en los

cuales el diagnóstico de la esclerosis diseminada pudo ser hecho con razonable certeza.

Entre estos 151 casos, el diagnóstico de neuromielitis óptica fue comprobado en 17 casos. Esto indica la mayor frecuencia de la esclerosis diseminada.

La esclerosis diseminada forma el 0.19% de las 16,064 admisiones en los servicios

neurológicos en Bombay, mientras que constituye 1.1% de los 2,912 casos de Delhi. La distribución por edad es casi la misma que la publicada en los países occidentales. Sin embargo en la India existe una predisposición evidentemente mayor para el sexo masculino.

En este estudio observamos que la frecuencia de la lesión de la neurona motora en Bombay fue dos o tres veces mayor que la de la esclerosis diseminada en los años

1956, 1957 y 1958, pero las dos enfermedades tuvieron una frecuencia casi igual en 1959 y 1960.

La forma clínica encontrada más a menudo fue la forma clásica, generalizada, tal como ocurre en los países occidentales. No obstante las formas cerebral, cerebelosa y de tronco son mucho más comunes en la India, mientras se encuentra con menos frecuencia la forma espinal progresiva.

R É S U M É

On dit que la sclérose disséminée est bien rare dans les pays tropicaux.

Ce travail essaye dans la forme d'un rapport préliminaire d'estimer la fréquence de cette maladie en analysant des admissions dans quelques des plus grands hôpitaux aux Indes pendant les années 1956-1960.

Dans cette groupe composée des cas observés dans les hôpitaux aux Indes on a trouvé 151 cas, dans lesquels la diagnose de la sclérose disséminée peut être faite avec certitude raisonnable.

Parmi ces 151 cas, la diagnose de neuro-myelitis optica fut constatée dans 17 cas. Cela représente une plus grande fréquence de la sclérose disséminée.

La sclérose disséminée forme 0.19% de tout les 16,064 cas admis dans les services neurologiques en Bombay, tandis que en

Delhi ces cas forment 1.1% des 2,912 cas admis. La distribution de l'âge est presque la même que celle publiée dans les pays occidentales. Mais aux Indes il y a une prédisposition bien évidente pour les hommes.

Dans cet étude la lesion du neurone motrice en Bombay fut deux ou trois fois plus fréquente que la sclérose disséminée dans les années 1956, 1957 et 1958, mais la fréquence des deux maladies fut presque la même dans les années 1959 et 1960.

La forme la plus fréquemment rencontrée fut la forme classique, généralisée, comme on la voit dans les pays occidentales. Mais des lesions cérébrales, du cervelet et celles du myelencephale et du metencephale sont beaucoup plus fréquents aux Indes, tandis que la forme spinale progressive est moins fréquente.

Z U S A M M E N F A S S U N G

Es wird behauptet disseminierte Sklerose vorkomme selten in Tropen.

Die vorliegende Arbeit ist ein Versuch die Häufigkeit dieser Krankheit vorläufig festzustellen. Zu diesem Zweck wurden die zu grösseren Krankenhäusern aufgenommene Kranken in gesamt Indien in den Jahren 1956-1960 analysiert.

In diesem Krankengut, das aus verschiedenen Krankenhäusern Indien zusammengesetzt wurde, fanden wir 151 Fälle, in denen die Diagnose der disseminierten Sklerose mit zuverlässiger Sicherheit festgestellt konnte.

Unter diesen 151 Fällen 17 wurden als

Neuromyelitis optica bezeichnet, was eine viel grössere Häufigkeit von disseminierten Sklerose bedeutet.

Disseminierte Sklerose ist für 0,19% von allen 16,064 Kranken, die in Bombay in die neurologischen Abteilungen aufgenommen waren verantwortlich, in Delhi dagegen für 1,1% von den 2912 aufgenommenen Nervenkranken.

Die Altersverteilung aller beobachteten Kranken ist ähnlich wie in den von Autoren im Westen veröffentlichten Statistiken. Aber die Geschlechtsverteilung aufweist eine viel grössere Predilektion für Männer.

Im beobachteten Krankengut in Bombay

war die amyotrofische laterale Sklerose zwei bis dreimal so häufig als die disseminierte Sklerose in den Jahren 1956, 1957, 1958, aber in den Jahren 1959, 1960 war die Häufigkeit beider Krankheiten beinahe die gleiche.

Die klassische generalisierte Form war das häufigste klinische Bild, wie es auch im Westen gibt. Die zerebrale, zerebellare und Hirnstammform ist aber hier viel häufiger, dagegen die progressive, spinale Form viel seltener.

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Personality

Prof. H. HOUSTON MERRITT

Few lives are so abundant in achievements as the one of Prof. H. Houston Merritt's at present Dean of the Medical School of Columbia University.

Due to his inquisitive mind a large part of the patients afflicted with epilepsy have been freed from this heavy burden or at least alleviated.

Cycles and rhythms govern every biological phenomenon: heart beat, respiration and brain electrical waves etc.



Only in great Symphonies can man grasp a faint glimpse of the inner harmonies that permeate life. Like a giant organism, cosmic life vibrates in its own rhythm and so every living cell whether in the leaves, in the blood, in the water or the air. Electrically charged they constitute hundreds of small rhythms within bigger ones.

One of the most dramatic ailments is generated by the discordance of electrical impulses that govern the silent functioning of the brain.

From ancient times, epilepsy has been a curse to mankind. Like lightning it strikes man and its appearance is frightening. See the shuddering twitching figure, the convulsively working jaws.

Nobody can help him.

Only a miracle can free him from his suffering and it is related to the Bible: "And one of the multitude answered and said, Master I have brought unto thee my son, which hath a dumb spirit. And wheresoever he taketh him, he teareth him: and he foameth, and gnasheth with his teeth, and pineth away, and I spoke to thy disciples that they should cast him out, and they could not."

"He answered him, and saith o faithless generation, how long shall I be with you? How long shall I suffer you? Bring him unto me. And they brought him unto him and when he saw him, straightway the spirit tare him; and he fell on the ground, and wallowed foaming. And he asked his father. How long is it ago since this came unto him? And he said of a child. And of time it hath cast him into the fire, and into the waters, to destroy him: but if thou canst do any thing, have compassion on us, and help us.

"Jesus said unto him, if thou canst believe, all things are possible to him".

"And straight away the father of the child cried out, and said with tears, Lord, I believe, help thou mine unbelief.

When Jesus saw the people running together, he rebuked the foul spirit, saying unto him. Thou dum and deaf spirit, I charge thee, come out of him, and enter no more unto him.

And the spirit cried, and rent him score, and came out of him, and he was as if dead, insomuch that many said, He is dead. But Jesus took him by the hand, and lifted him up and he arose".

The accurate description of a grand mal attack reminds us of the fact that nowadays, thanks to anticonvulsive drugs, the biblical miracle is repeated by thousands of practitioners all over the world. Since the discovery of Dilantin by Merritt and Putnam 25 years ago by applying the method of scientific inquiry, more progress has been made toward the understanding of the nature of epilepsy and its control, that had been made in the previous twenty-three centuries.

The use of Dilantin in Epilepsy has been one of the most important conquest of recent decades.

The advances in electrophysiology has contributed in a great measure to the knowledge of the mechanism of the brain function in epilepsy.

The EEG is an accurate tool for correct diagnosis and for localization of the electrical focus, and helps the surgeon engaged in its extirpation. But for the great mass of epileptic patients the discovery of most practical importance has been Dilantin because is useful not only to control the crisis, but to aid and diminish the dose of that other great antiepileptic, luminal. In this way the lethargic effect of luminal could be avoided and a more useful citizen returned to society.

From 1937 when Merritt and Putnam presented their first paper on anticonvulsive drugs, to November of 1945 over 700 compounds were tested. In this way they seemed have followed the wise words of Paracelsus "But we shall free the art of Medicine from its worst errors. Not by following that which those old taught, but with our own observation of nature, confirmed by extensive practice, and long experience."

With the discovery of Dilantin the practitioner has in his hands a medicine that like insulin aims to control the entire illness, keeping through its administration the patient within the boundaries of normalcy.

Moreover, since then new products have been discovered, and new vistas of epilepsy have been taken, more research has been encouraged, and social medicine has taken under its care the task to illustrate the general public about the one item called the "Sacred Disease". No doubt the hope that the discovery of Dilantin brought to this ailment is responsible for the different place that epileptic people have in our Society today.

We will not just refer to the discoveries and achievements of Dr. Merritt in this article, let us quote the wise words of Prof. George Sarton one of the greatest modern historians of Science "However, more lists

of discoveries and achievements are to the history of medicine hardly more than a skeleton is to a living body. *Discoveries may be important but personalities are infinitely more so*".

OUR ENCOUNTERS WITH DR. MERRITT

It was the beginning of 1947. Our training in the Yale Laboratories of Neurophysiology under Dr. Fulton, reached its end. And there we were talking with John Fulton in his office, about our plans for the future. It was our intention to go to a clinical service, to refresh our Neurology after concentrating on laboratory animals and being away from the care of our patients for more than a year. When we asked Dr. Fulton for advice he answered without hesitation, "Go with Merritt. He is one of the best clinicians of contemporary Neurology."

With an introductory letter, we went to the Montefiore Hospital and working with Merritt proved to be the most enlightening experience that we had in American Neurology.

Everyday early in the morning, after almost an hour of noisy rattling and bouncing on the 8th Av. subway, we arrived at the old Montefiore Hospital.

There, a group was waiting to go the rounds with Dr. Merritt, young physicians, residents, talking about some of the cases that were puzzling their minds. Many of them, just discharged from the Army, often chatted about war experiences or trophies they had from the battle field.

In a few moments all of them had surrounded Dr. Merritt and were greeting and smiling at him. The rounds began, among the young doctors that accompanied the "Chief" were Melvin Yahr, Sid Carter, Danny Sciarra, Joe Ransohoff, David Freeman, and many others. Merritt stopped at a bed. The clinical history is droned off by a resident, and several direct brief questions shot by Dr. Merritt gave us a hint that the diagnosis is on its way. The neurological examination is brief, all the unnecessary procedure discarded, and the diagnosis is reached with the precision of the one accustomed to always hitting the bullseye.

The clinical intuition that makes a real doctor is one of the gifts of Dr. Merritt.

In deep concentration, silently smoking his pipe, more than hearing we would say he usually absorbs a medical problem. He doesn't talk much, just the precise words following his inner thoughts and in many clinical pathological conferences the new doctors do not dare to stick their necks out or venture a diagnosis of a difficult problem without "smelling" what Dr. Merritt has in mind.

Friendly without losing authority, Dr. Merritt was loved by everyone of his collaborators. He was prompt to listen any request, to simplify any difficulty, and to give all the facilities of a well equipped Neurological service to those anxious to perfect their knowledge at the Montefiore Hospital.

His seriousness many times fooled us. In a solemn discussion he would suddenly slip in a humorous remark then his whole appearance would suffer a transformation.

The burst of laughter brightened his eyes, and he regains a boyish expression full of joy and zest of living. His rectitude his loyalty to the ideals of human brotherhood, his unselfish devotion to science, through books and teaching, has taken him to the highest position in Neurological Science. And today as a testimony of devoted affection to the "Chief", many of the one time residents of Montefiore Hospital now with a well won reputation of their own as distinguished neurologists still accompany

him, at Columbia University, where Dr. Merritt holds the rank of Dean. We can not close this remembrance of Montefiore Hospital without recalling those contemporaries who along with Dr. Merritt made it a world-known center of Neurological Science. There was Dr. Leo Davidoff an outstanding neurosurgeon whose neuroradiological sessions were very much praised by all of us. Dr. H. Zimmermann and Dr. M. Netsky, who beautified Neurology through colorful and enlightening slides; Dr. M. Rheimberger a well known electroencephalographist, lost to science through happy marriage. For everyone of us the Montefiore stay, left happy memories and a fruitful experience.

More than twenty years ago Charlotte Buhler, Professor at the University of Vienna and afterwards at Clark University (U.S.A.) wrote a book "Der Menschliche Lebenslauf als Psychologisches Problem", in which this well known psychologist, studied human life from a panoramic view point. In it she analyzed the lives of artists, statesmen, writers and scientists, drawing a chart on which the different peaks of the life span were shown. Were she studied Dr. Merritt's life the chart will show endless ascension.

HIS SCIENTIFIC LIFE

Born in Wilmington, North Carolina, Hiram Houston Merritt came in this world on January 12, 1902, son of Hiram Houston Merritt a businessman, and Dessie Cline Merritt. He attended the public school of native city, and while in high school he worked as a secretary of an accountant (maybe he derives from this early experience his spirit of exactness).

From 1919 he attended the University of North Carolina, and later he received his A.B. at Vanderbilt University in 1922. He studied Medicine at John Hopkins University where he earned his M.D. degree (1926).

The intership was spent at New Haven Hospital, Connecticut, where he was assistant resident in medicine from 1927-28.

Then he moved over to Harvard to spend one year as a resident in Neurology, and then as an assistant in Neuropathology at the medical school itself.

Thus his training was enriching his experience. But Europe was at that time a lure to young American neurologists and H. Houston Merritt went to Germany to spend one year at the Deutsche Forschungsanstalt in Munich, with a fellowship from the National Research Council.

Married from 1930 with Mabel Carmichael. He and his wife has won everlasting friends due to their friendship and sympathy toward everyone who share any period of their life.

Upon his return to the United States he again became associated with Harvard Medical School, and step by step was ascending, assistant, instructor, assistant professor, reaching in 1942 the post of associate professor of Neurology. For a decade Dr. Merritt was visiting neurologist of Boston City Hospital, and from 1939-44 consultant in neurology at Peter Bent Brigham Hospital. He then went to New York and since 1944 has remained as one of the leading figures at Columbia University. Until 1948 he was professor of clinical neurology and subsequently professor of neurology at the University's College of Physicians and Surgeons. From 1944 to 1948, he was also chief of the division of Neuropsychiatry at Montefiore Hospital (New York) and since 1948 has been Director of the Service of Neurology, Neurological Institute of the Presbyterian Hospital.

He was acting dean of the medical faculty there and acting vice-president in charge of medical affairs in 1958-59 becoming dean of the

Faculty of Medicine, Columbia University and vice-president in charge of medical affairs in the latter years.

In addition to his outstanding performance as professor at Columbia University, he has made valuable contributions to medical literature.

The widely read Neurological books written by Dr. Merritt, have also the unmistakable seal of his personality. From cover, to cover, his clear thinking in precise words gives the reader the most complete and accurate information about the subject matter. Thus, *The Cerebrospinal Fluid* (1937) with Frank Fremont Smith, *Neurosyphilis* (1946) with Raymonds D. Adams and Harry C. Salomon; "Fundamentals of Neurology" (1948) with Fred Mettler and Tracy J. Putnam (q.v.); "Headache" (1959) with Arnold Friedman; *A Textbook of Neurology* (1955) of which he was the sole author, appearing in a revised second edition in 1959.

It can be said that Dr. Merritt has contributed through his books to world neurological education, and every self-respecting neurologist has long since had his books enhancing his library. To this we must add more than 200 medical articles into which he poured his investigations on cerebrospinal fluid, brain vascular diseases, neurosyphilis, anticonvulsant drugs etc.

In the Republic of Plato, Socrates discusses the qualities that must have a ruler, and amongst other considerations, he finds that there must be "men intelligent in their business and capable, besides careful for their city. The most learned, must be chosen, and under their wise guidance the Republic flourish". So when Columbia University chose Dr. Merritt as a Dean of the Faculty of Medicine, the Socratic spirit of a good government prevailed.

It is not a rare coincidence that the Hebrew word that means to know also means to govern, as a deep philosophy embraces the relationship between both words. Several institutions have requested his valuable cooperation.

Prominent in philanthropic and civic activities related to medicine, Dr. Merritt has served with the study section on mental health of the U.S. Public Health Service during 1940-50; as consultant, Advisory Committee to the Administrator of the Veterans Administration, during 1950-56; as vice-president of the United Cerebral Palsy Associations, Inc. since 1950 and chairman of its medical professional advisory board; with the National Advisory Neurological Diseases and Blindness Council of the U.S. Public Health Service from 1951 to 1960, and as chairman of its program planning committee since 1956; as chairman of the medical advisory board, United Epilepsy Association, since 1954; as vice-president of the International League Against Epilepsy since 1955; as chairman of Honorary Consultants to the Surgeon General of the United States during 1956-58. At other times he has been active in behalf of the medical advisory boards of the Muscular Dystrophy Association and the National Foundation for Infantile Paralysis; as vice-president of the medical advisory board, Parkinson's Disease Foundation; as chairman of the committee on the nervous system, National Research Council; and as a member of the national committee for revision of the United States Pharmacopeia.

During the Second World War he was a consultant to the U.S. Army Specialised Training Program and the U.S. Navy Student Training Program from 1942-44, and member of the Dean's Screening Committee, U.S. Navy.

An honorary A.M. degree was conferred on him by Harvard University in 1942. He holds honorary membership in the Societe Francaise

de Neurologie, Boston Society of Psychiatry and Neurology, and Philadelphia (Pennsylvania) Neurological Society. A diplomate of the American Board of Psychiatry and Neurology, from 1942 to 1950 Dr. Merritt was a director and in 1950 its president. He also is a fellow of the New York Academy of Medicine, and member of the American Neurological (President 1956-57), American Psychiatric, and American Medical Associations, Association for Research in Nervous and Mental Disease (Pres. 1952), American Society for Clinical Investigation, American Academy of Neurology, American Association of Neuropathologists, American League Against Epilepsy, New York Neurological Society, the Massachusetts Medical Society, the Medical Society of the State of New York, the Cosmos Club of Washington, D.C., and the Century Association and University Club, both of New York city. Vice-president of the Sixth International Neurological Congress, Brussels, Belgium, and in 1961, Vice-president of the seventh such congress held in Rome.

Many Universities abroad have given him honorary degrees; Societies of Neurology have appointed him as Chairman, and during the last two decades, we can affirm that Dr. Merritt has been one of the most esteemed figures as a leader of contemporary Neurology.

Taking a panoramic view of Dr. Merritt activities one can see that heavy impact has been made in diverse directions.

In applied science he discovered an important therapeutic drug.

In education he has authored many books all widely read; has been Professor of Neurology in leading institutions and presently is Dean of Columbia University Medical School.

In his speciality he has been a propelling force in Neurological science occupying leading posts in many Neurological Foundations and Societies.

And for the last two decades Dr. Merritt has been and continues to be one of the foremost specialists in National and International circles, and a highly respected leader in contemporary neurology.

VICTOR SORIANO.

• News

THE FIRST ASIAN AND OCEANIAN CONGRESS OF NEUROLOGY NIPPON TOSHI - CENTER HALL, AKASAKA, TOKYO

October 7 to 10, 1962

The Organizing Committee: Chairman: Prof. Shigeo Okinaka; *Secretaries:* Dr. Tadao Tsubaki, Dr. Hirotaro Narabayashi; *Office:* The Third Department of Internal Medicine; Faculty of Medicine University of Tokyo Japan.

ANNOUNCEMENT

1. *The First Asian and Oceanian Congress of Neurology* will be held at *Nippon Toshi-Center Hall*, Akasaka, Tokyo, from October 7 to 10, 1962 under the auspices of the *Asian and Oceanian Association of Neurology (AOAN)*. This congress is supported by the *Japanese Society of Neurology*, the *World Federation of Neurology* and by the Grant N° B-4039(R1) of the *National Institute of Health*, Bethesda, U.S.A.

2. This Association (AOAN) was founded June 26, 1961 in Tokyo at the planning meeting for this Congress, under the support by the *World Federation of Neurology*.

3. President of the Congress will be Professor Shigeo Okinaka.

4. All communications from abroad regarding the Congress should be addressed to: Professor Shigeo Okinaka, M. D. The First Asian and Oceanian Congress of Neurology; The Third Department of Internal Medicine; Faculty of Medicine, University of Tokyo Hongo, Tokyo.

5. Topics of symposia and schedules of the Congress are listed below.

6. Registration: Registration for the Congress has started January 1, 1962 and ends at the noon of the second day of the Congress, i.e. October 8, 1962. Registration fee is of the amount of 5,000 Japanese Yen (approximately 14,00 U.S. Dollars), which will include registration, program and abs-

tracts of papers. This fee should be paid at the time of registration by cash, check or draft.

7. Presentation of Papers: A) Those who are scheduled to present papers at the Congress are requested to contact with the main desk in front of the Hall, and to give the slides or films, at the latest, until two hours before presentation. Speakers, whose presentation will be in the morning session, should give their slides within the afternoon before the day of presentation. B) *Size of slides:* Please prepare your slides in "35 mm. size", which can be most easily projected. Other sizes can be used, "if the size is specified immediately". C) Time Allowance for each paper, both in Symposia and in Scientific Sessions, is ten minutes, except for a few papers. Due to heavy crowdedness of papers, this time limitation should be kept very strictly, and your cooperation is cordially expected. As a rule, there will be no allowance for free discussions, but this depends on the decision by the chairman of each topic.

8. Hotel Reservation and Excursion Program: These will be taken care by Japan Travel Bureau. It should be emphasized that October is the busiest season for sight seeing in Japan and hotels rooms are very difficult to obtain without exact reservation.

9. Social Events: (Sun.) October 7th, 6:00 P.M. Get Together Party at Chinzan-So Restaurant (informal). (Mon.) October 8th, 6:00 P.M. Invitation by the President at Ryu-En Restaurant. (Tue.) October 9th, 6:00 P.M. Visit to Koku-Sai Theatre, famous Girl's Revue.

10. Ladies Committee: There is a very attracting ladies program.

11. Business Meeting in the Afternoon of October 6 will be held in the Room B of Nippon Toshi Center. As in Article 7 of the Statutes of *The Asian and Oceanian Association of Neurology*, which was formed June 26, 1961, two delegates from each member-country are invited to attend the Business Meeting. Observers of the limited number are permitted to attend.

12. *The 21st Annual Meeting of the Japan Neurosurgical Society* will meet on October 19 through 21, in Ise-City, Mie-Prefecture, which is about seven hour train ride from Tokyo. Members and Guests of the First Asian and Oceanian Congress of Neurology are cordially invited to attend this Meeting.

SCHEDULE OF SCIENTIFIC SESSIONS AND SYMPOSIA

Room A

Sunday, (October 7). - Opening Ceremony 8:00 to 8:40. Symposium A: Neuroepidemiology (A1 - A15) 8:40 - 12:00. Lectures by the Honored Guests 13:00 - 17:00.

Monday, (October 8). - Symposium B: Cerebrovascular Diseases I (B1 - B11) 9:00 to 12:00. Symposium B: Cerebrovascular Diseases II (B12 - B26) 13:00 - 17:00.

Tuesday (October 9). - Scientific Session (Nº 101 - 112), 9:00 - 12:00. Symposium E: Infectious, Parasitic, and Inflammatory Diseases (E1 - E18) 13:00 - 17:00.

Wednesday (October 10). - Symposium F: Nutritional, Toxic and Metabolic Diseases (F1 - F12) 9:00 - 12:00. Scientific Session (Nº 150 - 163) 13:00 - 17:00.

Room B

Saturday, (October 6). - Business Meeting: 13:00.

Monday (October 8). - Symposium C: Neuroradiology (C1 - C12) 9:00 - 12:00.

Symposium D: Epilepsies (D1 - D13) 13:00-17:00.

Tuesday (October 9). - Scientific Session (Nº 113 - 122) 9:00 - 12:00. Scientific Session (Nº 123 - 137) 13:00 - 17:00.

Wednesday (October 10). - Scientific Session (Nº 138 - 149) 9:00 - 12:00. Symposium G: Neurophysiological Topics (G1-G16) 13:00 - 17:00.

TOPICS OF SIMPOSIA

A) Neuroepidemiology: Demyelinating Disorders; Motor Neuron Diseases; Kuru.

B) Cerebrovascular Diseases: Incidence; Anatomy and Pathology; Clinical Aspects; Radiological Study and Neurosurgical Treatment.

C) Neuroradiology: Radiology of posterior fossa tumor; Iodo-ventriculography; Pneumoventriculography; Myelography; Miscellaneous.

D) Epilepsies: Incidence; Clinical study and treatment; Neurosurgical aspects.

E) Infectious, Parasitic and Inflammatory Disorders; Encephalitis; Postvaccinal Encephalomyelitis; Cerebral cysticercosis; Cerebral Paragonimiasis; Tuberculosis; Miscellaneous.

F) Nutritional, Toxic and Metabolic Disorders: Lathyrism; Manganese Intoxication; Minamata Disease; Hepato-Cerebral Diseases.

G) Neurophysiological Topics: Limbic System; Spinal Moto-neuron; Gamma System; Metabolism and Cerebral Function.