# International Journal of Neurology

ISSUE DEDICATED TO:

## MENINGITIS

VOLUME 4 NUMBER 2

# INTERNATIONAL JOURNAL OF NEUROLOGY

**CONTENTS OF VOL. 4 — NUMBER 2:**

# Editorial

Cuando un clínico tiene ante si un paciente afectado de meningitis, los problemas a resolver son varios y definidos: 1º, Debe procurarse desde el comienzo un diagnóstico etiológico acertado. 2º, El tratamiento tiene que ser correcto y aplicado lo más cerca posible del comienzo de la enfermedad. 3º Búsqueda del foco séptico que pudo dar origen a la meningitis. 4º En la evolución de la enfermedad debe reconocerse las manifestaciones de sufrimiento del parénquima nervioso. 5º Se procurará impedir las secuelas, y si ellas se instalan, serán diagnosticadas apenas se evidencien sus síntomas.

El diagnóstico de meningitis y de su agente causal está enteramente supeditado a los hallazgos del líquido céfalorraquídeo, cuyo examen cuidadoso se realizará desde que se sospecha de la enfermedad. En el líquido céfalorraquídeo hay datos que son muy significativos: el descenso de la glucosa sugiere la existencia de una meningitis bacteriana o fungosa; en las meningitis virósicas el líquido es claro y la glucosa es normal. La baja glucorraquia de las meningitis piógenas aparece relacionado con el excesivo consumo de glucosa por parte de los leucocitos polimorfonucleares en activa fagocitosis; en la meningitis tuberculosa este fenómeno puede estar relacionado con una alteración del transporte de glucosa entre la sangre y el líquido céfalorraquídeo.

La identificación del microorganismo en el líquido céfalorraquídeo define en forma categórica el factor etiológico determinante del proceso. Es importante conocer el número y la clase de leucocitos en el líquido. Si las cifras son muy altas, por encima de 2000 leucocitos, es casi seguro que se trata de una meningitis bacteriana. La actividad de la infección puede seguirse por la pleiocitosis del líquido céfalorraquídeo; esto es especialmente útil en la tuberculosa.

La albuminorraquia es un dato también de interés y traduce en general el estado inflamatorio; pero a veces se presenta alta, aunque la infección esté dominada, lo cual acontece a consecuencia del bloqueo del espacio subaracnoideo. En estos casos la leucocitosis del líquido es escasa.

El hallazgo de alcohol en el líquido céfalorraquídeo, si no hubo ingestión previa de esta sustancia, significa que la meningitis es producida por hongos.

El electroencefalograma nos auxilia para controlar la evolución del proceso, así como nos aporta elementos importantes para conocer el estado de las neuronas corticales.

En cuanto al tratamiento este se instituirá pronto; los antibióticos deben llegar a todas las partes de las vías cerebroespinales en adecuada concentración y durante un período de tiempo suficientemente prolongado. Se tratará la enfermedad causal. Las secuelas deben ser evitadas, y si aparecen, es preciso diagnosticarlas antes de que produzcan males irreparables en el tejido nervioso y tentar un tratamiento con participación del cirujano.

El presente número se refiere a un tema eminentemente práctico el cual debe ser dominado por el clínico puesto que al afrontar esta clase de enfermos su acción será enérgica y precisa. El tópico ha sido tratado por destacadísimas figuras de la neurología mundial a quienes agradecemos su valiosa cooperación.

Por lo que ha significado la estreptomicina en el pronóstico y tratamiento de la Meningitis Tuberculosa, nos place dedicar este número a su descubridor el Prof. Selman A. Waksman.

VICTOR SORIANO.

# Editorial

Various are the problems posed to a clinicien who is confronted with a patient affected by meningitis: 1) It has to be tried to attain an accurate etiological diagnosis from the beginning. 2) Treatment has to be correct and should be administered as soon as possible after the beginning of the disease. 3) The septic focus which might have originated meningitis should be looked for. 4) During the evolution of the disease the signs of nervous parenchyma damage should be recognized. 5) It should be tried to prevent sequelae, and if they appear, they should be diagnosed as soon as their symptoms come to evidence.

The diagnosis of meningitis and its causing agent is completely submitted to the cerebrospinal fluid findings, whose careful examination should be undertaken as soon as the disease is suspected.

The cerebrospinal fluid contains very significant data: the lowering of glucose suggests the existence of a bacterial or fungal meningitis; in virus meningitis the fluid is clear and the glucose content is normal. Low glucose in piogenous meningitis appears related to an excessive glucose consumption of polimorfonuclear leucocytes in active phagocitosis; in tuberculous meningitis this phenomenon may be related to a disturbance in glucose transport between blood and cerebrospinal fluid.

The identifying of microorganims in the cerebrospinal fluid cathegorically defines the determining etiological elements of the process.

It is most important to know the number and the sort of the leucocytes contained in the cerebrospinal fluid. If the figures are high, over 2000 leucocytes it is almost sure to be in presence of a bacterial meningitis. The infection activity may be followed by means of cerebrospinal fluid pleiocitosis, which is particularly useful in tuberculous meningitis.

Protein level also is an interesting data and shows the inflammatory state in general, but it is sometimes high even if the infection has not been eliminated. This happens as a consequence of the blockade of the subarachnoid space; in these cases fluid leucocytosis is scarce.

The presence of alcohol in the cerebrospinal fluid, when no previous ingestion of this substance has taken place, means that meningitis is produced by fungus.

Electroencephalogram aids to the control of the evolution, and adds important elements about the state of cortical neurons.

The treatment should be administered soon; antibiotics should reach every part of the cerebrospinal pathways in a proper concentration and during a sufficiently long period. The causing disease should be treated.

Sequelae should be prevented, and if they appear, they should be diagnosed before causing irreversible damages to the nervous tissue; a treatment with surgical aid should be tried. This issue treats a most practical topic, which should be known by the clinicien, as his action has to be precise and energic when he faces this sort of patient. The subject has been treated by outstanding world authorities in Neurology, to whose collaboration we are deeply indebted.

With streptomycin a very valuable therapeutic weapon has been placed in the physician's hands, for the treatment of tuberculous meningitis. It is a pleasure for us to render homage with this issue to its discoverer Prof. Selman Waksman.

VICTOR SORIANO.

# Cerebrospinal Fluid Changes in Meningitis

**DONALD H. HARTER*, M. D.; MELVIN D. YAHR**, M. D.**

From the Department of Neurology, Columbia University, College of Physicians and Surgeons, New York, New York, and the New York Neurological Institute Columbia Presbyterian Medical Center, New York, New York.

Examination of the cerebrospinal fluid (C.S.F.) is essential for the proper diagnosis and management of infections of the central nervous system. An understanding of the factors responsible for the changes that take place in the cerebrospinal fluid of patients with meningitis may also be helpful in clarifying some of the still unanswered questions about the pathogenesis and pathophysiology of meningeal infection[1]. The following is an analysis of the spinal fluid abnormalities in patients with meningitis and a review of what is known as to how these changes occur.

## General Considerations:

Based upon the appearance of the spinal fluid, its cellular response and sugar content, three distinct spinal fluid formulas can be recognized in meningitis (Table 1). Pyogenic bacteria produce a purulent reaction characterized by cloudy spinal fluid containing chiefly polymorphonuclear leucocytes and a decreased sugar content (hypoglycorrhachia). A mononuclear cellular response with a decrease in the C.S.F. sugar content is characteristic of meningitis due to M. tuberculosis or mycoses. Viral or aseptic meningitis typically results in a clear spinal fluid containing a normal amount of glucose and a predominance of mononuclear cells.

Although one may recognize certain characteristic spinal fluid syndromes, the spinal fluid in patients with meningitis is continuously changing throughout the course of the disease, and specific changes may only be found at a given phase of the infectious process. A single spinal fluid examination, particularly early in the course of the disease or in patients who have received antimicrobial agents prior to the recognition of meningitis, may be misleading. Under such circumstances, serial studies of the spinal fluid may indicate the direction in which the fluid is changing and help in establishing the correct diagnosis.

## Purulent Meningitis:

The spinal fluid in meningitis due to pyogenic micro-organisms is under increased pressure and is cloudy or frankly purulent. While the appearance of the fluid is usually of little help in determining the precise etiology of the infection, it may furnish valuable clues in certain situations. Meningitis due to Klebsiella pneumoniae may produce gelatinous spinal fluid[2]. On

---

* Captain, United States Airforce.

** Professor of Neurology, Columbia University, College of Physicians and Surgeons.

occasion, particularly in anthrax meningitis[3], the spinal fluid may be hemorrhagic. When there is a suspicion of meningitis and bloody spinal fluid is obtained, it should always be smeared and cultured for bacteria. Spinal fluid containing Pseudomonas aeruginosa, an organism which may gain access to the subarachnoid space at the time of lumbar puncture[4], shows a green fluorescence to ultraviolet light[5]. This property permits rapid bacteriologic diagnosis when iatrogenic meningitis in suspected.

A marked C.S.F. pleocytosis, usually greater than 1,000 per cu.mm. and often as high as 20,000 per cu.mm., is found. Polymorphonuclear leucocytes are the chief cell type. The C.S.F. cell counts of patients with pneumococcal and staphylococcal meningitis may be particularly low[6] and a low spinal fluid cell count in patients with pneumococcal meningitis may signify a poor prognosis[7].

The protein content of the spinal fluid in pyogenic meningitis is often markedly elevated. It is reported to be higher in patients with pneumococcal meningitis than in patients with meningitis due to N. meningitidis or H. influenzae[6]. An elevated C.S.F. protein may be the only abnormality found in spinal fluid obtained in the very early hours of meningeal infection[8]. As the spinal fluid chloride simply reflects non-specific changes in the blood chloride[9], measurements of the C.S.F. chloride is of little value in the differential diagnosis of meningitis.

A decreased or absent spinal fluid sugar is one of the hall-marks of bacterial meningitis, and the C.S.F. glucose is critical in differentiating bacterial or fungal meningitis from viral meningitis. The level of the C.S.F. sugar normally parallels that of the blood sugar[10] hence diabetes mellitus, transient hyperglycemia due to meningitis[11] or to the intravenous administration of glucose may mask low spinal fluid sugar values[6]. Whenever the C.S.F. sugar content is in question, a simultaneous blood sugar determination should be performed.

In approximately 75% of patients with pyogenic meningitis, the organism can be correctly identified on smear of the spinal fluid sediment with Gram's or methylene blue stain[6]. The organism is particularly easy to demonstrate in the spinal fluid of patients with pneumococcal meningitis. Because of its tendency to pleomorphism, H. influenzae may at times be mistaken for N. meningitidis on smear[12]. Gram-positive pleomorphic rods resembling diphtheroids suggest infection with Listeria monocytogenes[13]. Mima polymorpha, a pleomorphic Gram-negative bacillus which may appear in diplococcal forms and simulates N. meningitidis clinically and morphologically[14].

Other techniques may be used for rapid bacteriologic diagnosis. Capsular swelling on the addition of type specific antisera (Quellung reaction) may be used to identify D. pneumoniae and H. influenzae in spinal fluid sediment. A technique for demonstrating H. influenzae type B in C.S.F. sediments by the addition of fluorescein-labelled type specific antibody, has recently been described which appears sensitive and specific for the demonstration of H. influenzae in C.S.F. sediments[15].

In cases where bacterial meningitis is suspected, bacterial culture may be obtained directly from the lumbar puncture needle thus eliminating the chance of contamination or loss in transfer[16]. Material should be inoculated on blood and chocolate agar plates and incubated under aerobic and anaerobic conditions. Cerebrospinal fluid is a good medium for bacterial growth, and the organism may be recovered on the incubation of a tube of C.S.F. to which several drops of sterile glucose solution have been added[8, 16].

Despite the use of careful bacteriologic techniques, the causative organism cannot be recovered in a significant number of patients presenting the clinical and spinal fluid findings of purulent meningitis. Such patients usually comprise 20 to 25% of a reported series of patients with acute purulent meningitis[7, 17, 18, 19]. Antibiotics given before the initial lumbar puncture may be responsible for obscuring the bacteriological diagnosis in such cases. The incidence of antecedant antibiotic therapy is

higher among patients in whom the organism can not be recovered than among patients in whom a bacteriologic diagnosis can be made[7, 17]. In addition to making the bacteriologic diagnosis more difficult, inadequate doses of antimicrobials given before examination of the spinal fluid may suppress the infection to a point where mononuclear cells predominate and the C.S.F. glucose is normal[20].

**Mononuclear Reaction with Hypoglycorrhachia:**

The spinal fluid of patients with tuberculous or mycoses meningitis contains predominantly mononuclear cells and a decreased quantity of glucose. Similar spinal fluid changes may be seen in cases of sarcoidosis of the nervous system[21], acute syphilitic meningitis[22] and diffuse leptomeningeal carcinomatosis[23].

The spinal fluid is usually under increased pressure and may be clear, slightly cloudy or ground-glass in appearance. A pellicle or clot may form on standing. As a rule, the C.S.F. contains 25 to 500 cells per cu. mm. and mononuclear cells predominate. Under the counting chamber, fungi may be mistaken for atypical or bizarrely shaped lymphocytes. On occasion, the cellular response in tuberculous meningitis in composed chiefly of polymorphonuclear leucocytes. When this occurs, polymorphonuclear cells usually persist as the principal cell type over the entire course of the disease[16].

The spinal fluid protein may be moderately or markedly increased, but the very high protein values found in pyogenic meningitis rarely occur in tuberculous meningitis. C.S.F. protein values of over 500 mg. per cent in tuberculous meningitis are usually associated with partial or complete subarachnoid block[16]. The spinal fluid sugar is usually reduced to values below 40 mg. %, but only rarely does the C.S.F. sugar entirely disappear in tuberculous meningitis. A return of the sugar to normal levels may be one of the first indications of effectiveness of therapy in controlling the disease.

Tubercle bacilli may be demonstrated by Ziehl-Neelsen stain of a smear of the spinal fluid clot or sediment. An India ink preparation of the C.S.F. sediment will show the presence of Cryptococcus neoformans. Positive identification of M. tuberculosis and fungi can be made by culture on appropriate media and by animal inoculation. Antituberculous therapy should not be delayed for bacteriologic confirmation of M. tuberculosis in patients whose clinical and spinal fluid findings are otherwise compatible with tuberculous meningitis[24]. An increasing incidence of mycotic infections especially those of the Phycomycosis type can be expected in view of the many new drugs which prolong life in debilitating non-curable diseases.

**Mononuclear Response with Normal C.S.F. Sugar:**

Spinal fluid containing chiefly mononuclear cells and a normal quantity of glucose is characteristically found in patients with the syndrome of aseptic meningitis[25]. When all available methods of diagnosis are used, a specific etiologic diagnosis can now be made in about three-fourths of patients with aseptic meningitis. In 90 % of these cases a virus can be identified as the cause[26]. The most common viral etiologies in order of their frequency of occurrence are Group B Coxsackie, mumps, ECHO, lymphocytic choriomeningitis, poliovirus and herpes simplex or zoster. Approximately one-half the cases of viral meningitis are due to enterovirus or mumps virus[27]. Leptospirosis and protozoan infections are among the more important nonviral causes of aseptic meningitis, as are infectious mononucleosis and cerebral tumors in close proximity to the ventricular system.

The spinal fluid is clear or slightly opalescent and under normal or slightly increased pressure. In leptospiral meningitis, when jaundice is present it may be xanthrochromic[28]. Except in cases of mumps meningitis or lymphocytic choriomeningitis, the spinal fluid cell count rarely exceeds 1,000 per cu. mm. Mononuclear cells are

usually predominant but polymorphonuclear leucocytes may outnumber mononuclear cells in the early phases of the disease. Clinical evidence of meningitis and a spinal fluid containing more than 3,000 mononuclear cells per cu. mm. and a normal sugar level is diagnostic of lymphocytic choriomeningitis[29].

The C.S.F. protein is normal or slightly elevated. It increases in the later phases of the disease, but seldom reaches values exceeding 100 mg. %[29]. The C.S.F. sugar remains normal throughout the disease. No organisms can be found on smear of the spinal fluid sediment, and bacteriologic cultures are sterile. The etiology of the illness can be established by recovery of the agent from C.S.F., feces or pharyngeal washings and by changes in the immunologic response of acute and convalescent phase sera.

## Pathogenesis of C.S.F. Changes in Meningitis:

Despite adequate chemotherapy and supportive measures, the mortality in bacterial meningitis is still considerable[6, 7]. This persistent mortality, coupled with the introduction of a reproducible experimental model for bacterial meningitis[30] and the application of new techniques[31, 32], has prompted new inquiries into problems associated with the pathogenesis of meningitis,[30-33]. By studying the factors responsible for the spinal fluid changes in meningitis, it is anticipated that further fundamental information on the interrelationship between the infectious agent and the nervous system will be obtained.

## Cellular Response:

The cells found in the spinal fluid in patients with meningitis are derived in large part from blood elements and to a lesser extent from meningeal lining cells[34]. The suppression of C.S.F. pleocytosis in dogs made leucopenic by total body irradiation and later subjected to experimental pneumococcal meningitis supports this hypothesis[30].

Electron microscopic studies of experimental E. coli meningitis have demonstrated that the earliest defense response occurs in the plial lining cells[31]. These cells contain ingested bacteria within two hours after infection. Later in the infection, leucocytes are seen traversing vessel walls and in the process of phagocytosis. Although arachnoid lining cells can become phagocytes under conditions of extreme irritation[35], phagocytosis by these cells could not be demonstrated in the electron microscopic studies. As yet, these changes in ultrastructure have not been correlated with the changes taking place in the spinal fluid. Similar electron microscopic studies have not been reported in experimental tuberculous or viral meningitis.

## Protein:

Changes occurring in the protein electrophoretic[36] and immunoelectrophoretic[37] patterns of the spinal fluid in the course of meningitis have been reported. In the early stages of meningeal inflammation, the C.S.F. albumin fraction is increased. As the disease progresses, the immuno-globulins of the spinal fluid become prominent and with the subsidence of the infection, the elevation becomes localized to the gamma globulin fraction. Although these changes may reflect changes in the integrity of the blood-C.S.F. barrier to the passage of serum protein, it is entirely possible that a portion of the elevated gamma globulin found late in the course of meningitis may be formed within the nervous system itself.

## Sugar:

Cells, micro-organisms, alterations in the meningeal permeability and increased utilization of glucose by neural tissue have all been implicated as being partially or wholly responsible for the fall of spinal fluid sugar in bacterial meningitis.

The addition of viable organisms to cell-free spinal fluid in vitro has been attempted to show the glycolytic effect of micro-organisms. The results of such studies have

been inconsistent[38]. Some bacterial species were found to consume glucose avidly; others produced little fall in glucose concentration. When the micro-organism does produce glycolysis in cell-free C.S.F., the number of organisms added in vitro far exceeds the number found in the subarachnoid space of animals experimentally infected with the same micro-organism[39, 40].

Sterile, cell-free C.S.F. incubated for long periods at room or body temperature shows no alteration in glucose content. The addition of leucocytes to sterile, cell-free C.S.F. followed by incubation has resulted in a reduction of the C.S.F. glucose level[41]. Glycolysis is directly proportional to the number of cells present. Polymorphonuclear leucocytes utilize glucose more rapidly than mononuclear cells.

The discrepancy between the in vitro glycolytic effect of leucocytes and the normal C.S.F. glucose levels found in aseptic meningitis led to the suggestion that there is an increased transfer of glucose from blood into the spinal fluid in aseptic meningitis[38, 39]. The C.S.F. sugar is thereby replenished and fails to fall. Direct evidence for this hypothesis is still lacking.

An even greater discrepancy is presented by the finding that bacteria which did not enhance glucose consumption in vitro produced hypoglycorrhachia in vivo. The recent experiments of Petersdorf et al.[42-44] have clarified this problem. Animals made leucopenic by total body irradiation and subsequently given experimental pneumococcal meningitis did not develop hypoglycorrhachia[42]. These results, coupled with the finding that aseptic meningitis produced by the intracisternal instillation of sterile serum did not produce hypoglycorrhachia, suggested that both cells and bacteria were necessary to lower the C.S.F. glucose. In vitro studies of the incubation of live pneumococci and leucocytes in spinal fluid showed a synergistic effect on glycosis[43]. Heat-killed pneumococci incubated with C.S.F. containing leucocytes failed to produce a similar synergistic effect. These in vitro experiments imply that the consumption of glucose in C.S.F. containing leucocytes is primarily a function of viable and multiplying bacteria. In a third series of experiments[44], dogs with antecedent aseptic meningitis were infected with pneumococci intrathecally. A profound drop in C.S.F glucose occurred which was not observed in control animals given pneumococci without the antecedent production of aseptic meningitis or in animals with aseptic meningitis in the absence of superimposed bacterial infection. Hypoglycorrhachia also occurred when heat-killed pneumococci, India ink particles and bacterial endotoxin were administered intrathecally to animals with aseptic meningitis. These studies suggest that the fall in C.S.F. glucose in bacterial meningitis is probably the result of an increased consumption of glucose by leucocytes engaged in the active phagocytosis of bacteria.

Products of glycolysis have been measured in an attempt to identify their precursors. The lactic and pyruvic acid content

**TABLE I — CEREBROSPINAL FLUID SYNDROMES IN MENINGITIS**

| *Etiology* | *Appearance* | *Cell Type* | *Sugar* |
|---|---|---|---|
| Pyogenic Bacteria | Cloudy | Polymorphonuclear Leucocyte | Decreased or Absent |
| M. tuberculosis or Fungi | Clear or Cloudy | Mononuclear | Decreased |
| Viral or Leptospirosis (aseptic) | Clear | Mononuclear | Normal |

of the spinal fluid is elevated in bacterial meningitis[45, 46], but the relationship between the increase in these substances and the decrease in C.S.F. glucose is not a linear one. In cryptococcal meningitis, the ethyl alcohol level of the spinal fluid is elevated[47]. This would support the view that yeast organisms are consuming C.S.F. glucose.

The cause of hypoglycorrhachia in patients with tuberculous meningitis is also not clear. Both M. tuberculosis[48] and mononuclear cells utilize glucose slowly. Glucose administered intravenously to patients with tuberculous meningitis passes readily into the spinal fluid[49]. On the other hand, glucose administered intrathecally to such patients decays rapidly, and the spinal fluid glucose cannot be maintained at normal levels by intrathecal glucose injections[50]. These studies suggest that the lowered spinal fluid sugar content in tuberculous meningitis may be due to an increased transfer of glucose from spinal fluid to blood. If these interpretations are correct, it is paradoxical to postulate an increased passage of sugar into the spinal fluid to explain the normal C.S.F. sugar levels in aseptic meningitis and an increased passage of sugar out of the spinal fluid to explain the hypoglycorrhachia found in tuberculous meningitis. A better understanding of the ways in which glucose is actively transported into and out of the spinal fluid in the intact nervous system may be necessary before the significance of alterations in the blood-C.S.F. barrier to glucose in meningitis can be fully evaluated.

## SUMMARY

Three distinct cerebrospinal fluid responses to meningeal infection can be recognized. The cerebrospinal fluid in meningitis due to pyogenic bacteria is cloudy or turbid, contains an abundance of polymorphonuclear leucocytes and a decreased or absent C.S.F. sugar content. In tuberculous or mycotic meningitis, the spinal fluid is clear or slightly cloudy, contains predominantly mononuclear cells and a decreased quantity of sugar. Clear spinal fluid containing predominantly mononuclear cells and a normal glucose level is characteristically found in viral or aseptic meningitis.

Our understanding of how these spinal fluid changes come about is still imperfect. The spinal fluid cellular response is derived largely from blood elements and to a lesser degree from meningeal lining cells. The elevated protein content may be the result of changes in the permeability of the blood-C.S.F. barrier to protein. The increased amounts of immuno-globulins found in the later phases of meningeal inflammation may, in part, be formed within the nervous system. The lowered sugar content in pyogenic meningitis appears related to accelerated glucose consumption by actively phagocytosing polymorphonuclear leucocytes. In tuberculous meningitis, the lowered glucose content may be related to a disturbance in the transport of glucose between blood and C.S.F.

It is anticipated that further studies concerning the origin of the spinal fluid changes in meningitis will uncover additional fundamental information about the response of the nervous system to microbial infection and that this knowledge will, in turn, be put to clinical advantage.

## RESUMEN

Pueden ser reconocidas tres reacciones claramente diferenciadas del líquido cefalorraquídeo a la infección meníngea. En la meningitis provocada por una bacteria piógena el líquido cefalorraquídeo es oscuro o turbio, contiene leucocitos de núcleo po-

limorfo en abundancia y se ve disminuído o ausente el contenido de azúcar del L.C.R. En la meningitis micótica o tuberculosa el líquido raquídeo es claro o aparece ligeramente oscurecido, contiene células mononucleares y una cantidad disminuída de azúcar. Es típico encontrar en la meningitis virósica o aséptica un líquido cefalorraquídeo claro conteniendo predominantemente células mononucleares y un nivel normal de glucosa.

Aún es imperfecto nuestro conocimiento de como sobrevienen estos cambios de L.C.R. La reacción celular deriva en buena parte de elementos de la sangre y en menor grado de las células meníngeas circundantes. El elevado contenido de proteínas puede ser el resultado de cambios en la permeabilidad de la barrera sangre-L.C.R. frente a las proteínas. Las cantidades aumentadas de inmuno-glóbulos halladas en las etapas tardías de la inflamación meníngea pueden originarse en parte, dentro del sistema nervioso. El contenido disminuído de azúcar en la meningitis piógena aparece relacionado con el acelerado consumo de glucosa por parte de leucocitos de núcleo polimorfo, en activa fagocitosis. En la meningitis tuberculosa, el contenido disminuído de glucosa puede estar relacionado con una alteración del transporte de glucosa entre la sangre y el L.C.R.

Se anticipa que estudios adicionales en cuanto al origen de los cambios del líquido cefalorraquídeo durante la meningitis proporcionarán más informaciones fundamentales en cuanto a la reacción del sistema nervioso a la infección microbiana, y que estos conocimientos serán a su vez puestos al servicio del progreso clínico.

## RÉSUMÉ

Trois réactions distinctes du liquide céphalo-rachidien à une infection méningée peuvent être reconnues. Dans le cas de la meningite provoquée par une bactérie pyogène le liquide céphalo-rachidien est nebuleux ou trouble, il contient des leucocytes à noyau polimorphe en abondance et son contenu de sucre diminue ou disparaît. Dans la meningite micotique ou tuberculeuse le liquide céphalo-rachidien est clair ou légèrement nebuleux, il contient des cellules mononucléaires et une quantité plus petite de sucre. C'est typique de trouver dans une méningite virosique ou aseptique le liquide céphalorachidien contenant surtout des cellules mononucléaires et un niveau normal de glucose.

Nous connaissons assez imparfaitement encore comment ces changements du liquide céphalo-rachidien se font. La réaction cellulaire découle en grande partie de quelques éléments du sang et moins des céllules meningées environnantes. Le haut contenu de protéines peut être le résultat des changements dans la perméabilité de la barrière sang-L.C.R. en face des protéines. Les quantités augmentées d'immune-globules qu'on trouve aux étappes avancées de l'inflammation meningée peuvent surgir partiellement dans le système nerveux. Le contenu diminué de sucre dans la meningite pyogène est lié à une consommation accélérée de glucose de la part des leucocytes à noyau polimorphe en active phagocytose. Dans la méningite tuberculeuse, le contenu diminué de glucose peut être en rapport avec une altération dans le transport de glucose entre le sang et le L.C.R.

On annonce que des études aditionnelles quant à l'origine des changements du liquide céphalo-rachidien pendant la meningite, fourniront un plus grand nombre d'informations fondamentales en ce qui concerne la réaction du système nerveux à l'infection des microbes, et ces connaissances seront mises, à la fois, au service du progrès clinique.

## ZUSAMMENFASSUNG

Es können drei verschiedene Reaktionen der zerebro-spinalen Fluessigkeit (Z.S.F.) gegenueber der meningealen Infektion beobachtet werden. Bei der durch pyogene Bakterien verursachten Meningitis ist sie wolkig und trueb und enthaelt eine enorme Menge von polymorphonukleaeren Leukozyten, waehrend der Zuckergehalt niedrig oder gleich null ist. Bei der tuberkuloesen oder mykotischen Meningitis ist die Z.S.F. klar oder leicht getruebt; es herrschen die mononukleaeren Zellen vor und der Glukosegehalt ist herabgesetzt. Eine klare Spinalfluessigkeit wit vorherrschend mononukleaeren Zellen und normalen Glukosegehalt ist charakteristisch fuer die viroese oder aseptische Meningitis.

Wir wissen noch wenig wie diese Veraenderungen der Spinalfluessigkeit zustandekommen. Die Reaktion der Spinalfluessigkeit stammt zum grossen Teil von den Blutelementen und in geringerem Grade von den Deckzellen der Hirnhaeute. Der erhoehte Eiweissgehlat mag seine Ursache in Permaebilitaetsaendereungen der Blut-Liquor-Schranke fuer Eiweisse haben. Der erhoehte Gehalt an Immunoglobulinen in den spaeteren Etappen der meningealen Entzuendung entsteht vielleicht teilweise im Nervensystem selbst. Der erniedrigte Zuckerspiegel bei der pyogenen Meningitis scheint Beziehung zu haben mit dem erhoehten Glukosekonsum der aktiv phagozytierenden polymorphonuekleaeren Leukozyten. Bei der tuberkuloesen Meningitis mag der erniedrigte Glukosespiegel durch eine Stoerung im Transport der Glukose zwischen Blut und Liquor verursacht zu sein. Man ist sicher, dass weitere Forschungen ueber die Veraenderungen der Spinalfluessigket bei der Meningitis weitere fundamentale Tatsachen ueber die Reaktion des Nervensystems gegenueber der Mikrobeninfektion aufdecken werden und dass diese Kenntnisse ihrerseits von klinischem nutzen sein werden.

## REFERENCES

(1) *Harter, D. H. and Petersdorf, R. G.*: A consideration of the pathogenesis of bacterial meningitis. Review of experimental and clinical studies. Yale J. Biol. & Med. 32:280, 1960.

(2) *Thompson, A. J., Williams, E. B. Jr., Williams, E. D. and Anderson, J. M.*: Klebsiella pneumoniae meningitis: Review of literature and report of a case with bacteremia and pneumonia, with recover. A.M.A. Arch. Int. Med. 89:405, 1952.

(3) *Haight, T. H.*: Anthrax meningitis: Review of literature and report of two cases with recovery. Am. J. Med. 224:57, 1952.

(4) *Evans, F. L.*: Primary meningitis caused by Pseudomonas aeruginosa (Bacillus pyocyaneus). Med. Rec. 144:111, 172, 1936.

(5) *Cutler, M. and Cutler, P.*: Pseudomonas meningitis. Am. Pract. & Dig. Treat. 4:200, 1953.

(6) *Carpenter, R. R. and Petersdorf, R. G.*: The clinical spectrum of bacterial meningitis. Am. J. Med. 33:262, 1962.

(7) *Quaade, F. and Kristensen, K. P.*: Purulent meningitis. A review of 658 cases. Acta Med. Scand. 171:1, 1962.

(8) *Smith, M. H. D.*: Acute bacterial meningitis. Pediatrics 17:258. 1956.

(9) *Linder, G. C. and Carmichael, E. A.*: The chlorides and inorganic constituents of the serum and cerebrospinal fluid in meningitis. Biochem. J. 22:46, 1928.

(10) *Fremont-Smith, F., Dailey, M. E., Merritt, H. H., Carroll, M. P. and Thomas G. W.*: The equilibrium between cerebrospinal fluid and blood plasma. I. The composition of the human cerebrospinal fluid and blood plasma. A.M.A. Arch. Neurol. Psychiat. 25:1271, 1931.

(11) *Ferguson, F. and Barr, D.*: Glycosuria in meningitis. Ann. Int. Med. 21:173, 1944.

(12) *Appelbaum, E. and Abler, C.*: Advances in the diagnosis and treatment of acute pyogenic meningitis. New York State J. Med. 58:204, 363, 1958.

(13) *Finegold, S. M., Bradley, J. G., Campbell, M. K. and Greenberg, A. J.*: Listeria monocytogenes meningitis Summation of literature and report of two new cases. A.M.A. Arch. Int. Med. 93:515, 1954.

(14) *Vda. de Torregrosa, M. and Ortiz, A.*: Severe infections in children due to rare Gram-negative bacilli (Mima polymorpha and Bacillus anitratum) J. Pediatrics 59:35, 1961.

(15) *Page, R. H., Caldroney, G. L. and Stulberg, C. S.*: Immunofluorescence in diagnostic bacteriology. I. Direct identification of Hemophilus influenzae in smears of cerebrospinal fluid sediments. A.M.A. J. Dis. Child. 101:155, 1961.

(16) *Merritt, H. H. and Fremont-Smith, F.*: *The Cerebrospinal Fluid*, W. B. Saunders Company, Philadelphia, 1938.

(17) *Eigler, J. O. C., Wellman W. E., Rooke, E. D., Keith, H. M. and Svien, H. J.*: Bacterial Meningitis. I. General Review (294 cases). Proc. Staff Meet. Mayo Clin. 36:357, 1961.

(18) *Esrachowitz, S. R.*: Pyogenic meningitis. A study of 303 cases. S. African Med. J. 35:101, 1961.

(19) *Smith, E. S.*: Purulent meningitis in infants and children. A review of 409 cases. J. Pediat. 45:425, 1954.

(20) *Bennett, I. L. Jr. and Adams, R. D.*: Viral meningitis and the syndrome of aseptic meningitis. In Harrison's *Principles of Internal Medicine*, 4th edition, McGraw-Hill, New York, 1962.

(21) *Pennell, W. H.*: Boeck's sarcoid with involvement of the central nervous system. A.M.A. Arch. Neurol. & Psychiat. 66:728, 1951.

(22) *Merritt, H. H. and Moore, M.*: Acute syphilitic meningitis. Medicine 14:119, 1935.

(23) *Berg, L.*: Hypoglycorrhachia of non-infectious origin; diffuse meningeal neoplasia. Neurology 3:811, 1953.

(24) *Lincoln, E. M., Sordillo, S. V. R. and Davies, P. A.*: Tuberculous meningitis in children. A review of 167 untreated and 74 treated patients with special reference to early diagnosis. J. Pediat. 57:807, 1960.

(25) *Wallgren, A.*: Une nouvelle maladie infectieuse du systeme nerveux central? Acta Paediat. 4:158, 1925.

(26) *Meyer, H. M., Jr., Johnson, R. T., Crawford, I. P., Dascomb, H. E. and Rogers, N. G.*: Central nervous system syndromes of "viral" etiology. A study of 713 cases. Am. J. Med. 29:334, 1960.

(27) *Lepow, M. L., Carver, D. H., Wright, H. T., Woods, W. A. and Robbins, F. C.*: A clinical, epidemiologic and laboratory investigation of aseptic meningitis during the four year period, 1955-1958. I. Observations concerning etiology and epidemiology. New England J. Med. 266:1181, 1962.

(28) *Carghill, W. H., Jr. and Beeson, P. B.*: The value of spinal fluid examination as a diagnostic procedure in Weil's disease. Ann. Int. Med. 27:396, 1947.

(29) *Lepow, M. L., Coyne, N., Thompson, L. B., Carver, D. H. and Robbins, F. C.*: A clinical, epidemiologic and laboratory investigation of aseptic meningitis during the four-year period, 1955-1958. II. The clinical disease and its sequelae. New England J. Med. 266:1188, 1962.

(30) *Petersdorf, R. G. and Luttrell, C. N.*: Studies on the pathogenesis of meningitis. I. Intrathecal infection. J. Clin. Invest. 41:311, 1962.

(31) *Nelson, E., Blinzinger, K. and Hager, H.*: An electron-microscopic study of bacterial meningitis. I. Experimental alterations in the leptomeninges and subarachnoid space. A.M.A. Arch. Neurol. 6:390, 1962.

(32) *Bakary, L.*: The cerebral uptake of tritiated tetracycline from blood and cerebrospinal fluid under normal conditions and in experimental pneumococcal meningitis. J. Neuropath. & Exper. Neurol. 21:424, 1962.

(33) *Petersdorf, R. G., Swarner, D. R. and Garcia, M.*: Studies on the pathogenesis of meningitis. II. Development of meningitis during pneumococcal bacteremia. J. Clin. Invest. 41:320, 1962.

(34) *Fremont-Smith, F.*: Pathogenesis of the changes in the cerebrospinal fluid in meningitis. Ass. Res. nerv. ment. Dis. 12: 378, 1932.

(35) *Weed, L. H.*: The Meninges, with Special Reference to the cell coverings of the leptomeninges; Cytology and Cellular Pathology of the Nervous System, Volume 2, edited by W. Penfield, New York, Paul B. Hoeber, Inc. 1932, p. 611.

(36) *Matiar, H. and Schmidt, C.*: Die Veranderungen der Liquorproteine bei entzundlichen Erkrankungen der Meningen. Dtsc. Z. Nervenheilk. 176:200, 1957.

(37) *Ursing, B., Dencker, S. J. and Swahn, B.*: Protein pattern of cerebrospinal fluid in meningitis and meningo-encephalitis. Acta med. Scand. 171:715, 1962.

(38) *Petersdorf, R. G. and Harter, D. H.*: The fall of cerebrospinal fluid sugar in meningitis. A.M.A. Arch. Neurol. 4:21, 1961.

(39) *Baltch, A. and Osborne, W.*: Inquiry into causes of lowered spinal fluid sugar content: In vivo and in vitro observations. J. Lab. and Clin. Med. 49:882, 1957.

(40) *Goldring, S. and Harford, C. G.*: Effects of leucocytes and bacteria on glucose content of C.S.F. in meningitis. Proc. Soc. Exper. Biol. & Med. 75:669, 1950.

(41) *Hubbard, R. P. and Wilson, D. C.*: Note on the probable relationship between the glycolytic power of the spinal fluid and the number of cells present. Clifton M. Bull. 14:73, 1928.

(42) *Petersdorf, R. G., Garcia, M. and Swarner, D. R.*: Mechanism of hypoglycorrhachia in experimental pneumococcal meningitis. Proc. Soc. Exper. Biol. & Med. 102: 669, 1959.

(43) *Petersdorf, R. G., Swarner, D. R. and Garcia, M.*: Synergistic action of pneumococci and leukocytes in lowering cerebrospinal fluid glucose. Proc. Soc. Exper. Biol. & Med. 103:380, 1960.

(44) *Peterdorf, R. G., Swarner, D. R. and Garcia, M.*: Further observations on the mechanism of hypoglycorrhachia in experimental meningitis. Proc. Soc. Exper. Biol. & Med. 104:65, 1960.

(45) *DeSanctis, A. G., Killian, J. A. and Garcia, T.*: Lactic acid of spinal fluid in meningitis: Practical, diagnostic and prognostic value. Am. J. Dis. Child. 46:239, 1933.

(46) *Choremis, K., Constantinides, V. and Nicolaides, P.*: Pyruvic acid in cerebrospinal fluid during various infectious diseases with central nervous system involvement. Ann. paediat. 180: 337, 1953.

(47) *Tyler, R.*: Spinal fluid alcohol in yeast meningitis. Am. J. M. Sc. 232:560, 1956.

(48) *Loebel, R. O., Shorr, E. and Richardson, H. G.*: The influence of foodstuffs upon respiratory metabolism and growth of human tubercle bacilli. J. Bact. 26:139, 1933.

(49) *Sifontes, J. E., Williams, R. D. B., Lincoln, E. and Clemons, H.*: Observations on the effect of induced hyperglycemia on the glucose content of the cerebrospinal fluid in patients with tuberculous meningitis. Am. Rev. Tuberc. 6:732, 1953.

(50) *Wasz-Hockert, O., Brander, E. and Paatela, M.*: Reduced concentration of cerebrospinal fluid glucose in tuberculous meningitis. Experimental studies. Ann. paediat. Fenniae 2:320, 1956.

# Electroencephalography

**FREDERIC A. GIBBS, M. D.**

From the Department of Neurology and Neurological Surgery, University of Illinois College of Medicine, Chicago, Illinois.

Purulent meningeal infection, regardless of its severity, does not alter the electrical activity of the brain, if it remains confined to the meninges (Radermecker, 1956). Some degree of encephalitis, however, is common in meningitis and during the acute phase of meningococcus meningitis slow activity is usually present (Turrell and Roseman, 1955). The slowing is less marked than in encephalitis, being diffuse but moderate and consisting of 3-5 per second activity in children and 5-7 per second activity in adults. As a rule the slowing lasts a week or so and then clears rapidly and completely. In cases of influenzal and pneumococcal meningitis similar changes occur (Hughes et al, 1951).

Serial electroencephalograms are far more informative than a single recording because the patient becomes his own control. During the acute phase of meningitis the slow activity, which is characteristically present, is more clearly observable in the awake recording; it may disappear in sleep. In the post-acute phase, if an epileptic process is developing, beginning seizure activity is likely to be observed only during sleep. More than the usual degree of slowing in the acute phase of the illness or a retarded return to normal, and especially the development of spike discharges or focal abnormalities, are ominous signs. One or more of these is almost invariably present in cases where consciousness is impaired or where convulsions have developed. They can occur in the absence of clinical signs or symptoms of brain disorder and they may be the only evidence of such disorder. In some cases these abnormalities increase over a period of weeks or months and then subside without the occurrence of symptoms, but on the other hand they may increase and become clinically expressed years later.

## Aseptic Meningitis

In spite of the generally benign course of aseptic meningitis, signs and symptoms of brain disorder are common in the acute phase, and it is occasionally the presumptive cause of persistent neurological deficits or seizures. From the electroencephalographic as well as from the clinical point of view, aseptic meningitis is a relatively mild illness (Gibbs et al, 1962). It is associated with less electroencephalographic disorder than uncomplicated measles (which produces slow activity in 50 per cent of cases) (Gibbs et al, 1959). It resembles uncomplicated cases of mumps in having a 33 percent incidence of electroencephalographic abnormality in the acute and immediate post-acute phase. Slow activity during aseptic meningitis is more commonly observed if the infection is caused by ECHO virus (26 percent), than if it is caused by Coxsackie (14 percent). When caused by non identifiable agents the incidence of abnormality is slightly higher than when caused by an identified virus. Almost invariably the slowing clears up within 2 or 3 days after the patient has become afebrile. Extreme slowing during the acute phase, an

unusual persistence of slow activity, or the development of spike discharges or focal abnormalities indicates that the case is atypical and that the disease process is not following the usual benign course of aseptic meningitis. Such findings warn of possible complications.

### Tuberculous Meningitis

More electroencephalographic abnormality occurs in tuberculous meningitis than in other types of meningitis, but the findings vary with the age of the patient (Turrell et al, 1953), the extent and duration of the meningitis, the severity of the associated symptomatology, and with the response to treatment (Choremis et al, 1957; Wasz-Hockert, et al, 1963).

In untreated adults the initial electroencephalogram is usually only mildly slow and even in terminal stages the recording may be only moderately slow. However, untreated children usually have very slow activity initially. The electroencephalogram in children has differential diagnostic value; if a child with a lymphocytic meningitis has an initial electroencephalogram which is very slow, this is evidence in favor of tuberculous meningitis (Turrell et al, 1953; Ruf, 1949).

Prognostically electroencephalographic changes usually parallel or precede the clinical changes (Radermecker, 1956). With improvement in the patient's condition the electroencephalogram becomes less slow and more normal. Serial recordings in tuberculous meningitis, as in other conditions, make it possible to predict with some reliability the development of seizures from the presence of spike discharges or a relapse from an increase in slow activity. The prognosis is poor, if very slow activity or an amplitude asymmetry persists for 2 weeks or more. As might be expected, from the commonness of clinical seizures in this condition, spike discharges are a frequent finding. Choremis and his associates (1957) reported that diffuse abnormalities usually cleared up in 1-2 months when cortisone or streptomycin are given either intramuscularly or intrathecally. Focal abnormalities, however, often persist and are commonly resistant to treatment.

Follow-up studies on treated cases show minor electroencephalographic residuals in 60 percent and major in 10 percent (Chaptal et al, 1954). Among patients considered cured for one year, very abnormal tracings occurred in 50 percent of those with continuing symptoms and in only 7 percent of those who were asymptomatic (Lefebvre et al, 1954).

## SUMMARY

The distinction between meningitis and meningoencephalitis is valid and important. The electroencephalograph is a sensitive indicator of infection, inflammation and irritation in the vicinity of cortical neurones. It is, therefore, of great value for detecting the spread of the disease process from the meninges to the substance of the brain, for prognosis, as a guide to treatment and for revealing asymptomatic and symptomatic sequels of the infection.

## RESUMEN

La distinción entre meningitis y meningoencefalitis es válida e importante. El electroencefalógrafo es un indicador sensible de infecciones, inflamaciones e irritaciones situadas cerca de las neuronas corticales. Su empleo es muy útil para determinar la difusión del proceso de la enfermedad de las meninges a la sustancia del cerebro, para el pronóstico, como guía para su tratamiento y para revelar las consecuencias sintomáticas y asintomáticas de la infección.

## RÉSUMÉ

La distinction entre meningite et meningoencephalite est valide et importante. L'electroencephalographe est un indiqueur sensible des infections, des inflammations et des irritations situées près des neurones corticales. Son emploi est très utile pour déterminer la diffusion du procés de la maladie des meninges à la substance du cerveau, pour le prognostique, comme guide pour son traitement et pour révéler les séquelles symptomatiques et asymptomatiques de l'infection.

## ZUSAMMENFASSUNG

Die Unterscheidung zwischen Meningitis und Meningoenzephalitis ist sehr wichtig. Das EEG ist ein feinfuehliger Anzeiger der Infektion, Entzuendung und Irritation in der Nachbarschaft der kortikalen Neuronen Deshalb ist es von grossem Wert fuer die Entdeckung der Ausbreitung des krankhaften Prozesses von den Hirnhaeuten auf die Hirnsubstanz, indem es eine Handhabe fuer Prognose, die Behandlungstaktik und die Diagnose asymptomatischer und symptomatischer Folgezustaende der Infektion darstellt.


## BIBLIOGRAPHY


(1) *Chaptal, J., et al*: Signes électro-encéphalographiques des séquelles de méningite tuberculeuse, Rev. Neurol., 90: 830-834, 1954.

(2) *Choremis, C., Kyriakides, B., Drossos, C., and Chatsidimitriou, E.*: Electroencephalogram in the course of tuberculous meningitis treated with cortisone; a comparative study, Ann. Paediat. Fenn., 3:323-334, 1957.

(3) *Gibbs, F. A., Gibbs, E. L., Carpenter, P. R., and Spies, H. W*: Electroencephalographic abnormality in "uncomplicated" childhood diseases, J.A.M.A., 171:408-411, 1959.

(4) *Gibbs, F. A., Gibbs, E. L., Carpenter, P. R., and Spies, H. W.*: Electroencephalographic study of patients with acute aseptic meningitis, Pediatrics, 29:181-186, 1962.

(5) *Hughes, J., Davis, B. C., and Carpenter, A.*: Relationship of electroencephalographic findings to clinical factors during and after acute purulent meningitis, A.M.A. J. Dis. Child., 82:268-281, 1951.

(6) *Lefebvre, J., et al*: Séquelles électro-encéphalographiques et radiographiques des méningites tuberculeuses chez enfants considérés comme guéris depuis plus d'un an, Rev. Neurol., 90:834-842, 1954.

7) *Radermecker, J.*: Systématique et Electroencéphalographie des Encéphalites et Encéphalopathies, Masson & Cie, Paris, 1956, 256 p.

(8) *Ruf, H.*: Das Elektroencephalogramm bei der lymphocytaren Meningitis, Arch. Psych. Nervenheilk., 183:146-162, 1949.

(9) *Turrell, R., et al*: Electroencephalographic studies of the encephalopathies. II. Serial studies in tuberculous meningitis, Electroenceph. Clin. Neurophysiol., 5:53-63, 1953.

(10) *Turrell, R., and Roseman, E.*: Electroencephalographic studies of the encephalopathies. IV. Serial studies in meningococcus meningitis, Arch. Neurol. Psych., 73:141-148, 1955.

(11) *Wasz- Hockert, O., et al*: Late prognosis in tuberculous meningitis. A clinical, neurological, ophthalmological ,otological, psychological, medical study, Acta Paediat., 51:1-119, 1963.

# Les Méningites Purulentes du Nouveau-Né

## (à propos de 43 observations)

J. CHAPTAL, R. JEAN, J. CADILHAC, M. NAVARRO et F. MEYLAN

Les méningites purulentes comptent parmi les plus sévères des infections du nouveau-né: leur mortalité se situe encore aux environs de 65% des cas, et une fois sur trois persistent des séquelles neuropsychiques sévères.

Cette gravité tient à divers facteurs, et en premier lieu à la susceptibilité des centres nerveux du nouveau-né aux divers agents agresseurs. La gamme limitée des réactions possibles à cet âge fait aussi que la maladie prend très souvent un masque trompeur, évolue à bas bruit, ce qui retarde parfois de façon considérable le diagnostic et le traitement. Enfin, les germes intestinaux, responsables de bon nombre de ces méningites, sont demeurés jusqu'à présent difficilement accessibles à l'antibiothérapie.

Le présent exposé est basé sur l'étude des méningites purulentes néonatales observées à la clinique des maladies des enfants et d'hygiène du premier âge depuis 1948, ainsi que des séries comparables publiées depuis 1954.

### I. ETUDE D'ENSEMBLE DE NOS OBSERVATIONS

43 cas de méningite purulente ont été observés dans le service depuis 1948 chez des enfants de moins d'un mois (les sujets porteurs de malformation du système nerveux central exclus). Onze d'entre eux ont survécu.

#### A) Notions étiologiques

Les germes en cause ont été identifiés dans 33 cas. Il s'agissait d'enterobactéries 17 fois, de pneumocoques 10 fois, les autres germes étant beaucoup plus rares.

**TABLEAU I — REPARTITION DES GERMES CAUSAUX**

| *Germes* | *Nombre de cas* | | *Survies* | |
|---|---|---|---|---|
| Escherichia coli | 9 | 17 | 1 | 2 |
| Proteus | 5 | | 1 | |
| Klebsiella | 3 | | 0 | |
| Pneumocoque | 10 | | 2 | |
| Streptocoque | 2 | | 1 | |
| Hemophilus influenzae | 1 | | 0 | |
| Méningocoque | 1 | | 0 | |
| "Cocci Gram +" (1) | 1 | | 1 | |
| Germe inconnu | 11 | | 5 | |
| *Total* | 43 | | 11 | |

(1) *A l'examen direct seulement.*

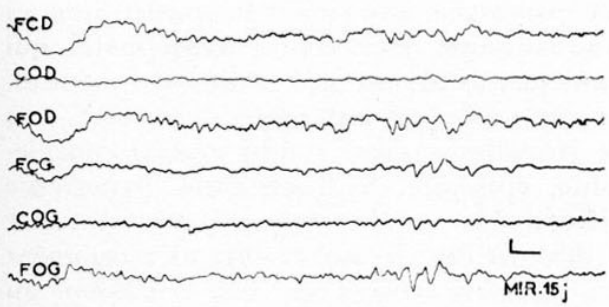



Fig. 1. — *Méningite purulente à germe inconnu. EEG á 15 jours: bouffées d'ondes lentes bifrontales sur une activité de fond peu altérée. Guérison.*

Un incident obstétrical a été retenu 12 fois: accouchement lent, dystocique et anoxie néonatale. Dix des malades étaient des prématurés.

### B) Notions cliniques

La date des premières manifestations morbides fut variable; dans la moitié des cas elle se situait avant le cinquième jour, mais pour 9 nourrissons les signes d'alerte ne furent notés qu'après le quinzième jour. Ces premières manifestations furent de deux ordres: les unes extériorisaient de façon évidente la souffrance du système nerveux (20 cas), ce furent des convulsions 15 fois, un syndrome d'hypertonie, des troubles de la déglutition, un strabisme net, une augmentation rapide du périmètre cranien, enfin un coma brutal. Mais dans 23 cas la symptomatologie initiale fut anonyme et trompeuse, caractérisée par des troubles digestifs, une anorexie, de la dyspnée, une cyanose, une hyperthermie apparemment isolée, un syndrome de déshydratation. Dix-sept nourrissons seulement présentaient de la fièvre à la phase d'état, deux autres au contraire ètaient hypothermiques.

Lors de l'hospitalisation, un syndrome méningé net avec hypertonie n'existait que dans 14 cas, mais la fontanelle était tendue 24 fois.

L'absence de symptomatologie univoque dans de nombreux cas explique que pour plusieurs malades un long délai se soit écoulé entre le moment où sont apparus les premiers signes anormaux et celui où le diagnostic a été porté. C'est ainsi que si ce délai n'a pas excédé quatre jours dans la moitié des cas (22), il s'étageait de 9 à 32 jours pour 9 nourrissons.

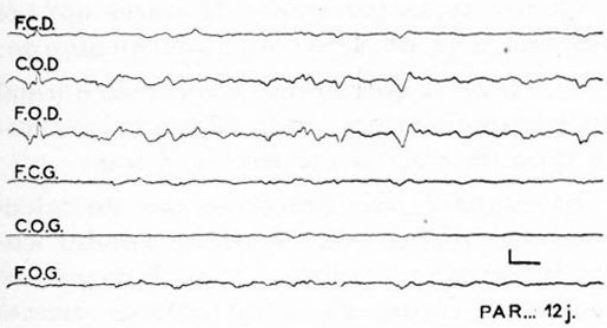



Fig. 2. — *Méningite purulente à germe inconnu. Hypertonie modérée. EEG à 12 jours: asymétrie avec tracé peu volté à gauche et ondes lentes à droite. Survie.*

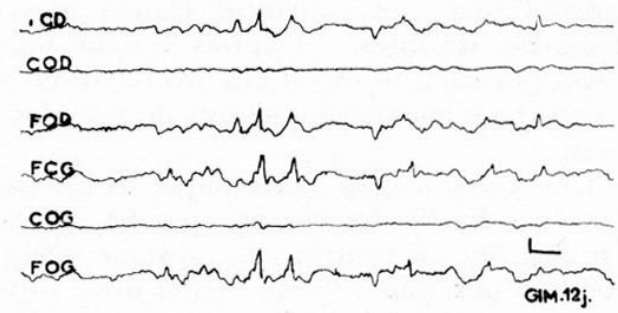



Fig. 3. — *Méningite purulente à E. Coli. Hypertonie. EEG à 12 jours: décharges d'ondes lentes à pente raide (sharp waves) bifrontales. Décès à 15 jours.*

La méningite suppurée s'accompagnait 4 fois d'une autre localisation infectieuse: arthrite suppurée, abcès sous-cutané et dans un cas hépatite suppurée.

### C) Evolution

7 des 43 malades sont décédés avant tout traitement ou dans le premières heures suivant son instauration. Pour les 36 autres, la thérapeutique, bien que variable, d'un cas à l'autre, comporta toujour pénicilline et antibiotique à large spectre, administrés par voie veineuse en association pour les 21 derniers cas à des corticoïdes et des sulfamides par voie buccale ou intra-musculaire.

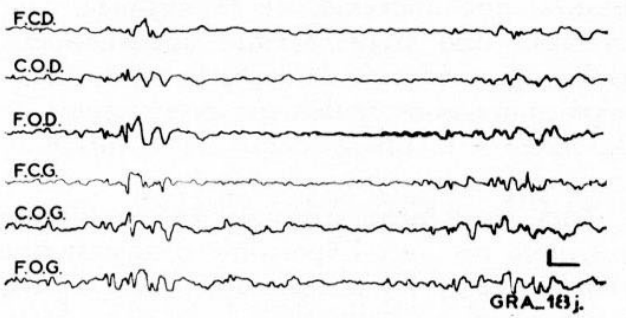



Fig. 4. — *Méningite purulente à pneumocoque. Convulsions. EEG à 18 jours: Décharges de pointes ondes disséminées. Décès à 22 jours.*

25 de ces malades sont décédés, l'évolution totale ayant duré de 3 jours à un ou deux mois pour la majorité. Lors du décès, trois d'entre eux seulement étaient apparemment stérilisés; 19 autres étaient toujours porteurs de méningite évolutive et 3 autres présentaient des lésions de surinfection.

Une complication anatomique manifeste put être décelée 16 fois, soit par les explorations, soit au contrôle nécropsique. Onze fois existait une énorme ventriculite suppurée, parfois cloisonnée; chez deux malades l'intervention neuro-chirurgicale mit en évidence la présence de cavités néoformées sans relation avec les ventricules; dans un cas, ne persistait plus qu'une mince coque de parenchyme cérébral entourant un magma nécrotique; enfin, à deux reprises, a été découvert un empyème sous-dural.

Parmi les onze malades qui ont survécu, la stérilisation du liquide céphalorachidien fut obtenue 10 fois en moins de 15 jours; l'évolution de la méningite chez le onzième

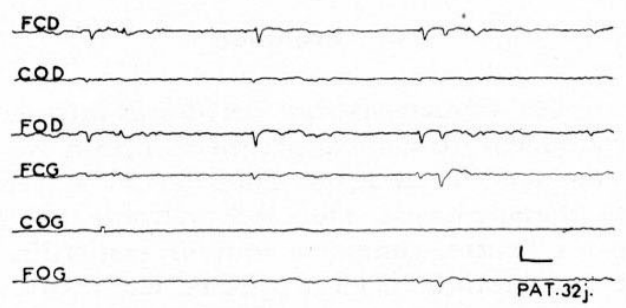



Fig. 5. — *Méningite purulente à E. Coli. Convulsions. EEG à 32 jours: tracé plat entrecoupé de pointes lentes isolées. Décès à 43 jours.*

fut prolongée, entrainant la constitution au cinquantième jour d'une pyocéphalie qui finalement cèda au seul traitement médical. La survie de ces enfants fut grevée 5 fois de séquelles graves: retard mental considérable, épilepsie, hydrocéphalie, hypertonie diffuse. Un recul manque pour apprécier le devenir des six autres enfants récemment traités, mais trois d'etre eux paraissent au bout de quelques mois présenter déjà un retard du développement psycho-moteur.

### D) Etude électroencéphalographique

Chez 18 malades un ou plusieurs tracés EEG ont été enregistrés. L'analyse de ces tracés permet d'isoler plusieurs aspects:

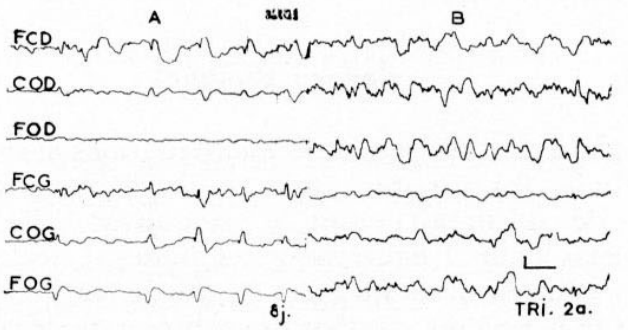



Fig. 6. — *Méningite purulente à proteus A) EEG à 7 jours alors que l'enfant présente des convulsions: pointes rythmiques bilatérales. B) EEG à 2 ans alors qu'il existe un important retard mental avec comitialité: asymétrie avec ondes lentes à pente raide á droite.*

#### 1º Tracés EEG enregistrés à la phase d'état de la méningite

Quatre types différents de tracés ont été observés à la phase d'état de la méningite:

a) *type 1:* correspond à un tracé normal ou presque normal pour l'âge de l'enfant: ce type de tracé a été trouvé 3 fois.

b) *type 2:* est caractérisé par un ralentissement diffus avec bouffées d'ondes lentes bifrontales (figure 1) ou par une assymétrie (figure 2): cinq enfants présentèrent ce tracé.

c) *type 3:* comporte sur un fond de tracé lent l'inscription d'anomalies irritatives:

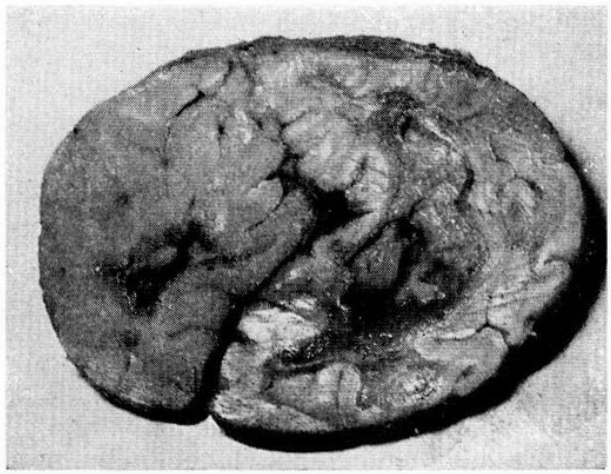


Fig. 7. — *Méningite à proteus. Décès au 56e jour: Pyocéphalie avec dilatation modérée du ventricule gauche, bien plus importante du ventricule droit, et nécrose parenchymateuse péri-ventriculaire.*

— trois fois ces anomalies se caractérisaient par des ondes lentes à pente raide, bilatérales (figure 3).
— cinq fois existaient des décharges épileptiques, soit d'ondes lentes ou de pointes uni ou bilatérales, soit de pointes rythmiques, soit de pointes-ondes disséminées et assynchrones, revêtant dans un cas un aspect d'hyperrythmie périodique (figure 4).

d) *type 4:* est marqué par un tracé totalement plat, sur ce type de tracé de fond rencontré deux fois s'inscrivaient dans un cas quelques rares pointes (figure 5).

### 2° Aspect évolutif des tracés EEG au cours de la maladie

L'évolution électro-encéphalographique a pu être suivie chez 8 malades:

a) un des enfants dont le premier tracé était normal conservait deux mois plus tard un tracé normal.

b) parmi 3 malades dont le premier tracé était de type 2, deux présentaient un tracé normal deux et trois mois plus tard. Chez le troisième au contraire, les anomalies EEG allérent en s'aggravant par l'apparition de décharges d'ondes pointes lors de la constitution d'un blocage de la base.

c) trois enfants seulement dont le tracé présentait des anomalies épileptiques ont pu être suivis; chez deux d'entre eux 10 jours plus tard, les mêmes anomalies persistaient, aggravées même dans un cas. Pour le troisième par contre, le tracé un mois plus tard était normalisé.

d) un des malades parmi lesquels le premier tracé était complètement plat, conservait la même absence d'activité électrique douze jours plus tard.

### 3° Confrontations électro-cliniques

Il est prématuré de tirer des conclusions précises, cependant dès à présent, l'étude électroencéphalographique réalisée à la période d'état permet d'obtenir certains renseignements de valeur orientative. Les trois malades dont le tracé initial était normal ont guéri, un seul conserve des séquelles psychomotrices discrètes. Les dix malades dont le premier tracé était de type 3 et 4 présentaient des signes cliniques également sévères: 8 d'entre eux sont morts, et l'un des deux survivants conserve des séquelles très importantes. Enfin, parmi les trois malades dont le premier tracé était de type 2, l'un est décédé et les deux autres ont guéri avec des séquelles de gravité variable.

## II. DISCUSSION GENERALE

En 1954, le Professeur Debre, Mozziconacci et Berkman[2], étudiant les méningites néonatales traitées par les antibiotiques, relevaient 33 observations dans la littérature, auxquelles ils ajoutaient 13 cas personnels. Depuis cette date, en dehors de nombreuses publications concernant des cas isolés ou peu nombreux, plusieurs auteurs ont rapporté leur expérience fondée sur des séries personnelles importantes, s'étendant sur huit à onze ans d'étude[3, 4, 8, 9, 10].

La comparaison de ces séries entre elles et avec les nôtres, permet de dégager quelques considérations d'ensemble.

### A) Notions étiologiques

Parmi les germes responsables des méningites purulentes, les entérobactéries représentent environ la moitié des cas, l'Esche-

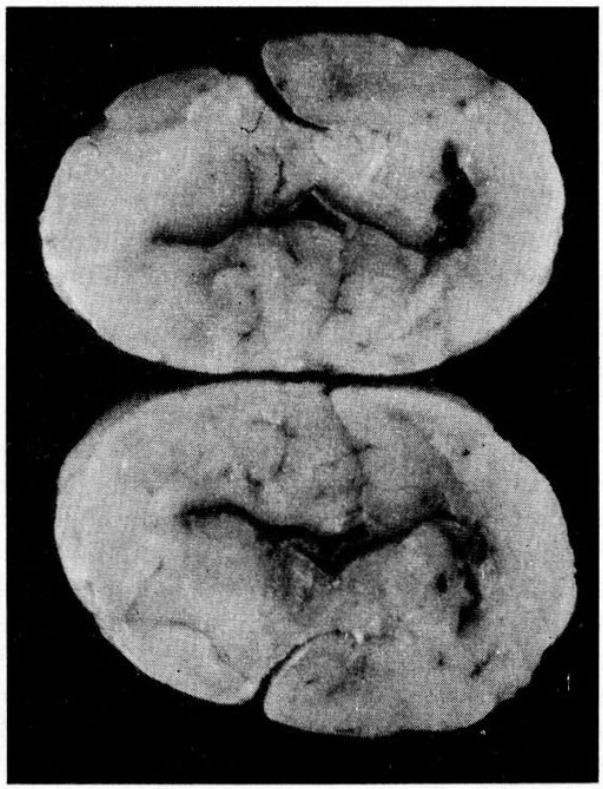


Fig. 8. — *Méningite à pneumocoque. Décès au 62e jour: Dilatation ventriculaire importante, mal visible du fait de l'affaissement avant la fixation, cavité nécrotique au contact du toit de la corne frontale droite*

richia coli étant le plus fréquemment rencontré; puis viennent les "paracolons", proteus, klebsiella, salmonella... Assez loin derrière se placent les cocci gram positif (pneumocoque, staphylocoque, streptocoque), avec des fréquences respectives variables d'un auteur à l'autre; le méningocoque n'est que très rarement observé. Depuis quelques années, de nombreux cas de méningite du nouveau-né à Listeria monocytogenes ont été signalés; Nichols et Wooley en relèvent 43 dans la seule littérature Nord américaine, de 1954 à 1962[6]. La fréquence par rapport aux autres méningites est encore difficile à fixer, allant de 0 à 17 %[6] selon les statistiques.

Le rôle favorisant des conditions pathologiques de la fin de la grossesse et de l'accouchement est unanimement admis. Ces facteurs interviennent, soit en permettant la contamination de l'enfant, soit en le plaçant dans des conditions de moindre résistance à l'infection et souvent par ces deux éléments conjugués. L'accouchement long et difficile, la rupture prématurée des membranes, l'anoxie néonatale, les infections chez la mère, enfin et surtout la prématurité sont fréquemment signalés.

### B) Notions cliniques et pronostiques

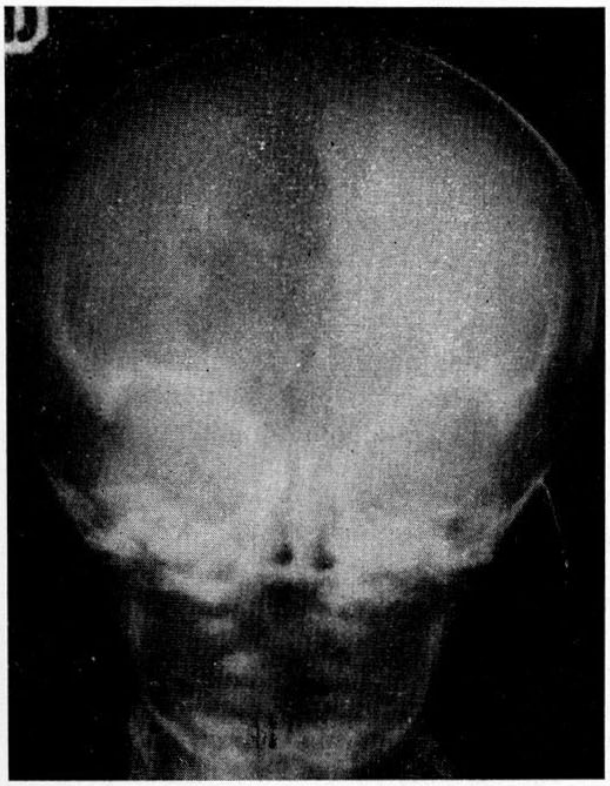
Tous les auteurs insistent à juste titre sur la fréquente banalité des signes et symptômes initiaux des méningites du nouveau-né qu'il faut savoir dépister derrière des troubles digestifs ou respiratoires, ou des modifications parfois discrètes du comportement. Les manifestations qui attirent directement l'attention sur le système nerveux traduisent déjà, en général, une souffrance neurologique grave. Aussi est-ce une caractéristique de ces méningites que le retard fréquent, et parfois considérable, avec lequel elles sont diagnostiquées et traitées: sur les 39 cas de Groover et coll.[4], le diagnostic fut retardé 14 fois, et découvert seulement à l'autopsie 10 fois.

Le pronostic global demeure extrêmement sévère, malgré les antibiotiques actuellement utilisés. Le taux de survie ne dépasse pas 25 à 35 %, si l'on excepte la statistique de Nichols et Wooley (67,4 % sur 46 cas) et celles, numériquement bien plus réduites, de Debre[2] et de Dygue[3]. De plus, dans une proportion qui peut atteindre la moitié des cas, la survie est gravée de séquelles neuropsychiques, souvent graves.

L'étude des statistiques permet d'assigner une valeur nettement péjorative à éléments étiologiques, cliniques et thérapeutiques.

La nature du germe influe considérablement sur le pronostic (tableau I): les entérobactéries qui sont aussi le plus souvent en cause, sont toujours responsables du plus fort taux de mortalité. L'influence de la prématurité est manifeste dans le série de Groover et coll.[4]: 19 % de survie sur 16 prématurés, contre 43 % sur 23 enfants à terme.

La survenue de convulsions ou de coma comme première manifestation de la méningite a une signification défavorable: le pourcentage de survie des nourrissons de ce



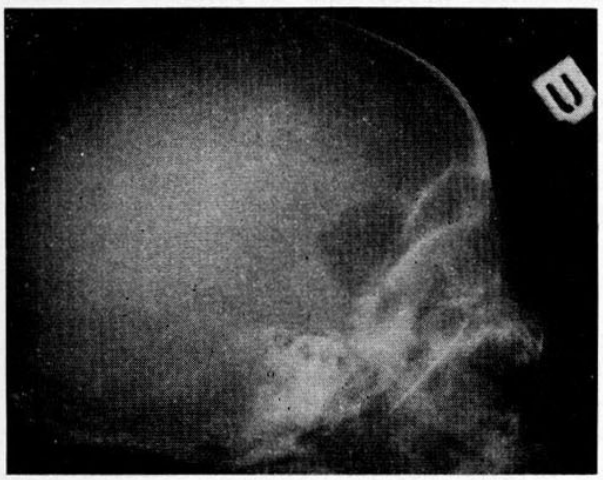


Fig. 9 et 10. — *Méningite à pneumocoque: Injection d'air dans une poche intracérébrale. Pas de communication avec les ventricules.*

groupe fut de 15 % dans notre statistique, contre 39 % pour les autres cas. Aucun des 5 malades de Groover ayant réalisé des convulsions précoces n'a survécu.

L'étude des méningites purulentes confirme donc cette notion générale que les convulsions du nouveau-né, lorsqu'elles se produisent au cours d'une atteinte organique du système nerveux, dépendent presque toujours de désordres cérébraux graves[7].

Nous avons déjà signalé par ailleurs la signification très péjorative des tracés EEG comportant des anomalies épileptiques.

Le traitement appliqué par la majorité des auteurs est, malgré quelques variantes, assez comparable dans tous les cas pour que sa nature influe peu, semble-t-il, sur le pronostic. Par contre, le retard de sa mise en train est d'une importance capitale. Dans notre série 41 % de survies pour les malades traités avant le quatrième jour de maladie, 20 % entre le cinquième et le septième jours, aucune survie au delà; Groover n'a obtenu aucune survie lorsque le traitement a été entrepris après le quatrième jour.

### C) Considérations physiopathologiques

La gravité et les aspects particuliers des méningites néonatales peuvent trouver une explication au moins partielle dans certaines caractéristiques, physiologiques, anatomiques et biologiques, propres à cet âge.

#### 1° Lésions anatomiques particulières

Au cours des méningites suppurées de la période néonatale peuvent s'observer, comme plus tard, des lésions d'arachnoïdite suppurée des sillons corticaux et de la base, compliquées de thrombose vasculaire et d'empyèmes sousduraux, mais l'originalité des altérations à cette période de la vie est représentée par l'importance des lésions ventriculaires et péri-ventriculaires. Dans certains cas, le ventricule considérablement dilaté correspond à une vaste poche purulente plus ou moins cloisonnée, dans d'autres le ventricule est lui-même peu hypertrophié mais entoure des lésions graves et étendues de fontes nécrotiques, d'abcès, de cavités porencéphaliques.

Ces destructions larges du parenchyme cérébral relèvent probablement de plusieurs facteurs sur lesquels ont insisté divers auteurs, en particulier E. Bargeton: l'épendyme à cet âge, souvent discontinu, représente une barrière peu efficace.

L'absence de myélinisation de la substance blanche hémisphérique la rend particulièrement friable et sensible aux phénomènes inflammatoires et trophi-

ques. Ainsi les lésions inflammatoires périventriculaires sous-épendymaires et la réaction oedémateuse périfocale extensive, aggravée par la pénétration directe du liquide ventriculaire pathologique et par des troubles de la perméabilité vasculaire, conduisent-elles à des lésions de nécrose oedémateuse diffuse de type périfocal.

Chez l'un de nos malades existait une fonte nécrotique étendue des hémisphères cérébraux; chez un autre, l'exploration neuro-chirurgicale permit de découvrir deux vastes poches frontales intra-parenchymateuses ne communiquant pas avec les ventricules.

On conçoit que de telles lésions soient responsables soit de troubles fonctionnels irréversibles, soit de séquelles particulièrement sévères.

### 2° Conditions immunologiques

Nous n'insisterons pas sur les caractéristiques immunologiques qui conditionnent les mauvaises réactions aux infections bactériennes générales et aux méningites suppurées en particulier du nouveau-né. Indiquons seulement que pour Yu et Grauaug[9], la grande fréquence des méningites à germes intestinaux dans le première quinzaine de la vie s'expliquerait par le fait que les anticorps maternels contre ces germes ne traversent pas le placenta.

### 3° Conditions de traitement

Nous avons déjà suffisamment insisté sur le fait que la latence ou l'atypie fréquentes du début des méningites purulentes néonatales conduit dans un grand nombre de cas à entreprendre tardivement le traitement. Dès lors, des lésions déjà importantes se sont constituées, qui encerclent les germes responsables dans des zones mal irriguées par suite des altérations vasculaires. Cette mauvaise pénétration de l'antibiotique, jointe à la résistance fréquente des germes, rend compte pour une part de l'insuffisance d'activité du traitement dans nombre de cas de méningite suppurée néonatale.

### 4° Retentissement métabolique général

L'imprégnation toxi-infectieuse, l'altération de zones importantes de la régulation végétative et sans doute aussi l'action nocive sur certains processus métaboliques, en particulier hépatiques et rénaux, des antibiotiques administrés à forte dose sont des facteurs responsables de troubles graves de la nutrition: déséquilibre hydroélectrolytique, troubles de la régulation glycémique, hypocalcémie, hypoxie représentent des complications fréquemment observées à la correction desquelles on doit tout particulièrement s'attacher.

## RÉSUMÉ

Les méningites suppurées de la période néonatale demeurent des affections encore fréquentes pour lesquelles l'utilisation des antibiotiques n'a pas permis d'obtenir les résultats favorables observés à un âge plus avancé. Cet échec du traitement responsable d'un taux important de mortalité ou de la persistance de séquelles souvent graves tire son origine des particularités étiologiques, immunologiques, anatomiques des méningites suppurées observées à cet âge, aggravée dans nombre de cas par la tardivité du diagnostic.

## RESUMEN

Las meningitis supuradas del período neonatal siguen siendo afecciones frecuentes y en ellas la utilización de los antibióticos no ha permitido la obtención de resultados favorables observados en edades más avanzadas. El fracaso de este tratamiento, responsable de una elevada tasa de mortalidad o de la persistencia de secuelas a menudo graves, se debe a particularidades etiológicas, inmunológicas, anatómicas de las meningitis supuradas observadas a esa edad, que en gran número de casos se ven agravadas por diagnósticos tardíos.

## SUMMARY

Suppurated meningitis of the neonatal period are still frequent and their treatment with antibiotics has not allowed to obtain the successful results it brings about in older persons. The failure of this treatment is responsible for a high degree of mortality or for the persistance of often serious sequelae; it is due to etiological, immunological, anatomic characteristics of suppurated meningitis observed at that age, which in a great number of cases become still more serious as a consequence of late diagnosis.



## ZUSAMMENFASSUNG

Die eitrigen Meningitiden, die kurz nach der Geburt auftreten, sind haeufig noch Krankheiten bei denen die Antibiotica noch nicht die guenstigen Erfolge erzielen, die man bei etwas aelteren Patienten beobachtet Diese Erfolglosigkeit der Behandlung, die schuld ist fuer die hohe Mortalitaet und das Weiterbestehen oft schwerer Folgezustaende, hat ihre Ursache in aetiologischen immunologischen und anatomischen Eigentuemlichkeiten der eitrigen Meningitiden dieses Alters, worbei die spaete Diagnosestellung in vielen Faellen als verschlimmernder Faktor hinzukommt.


## BIBLIOGRAPHIE


(1) *Bargeton, E.*: Particularités anatomiques des méningites suppurées du nourrisson. Journées de Pédiatrie (Prof. Debré) 1960.

(2) *Debré, R., Mozziconacci, P., Berkmann, M.*: Les méningites purulentes du nouveau-né. Sem. Hôp. Paris, 30: 4479, 1954.

(3) *Dygue, H.*: Prognosis in meningitis neonatorum. Acta Paediat. 51: 303, 1962.

(4) *Groover, R. V., Sutherland, J. M., Landing, B. H.*: Purulent meningitis of newborn infants. Eleven-year experience in the antibiotic aera. New England J. Med. 264: 1115, 1961.

(5) *Martin C. L.*: Mécanismes pathogéniques des méningites aiguës purulentes et de leurs complications. J. Méd. Bordeaux 137: 482, 1960.

(6) *Nichols, W., Wooley, P. V.*: Listeria monocytogenes meningitis. J. Pediat. 61: 337, 1962.

(7) *Ribstein, M., Walter, M.*: Convulsions du premier mois. Rev. Neurol. 99: 91, 1958.

(8) *Watson, D. G.*: Purulent neonatal meningitis. J. Pediat. 50: 352, 1957.

(9) *Yu, J. S., Grauaug, A.*: Purulent meningitis in the neonatal period. Arch. Dis. Childh. 38: 391, 1963.

(10) *Ziai, M., Haggery, R. J.*: Neonatal meningitis. New England J. Med. 264· 114, 1961.

# Tuberculous Meningitis

**HONOR V. SMITH**
From the Department of Neurology,
United Oxford Hospitals, England.

Tuberculous meningitis was first described towards the end of the eighteenth century by the scotch physician, Sir Robert Whytt (1768). After giving a vivid account of the clinical picture he discusses the treatment and prognosis: "I freely own", he writes, "that I have never been so fortunate as to cure one patient who had those symptoms which with certainty denote the disease". Until the advent of streptomycin over 150 years later these words remained as true as on the day they were written. Today, however, with modern chemotherapy, recovery can and should be expected in the great majority of cases. Nevertheless, it must always be remembered that potentially tuberculous meningitis remains a killing disease, and that if treatment is unduly delayed, or if it is inadequate, then sooner or later the patient will die.

Since Whytt's first account a very large literature on the subject or tuberculous meningitis has accumulated. No attempt is made here to review this literature. Rather, a short account of the disease is given with special emphasis on those aspects that experience gained at Oxford has shewn to be particularly important, especially in regard to diagnosis, prognosis and treatment.

## Aetiology

Tuberculous meningitis is always secondary to tuberculosis elsewhere in the body, and can complicate any form of the disease. Its distribution is accordingly world wide and both sexes are affected. Since a poor standard of living favours the spread of tuberculosis, it is commoner among the under-privileged than among the better-to-do. An example of this is the high proportion of the children treated at Oxford who were illegitimate or came from broken or otherwise unsatisfactory homes (Ounsted, Smith 1955).

In any given community the incidence of tuberculous meningitis varies directly with that of tuberculosis as a whole. In countries where a rising standard of living, appropriate public health measures and effective treatment of infectious cases is bringing tuberculosis under control, tubercolous meningitis is growing less common. In England, for example, the number of notifications of tuberculosis fell progressively from 51,725 in 1947 —when our study of the chemotherapy of tuberculous meningitis was begun— to 23,605 in 1960. (Report of the Ministry of Health, 1961). Table 1 shows the number of patients with tuberculous meningitis treated at Oxford in successive 2-yearly periods between the same dates. As all service men, their wives and children, and all patients sent to us from elsewhere for special reasons have been excluded, these figures may be taken as indicative of the prevalence of tuberculous meningitis within approximately a 100 mile radius of Oxford. The progressive fall in the numbers of patients coming for treatment is obvious.

As regards age incidence, the classical teaching, that tuberculous meningitis is preeminently a disease of childhood, needs con-

siderable modification. It may arise at any time during the course of chronic tuberculosis when, if not treated, it constitutes the terminal event. Such cases are not uncommon and naturally the patients tend to belong to the older age groups. Thus of the 210 patients listed in Table I, one in five was over 30 years old, no fewer than 30 were over 40 years old, and 10 were over 50 years old. Owing to the widespread belief that tuberculous meningitis only attacks children, these older patients are often seriously at risk as, unless they are known to have tuberculosis, the nature of the meningitis may not be suspected until the disease has reached the irreversible stage.

Most commonly, however, tuberculous meningitis arises as a complication, immediate or remote, of the primary infection. The peak incidence in any community will therefore depend on the age at which the majority of the population first became infected. The teaching that tuberculous meningitis is essentially a disease of children derives from the time when most people became infected in childhood. As, however, tuberculosis is brought under control, so, not only does the overall incidence of the disease fall, but the age at which primary infection occurs tends to increase. This, too, is well illustrated by the figures in Table I. Since the end of 1950 the number of children under 15 years old has steadily diminished with a consequent increase in the mean age of our patients. Today in England the peak incidence for primary infection, and therefore for tuberculous meningitis, is in adolescence or early adult life.

## Pathogenesis

Whether the meningitis occurs as a complication of the primary infection or of chronic tuberculosis, the infection nearly always reaches the central nervous system by way of the blood stream. Before the advent of streptomycin a concomitant miliary spread was found *post-mortem* in an overwhelming majority of cases, whether or not it had been recognised in life. Conversely, meningitis was found in the great majority of patients dying of miliary tuberculosis (Blacklock and Griffin, 1935). For a long time, therefore, it was believed that tuberculous meningitis was, in effect, simply miliary tuberculosis of the meninges. Rich strongly challenged this view (Rich and McCordock, 1933; Rich, 1946). He produced evidence to shew that the meningitis arises in two stages. First, during some stage of bacteraemia, tuberculous lesions —the so called "Rich's foci"— are seeded in the brain or meninges and, later, one or more of these rupture: their contents, which include living *M. Tuberculosis* are discharged into the cerebro-spinal fluid (C.S.F.) when a generalised meningitis results. Although no attempt has been made at Oxford to repeat Rich's painstaking search for small tuberculomata, "Rich's foci" have nevertheless been found in a considerable number of fatal cases. Moreover, unusual C.S.F. findings (Cairns and Smith, 1952) and certain clinical anomalies such as the acute onset (Taylor, Smith and Vollum, 1955) are most easily explained on Rich's hypothesis. Nevertheless this hypothesis fails to explain why tuberculous meningitis should be so much more closely associated with miliary tuberculosis than are the other varities of haematogenous tuberculosis, such as renal, or bone and joint disease.

Occasionally the meninges become infected by direct spread from a neighbouring tuberculous focus, notably otitis media or spinal caries. The true identity of the otitis, and therefore of the meningitis, may be overlooked for a considerable time; partly because infection of the middle ear with intracranial extension is so much more commonly pyogenic, and partly because the tuberculous nature of the otitis may be masked by a superimposed pyogenic infection.

Tuberculous meningitis and spinal caries are not infrequently associated and there is no doubt that infection by direct spread does occur. Thus in one of our fatal cases a large cavity in the body of one of the lumbar vertebrae was found *post-mortem* to communicate directly with the subarachnoid space, and caseous material was actually seen lying free in the sacrak *cul-de-sac*. In such cases the meningitis is often preceded by signs of incipient Pott's para-

plegia. It is, however, unusual to find spinal caries and meningitis in association without other evidence of tuberculosis. In chronic cases there may be pulmonary or renal disease also, while in some acute cases, with a heavy miliary spread, there is the possibility that the spinal caries is rather another manifestation of the blood-born infection than the direct cause of the meningitis. In these acute cases the spinal lesion may be overlooked owing to the natural tendency to attribute pain and stiffness of the back to the meningitis.

Intercurrent infections (Smith and Daniel, 1947) and especially measles (Lincoln and Sewell, 1963), head injury (Debre and Brissaud, 1953), and tuberculin testing (Lincoln, 1947) have all been noted as possible precipitating factors. Although none has yet been definitely incriminated, it is not unreasonable to suppose that if a patient is struggling to contain his tuberculous infection, some such insult may well tip the scales against him. From the practical point of view, it is important not to attribute the early symptoms of the meningitis to, for example, an antecedent intercurrent infection. If the patient does not rapidly regain his normal health after the signs of the intercurrent infection have subsided, then the possibility that he may be developing tuberculous meningitis should be born in mind.

## PATHOLOGY

The term "tuberculous meningitis" is, in some degree, a misnomer since the infection is not limited to the subarachnoid space and its blood vessels but also involves the ventricular system and choroid plexuses. Full descriptions of the pathological findings in both untreated and treated cases are readily available in the literature (Greenfield, 1958; Debre et Brissaud, 1956; Daniel, 1949; Smith and Daniel, 1947). Here those changes are discussed that most directly influence treatment and prognosis. Chief among them are the meningeal exudate and the obliterative arteritis. These are essential components of the disease process and, as such, are always present in some degree except, possibly, when this is cut short at a very early stage by appropriate chemotherapy. Much rarer, but still important in that when they occur they require special treatment, are diffuse cerebral oedema, the large tuberculoma, and occlusion of the aqueduct of Sylvius.

### Meningeal exudate

In exceptional cases in which death occurred very early in the illness an intense cellular exudate has been found distributed diffusely throughout the subarachnoid space (Taylor, Smith and Vollum, 1955), or limited to the immediate vicinity of a "Rich's focus" (Macgreggor and Green, 1937). Typically, however, the exudate is at its most intense in the more anterior of the basal cisterns —the *cisterna chiasmatica et interpeduncularis*— whence it spreads through the *cisterna ambiens* and along the Sylvian fissures. This highly characteristic distribution is, in all probability, a function of the subacute course of the illness since it is seen also in diffuse neoplasia of the meninges and in purulent meningitis when inadequate chemotherapy has prolonged the illness without effecting a cure. By virtue of its anatomical distribution this exudate causes the common pareses of the sixth and third cranial nerves, the communicating hydrocephalus that is such a notorious complication of the disease (Cairns and Smith, 1952) and, in all probability, the characteristic mental changes (Williams and Smith, 1954).

In the most acute cases this exudate may be almost semi-purulent. After some months of chemotherapy, however, it becomes not only very thick but almost as hard as cartilage (Daniel, 1949). It still contains streaks of caseous material in which, on careful search, *M. tuberculosis* can be recognised (Cairns, 1949). These organisms are sheltered from the action of the antibiotics and are thus able to keep the infection smouldering. In very long standing cases there may be incipient organisation as shown by the presence of fibroblasts and capillary ingrowths. In some successful cases this organisation presumably becomes complete as judged by the calcification seen on radiography (Acheson, 1957).

In summary, then, the classical basal exudate is a serious obstacle to successful treatment, both because it impedes free access of the antibiotics to the site of infection and because it may give rise to a crippling hydrocephalus.

### Obliterative arteritis

Even more serious is the obliterative arteritis that affects the blood vessels in the vicinity of a tuberculous focus (Smith and Daniel, 1947). Owing to the characteristic distribution of the basal exudate the vessels most at risk are the middle and anterior cerebral arteries and their branches. Vessels of every calibre may be involved from the smallest arterioles to the basilar artery itself. Inevitably infarction of the brain tissue results and this, by definition, is irreversible. Depending on the number and extent of the infarcts the neurological deficit can vary from a mild and transient hemiparesis to complete and permanent decerebration. As brain tissue is destroyed, so the ventricle or ventricles enlarge and the gross enlargement seen in unsuccessfully treated cases is almost always a combination of constructive and compensatory hydrocephalus. A similar arteritis followed by disastrous infarction can occur in purulent meningitis if the infection is not rapidly eradicated (Cairns and Russell, 1946; Smith, Norman and Urich, 1957).

### Diffuse cerebral oedema

During the first few days of treatment a patient will, very occasionally, develop signs of an intense rise in intracranial pressure due, not to the common communicating hydrocephalus, but to diffuse cerebral oedema. This oedema is, presumably, inflammatory in origin and akin to that so brilliantly shewn by Ebert and Barclay (1952) to take place in the immediate vicinity of a tuberculous focus. Similarly, acute pulmonary oedema of inflammatory origin may occur in cases in which there is an overwhelming miliary spread. Before corticosteroids became available both these conditions were, in our experience, invariably fatal. Following Ebert's work, however, we have found that both can be successfully controlled by cortisone.

### Tuberculoma

Tuberculomata, other than the small "Rich's focus" described above, are not common. They are, however, important because if so situated that they obstruct the circulation of the C.S.F. they demand surgical intervention. They may be single or multiple and very greatly in size. The commonest tuberculoma is essentially a cold abscess with caseous or liquid contents; more rarely it may be a solid granuloma. They are occasionally found in the spinal canal where they compress the cord, and intramedullary spinal tuberculomata have also been described.

### Occlusion of the aqueduct of Sylvius

In most fatal cases a severe granular ependymitis is found at autopsy. Occasionally, however, the lateral and third ventricles are found lined with a thick, pinkish gelatinous exudate. This may extend throughout the aqueduct of Sylvius and completely occlude it. When this happens a non-communicating hydrocephalus is set up which again demands surgical intervention.

### Pathology in relation to prognosis

Even before the possible curative value of streptomycin in tuberculous meningitis was confirmed, it was realised that success or failure would depend on the extent and degree of the exudate and obliterative arteritis present when treatment was begun (Smith and Daniel, 1947). Later experience has fully confirmed this. The basal exudate not only produces the clinical syndrome of squint, mental confusion and raised intracranial pressure, but also causes characteristic abnormalities in the pneumoencephalogram (Smith, Vollum and Cairns, 1948; Salvaing, 1954). The extent and intensity of the exudate can be infered from these abnormalities and a close correlation has

been shewn to exist between the degree of the pneumoencephalographic abnormalities and both the clinical condition of the patient at the outset of treatment and the prognosis (Lorber, 1951; Muller, 1953; Acheson and Smith, 1958). Efforts to demonstrate the extent and degree of vascular damage by angiography have been less successful, as it is difficult to detect occlusion of the smaller vessels. However, infarcts of the basal ganglia and internal capsule —a common site— produce well marked physical signs and typically cause an asymmetrical enlargement of the lateral ventricles as shewn by pneumoencephalography.

There is thus a sound pathological basis for the simple clinical classification of severity that has, in practice, proved so useful in assessing the prognosis (M.R.C. report, 1948; Smith, Vollum, Taylor and Taylor, 1956; Fitzsimons, 1963); namely:

Group I Patients are fully conscious and rational, with signs of meningeal irritation but with no focal neurological signs, or signs of hydrocephalus.

Group II Patients are mentally confused, and/or have such focal neurological signs as squints or hemiparesis.

Group III Patients are mentally inaccessible owing to the depth of stupor or delirium on admission, and/or have a complete hemiplegia or paraplegia.

## The cerebro-spinal fluid

The changes in the C.S.F. in untreated tuberculous meningitis are well documented (Merritt and Freemont-Smith, 1938; Lincoln, 1947; Smith and Daniel, 1947). Typically, there is a moderate pleocytosis (60 to 400 cells per cu mm) which is predominantly but not exclusively lymphocytic; an increase in protein that closely parallels the cell count (80 to 400 mg per 100 ml), while the sugar and, in advanced cases, the chloride contents are diminished. The permeability of the blood-C.S.F. barrier to bromide is greatly increased so that the ratio of serum-bromide to C.S.F.-bromide is raised from the normal value of between 0.3 and 0.5 to over 0.6 and often to the order of unity (Taylor, Smith and Hunter, 1954).

There is a considerable body of circumstantial evidence to shew that the C.S.F. changes in tuberculous meningitis are the expression of spontaneous intrathecal tuberculin reactions, provoked by the presence in the C.S.F. of M. tuberculosis substances containing tuberculin (Cairns and Smith, 1954; Taylor, Smith and Vollum, 1955). The intensity of these reactions varies both with the amount of antigen and with the sensitivity of the subject (Swithinbank, Smith and Vollum, 1953). Wide departures from the characteristic picture are therefore to be expected and are in practice seen with fair frequency. These departures are of some importance as they tend to obscure the diagnosis.

The characteristic C.S.F. responses may be either diminished or exaggerated.

## Diminished C.S.F. responses

Very early in the illness the abnormalities in the C.S.F. may be minimal, but minor changes are also sometimes seen in advanced cases. It has long been known that in tuberculous meningitis the intracranial reaction to tuberculin may be diminished or lost (Happ and Casperis, 1922; Taylor, Smith and Vollum, 1953). When this happens the cell counts in the C.S.F. are often low —below, for example, 40 or even 30 per cu mm— presumably because the sensitivity of the meninges is also diminished. The protein content may also shew only a small increase. Unless this association between meningeal and intradermal sensitivity is remembered, it may be thought that such minor changes in the C.S.F., together with a negative Mantoux test, exclude the diagnosis of tuberculous meningitis. A very similar effect is produced by the corticosteroids and if these are exhibited in an unconfirmed case, serious confusion may result.

### Exaggerated C.S.F. response

There is a small but well attested group of cases in which both the clinical events and C.S.F. findings differ sharply from the standard pattern. This syndrome has been described as "Tuberculous Meningitis of acute onset". As the name implies the onset is acute or even abrupt. There is often a well marked, spontaneous remission of symptoms early in the illness while with chemotherapy the prognosis is, on the whole, good. The numbers of cells in the C.S.F. exceed the commonly accepted maximum and counts of above 1000 per cu mm have been recorded. The differential count, too, is not typical in that either an unusually large number of polymorphonuclear leucocytes may be present or, more commonly, virtually all the cells may be lymphocytes. There is good reason to suppose that this syndrome reflects the sudden discharge of large amounts of tuberculin containing material into the C.S.F. (Taylor, Smith and Vollum, 1955).

It will be readily understood from this short description that diagnosis may be extremely difficult, especially as the sugar content may still be normal when the C.S.F. is first examined. If, however, the existence of this unusual variant is remembered, and repeated samples of C.S.F. appropriately stained and carefully searched for *M. tuberculosis,* it should be possible to make the correct diagnosis.

### Bacteriology

Ultimate proof of the diagnosis rests on the identification of M. tuberculosis in the C.S.F. by examination of smears, or by culture or guinea pig innoculation. The number of positive results obtained depends both on the time devoted to searching the smears and to the number of specimens examined. Methods that have proved successful in about 90 % of fresh cases have been described (Smith, Vollum, 1954).

One point of some practical importance is that *M. tuberculosis* are more frequently found in ventricular than in lumbar C.S.F. and in certain successful cases organisms have been found in ventricular fluid long after the lumbar C.S.F. has become permanently sterile. If, therefore, there is an opportunity of obtaining ventricular C.S.F. in an unconfirmed case —as, for example, at ventriculography— the specimen should be examined with more than ordinary care.

### The C.S.F. under treatment

Provided that corticosteroids are not exhibited the cell counts and protein content in the C.S.F. during the first four to six weeks of treatment alter in a way that is sufficiently characteristic to have diagnostic value.

### Cell counts

The characteristic variations in the cell counts are apparent when the C.S.F. is examined daily, as when intrathecal medication is used. Typically, at some time during the first ten days of treatment, sharp fluctuations begin, the counts rising from their base level of, for example, 250 per cu mm to 700 or 800 per cu mm or more, only to fall again by the following day. At the peak of these fluctuations the majority are polymorphonuclear leocucytes. Often, too, films or cultures are again positive for M. tuberculosis. These sharp fluctuations are not caused by irritation from the intrathecal medication but are exaggerated spontaneous tuberculous reactions, provoked by the liberation of breakdown products of the organisms that are dying under the influence of the chemotherapy (Smith and Vollum, 1950). They are specific for tuberculous meningitis and they disappear when the infection is obsolescent.

### Protein content

At some time during the first few weeks of treatment it is the rule for a sustained rise in the protein content to begin. This usually continues until the infection is brought under control when the curve first levels off and then declines. It may, however, be many months before the sustained

fall begins and during this time it is quite common to obtain occasional positive films or cultures, certain proof that the infection is still active. This characteristic rise in protein content in seen whether or not intrathecal medication is given.

If a manometric spinal block develops, the protein content rises to well over 1000 mg per 100 ml and only falls as the block resolves.

### The C.S.F. changes and corticosteroids

If corticosteroids are exhibited these changes in cell counts and protein content are not seen. Instead there is a sharp fall in cell count, often to the order of 20 or 30 per cu mm. The protein content may also fall but this is usually less dramatic than the fall in cell counts.

### The C.S.F. changes and prognosis

When no adjuvant to chemotherapy is being used, the pattern of the C.S.F. changes during treatment have a certain prognostic significance. Early in treatment well marked fluctuations in the cell counts is an encouraging sign. Later, when the patient is shewing a sustained and satisfactory clinical improvement, a return of the C.S.F. towards normal is confirmatory evidence that the infection is obsolescent. When, however, the patient remains gravely ill, then an inactive fluid with low cell counts which shew no well marked fluctuations is a very ominous sign indeed, and a C.S.F. in which the cell count and protein content are approaching normal is fully compatible with the presence of the grossest intracranial exudate. The same combination of a critically ill patient, with an unusually extensive intracranial exudate as shewn by pneumoencephalography or *post mortem*, and minimal changes in the C.S.F. has been seen after treatment with corticosteroids.

## THE CLINICAL PICTURE

The clinical picture of tuberculous meningitis has been frequently described (Osler, 1892; Still, 1909; Smith and Daniel, 1947; Debre and Brissaud, 1953; Lincoln and Sewell, 1963), while ever since the introduction of streptomycin the importance of early diagnosis has constantly been emphasized. In spite of this, early diagnosis has never been the rule while now that tuberculous meningitis is becoming less common the proportion of late to early cases is again increasing. Accordingly, the salient clinical features will be briefly described, together with certain variants that are likely to confuse the diagnosis.

### The onset

Classically the onset is insidious and lasts from between one and two or three weeks, or even longer. Ideally, it is during this stage that the diagnosis should be made and treatment begun, but it is also at this stage that diagnosis is most difficult. Children become listless, easily tired and rather irritable; they are reluctant to eat, often they vomit, complain of abdominal pain and are constipated. Adults complain of feeling ill and of headache or, sometimes, pain in the back. They, too, lose their appetite and may be nauseated and vomit. Some degree of fever is the rule.

Thus when the patient is first examined there may be nothing to suggest he is seriously ill; in particular, it must be remembered that at this stage of the illness, stiffness of the neck is only too often inconspicous or even absent. When, however, he is re-examined 4 or 5 days later it is found that, while no specific illness has declared itself, the patient is no better but is still feverish and losing weight. There may be thus nothing to distinguish the early symptoms of tuberculous meningitis from those of other, often quite trivial, febrile illnesses, *except that they persist.* This should at once arouse suspicion and this suspicion is strengthened if there is a history of contact or of previous tuberculosis, or, in a child, if the Mantoux test is positive. In women, amenorrhea is an almost constant finding. If at the end of another day or two the patient is still unwell, or if the slightest trace of neck stiffness is found, then the

C.S.F. should be examined without further delay.

At the earliest stage of the illness, therefore, the chief difficulty is to recognise the presence of the meningitis. Once signs of meningeal irritation develop, as they commonly do soon after the patient comes under observation, the problem is to determine the nature of the meningitis. Even at this stage the presence of the meningitis may be missed in infants unless it is remembered that in this age group the cardinal sign of meningitis is *not* stiffness of the neck but fullness of the fontanelle. But so long as treatment is begun while the patient is still fully rational and before any focal neurological signs have developed, the prognosis should be excellent.

### Anomalies of onset

The onset may either be unusually prolonged or curtailed. The latter is the more likely to confuse the diagnosis. The syndrome of tuberculous meningitis of acute onset has already been described. Another variant of the onset is seen in cases in which the presenting symptom is a fit. This is commonly focal and followed by Todd's paralysis. Sometimes, too, the first definite event is the abrupt appearance of focal neurological signs, such as aphasia or hemiparesis. These events are, in all probability, vascular in origin and shew how early in the illness the endarteritis begins.

### The fully developed picture

Sooner or later the picture of indefinite ill-health gives way to one of definite meningitis and it now becomes clear that the patient is seriously ill. Perhaps the most constant and characteristic finding at this stage is the mental confusion (Williams and Smith, 1954). Drowsy and irritable during the early stages of the illness, the patient now also grows forgetful; he is unable to give a lucid history, and is uncertain of his whereabouts in space and time. Focal neurological signs appear, notably squints and mono— or hemipareses, together, often, with some degree of papilloedema. A curiously common finding is preservation of the ankle jerks with depression or absence of the knee jerks. The cause of this is unknown.

By now the picture is almost unmistakable but by now, too, the patients' chances of a full recovery have already been prejudiced. If treatment is further delayed the stupor deepens to coma. The neurological signs become more pronounced. The patient may go blind, and in the end, the full picture of decerebrate rigidity may supervene.

## DIFFERENTIAL DIAGNOSIS

In the early stages of the illness, before definite signs of meningeal irritation have appeared, the diagnosis is from other febrile illnesses. Pressure from tuberculous glands on the trachea or a main bronchus may set up an irritating cough and suggest a diagnosis of acute bronchitis. Influenza and acute rheumatic fever may well cause confusion as headache is often severe and accompanied by pain and stiffness in the back. In countries in which it is common, typhoid fever must also be distinguished. Careful examination including ophthalmoscopy, together with radiography of the chest and tuberculin testing, may reveal evidence of systemic tuberculosis or even of a miliary spread. The critical investigation, however, is examination of the C.S.F. and in any case in which the diagnosis remains obscure lumbar puncture should not be delayed. It is worth remembering that examination of the blood is of little use in the differential diagnosis of tuberculous meningitis as often the erythrocyte sedimentation rate is quite low while a moderate polymorphonuclear leucocytosis, up to 15,000 per cu mm or even higher, is not uncommon.

Once the presence of a meningitis is detected the diagnosis is from other forms of meningitis in which leucocytes predominate in the C.S.F. Of these the most important are virus infections, such as pre— or non— paralytic poliomyelitis, glandular fever and mumps meningoencephalitis pyogenic infections and particularly brain abscess; spi-

rochactal infections, especially syphilis and leptospirosis; yeast infections, such as that due to *cryptococcus neoformans;* and tumours, particularly diffuse neoplasia of the meninges. Among these, the most important to distinguish quickly is brain abscess; not because it is the commonest cause of confusion but because disaster will follow if it is not promptly diagnosed.

Clinically, one of the most helpful pointers to the diagnosis is the mental state, since full mental alertness and lucidity in a patient who is obviously and seriously ill are very rare in tuberculous meningitis. In the C.S.F. it is the tendency for the elevation of the protein content to keep pace with the cell count and, except in the earliest stages, for the sugar content to fall that are most helpful, in distinguishing tuberculous meningitis from most other varieties of so-called "lymphocytic" meningitis.

In diffuse neoplasia of the meninges, however, the changes in the C.S.F. may be distinguishable from those of tuberculous meningitis. Moreover, not only the history and many of the clinical findings but also the results of the bromide test and of air encephalography may all be remarkably similar in the two conditions. Typically, however, in neoplasia of the meninges the patient is afebrile and, even when obviously ill, is mentally lucid, while all the tendon reflexes tend to be diminished or absent. Ultimate proof of the diagnosis rests on the identification of malignant cells in the C.S.F. and these should be sought with the same assiduity and frequency as *M. tuberculosis* (Hughes, Hume Adams, and Ilbert, 1963).

## Special investigations

The special investigations other than radiography of the chest and skull and the Mantoux test, that have proved most useful in diagnosis are the bromide test and air encephalography.

The bromide test is performed by administering sodium bromide either by mouth or intravenous injection, allowing time for equilibrium to become established, and then estimating the ratio between the bromide content of the C.S.F. and that of the serum (Taylor, Smith and Hunter, 1954). In the normal, values for this ratio vary between about 0.3 and 0.5. In tuberculous meningitis the permeability of the blood-C.S.F. barrier to bromide is greatly increased so that in at least 90 % of cases the ratio is above 0.6 and is often of the order of unity. An exactly similar elevation of the bromide ratio accompanies artificially provoked intrathecal tuberculin reactions (Smith, Taylor and Hunter, 1955). By contrast, in other varieties of meningitis shewing comparable changes in the C.S.F. the bromide ratio seldom exceeds 0.6. The only other condition in which we have found the bromide ratio to be as constantly and markedly elevated as in tuberculous meningitis is diffuse neoplasia of the meninges.

## Air encephalography

The distribution of the basal exudate produces characteristic changes in the pneumoencephalograph. Typically the ventricular system is dilated and though in the earliest cases this may be minimal, even a little rounding of the frontal horns of the lateral ventricles almost excludes a virus infection. In all except the earliest cases, not only are the lateral ventricles enlarged but the air is held up in the pontine cistern so that none in seen in the basal cisterns anterior to the posterior clinoid processes or over the cerebral hemisphere. These appearances, which are best seen in the lateral projection taken in the brow up position, and which have been named the *"syndrome de Cairns"* (Salvaing, 1954), are pathognomonic of basal meningitis, and among such meningitides, tuberculous meningitis is by far the most commonest.

Lumbar pneumoencephalograph is well tolerated by patients with meningitis provided that only small amounts of air are injected. In cases, however, in which cerebral abscess or a massive tuberculoma are suspected, or in which an unusual degree of papilloedema is seen, angiography or

ventricular estimation through bilateral burr-holes, followed if necessary by ventriculography, should be used instead.

### The test of treatment

In any case in which the possibility of tuberculous meningitis has seriously to be considered, anti-tuberculous treatment should be begun without delay. In the great majority of cases all doubts as to the diagnosis will be resolved by the end of 4 to 6 weeks by the patient's progress and by the behaviour of the C.S.F. There is, unhappily, no doubt that many lives and much serious disability would have been saved had this policy been more widely adopted. It is still frequently said that once intrathecal streptomycin is given the C.S.F. picture becomes so distorted that diagnosis is obscured, since the subsequent changes in the cell counts and protein contents must be attributed to irritation by the intrathecal medication. This is a fallacy, as any reasonably critical appraisal of the evidence shews (Smith and Vollum, 1950). Blood in the C.S.F. such as follows a traumatic tap, is a potent source of artefact but provided the lumbar punctures are reasonably atraumatic, doses of up to 100 mgms of streptomycin are remarkably bland. In our experience the sharp fluctuations in the cell counts described above are almost pathognomonic for tuberculous meningitis. When a mistake has been made in diagnosis the pleocytosis subsides steadily and the characteristic slow rise of the protein content does not occur. In tuberculous meningitis the clinical course, too, is characteristic in that however satisfactory the patient's progress, he is seldom strictly apyrexial and steadily gaining weight by the end of 4 to 6 weeks of treatment.

## TREATMENT

The treatment of tuberculous meningitis consists of the chemotherapy, the use of adjuvants, general measures, and treatment of the systemic disease.

### Chemotherapy

The most useful drugs in treatment are streptomycin and iso-nicotinic acid hydrazide (I.N.A.H.), ethionamide, and para-amino benzoic acid (P.A.S.), in that order.

### Streptomycin and I.N.A.H.

The regimes of treatment used at different centres vary greatly but all authorities agree that prolonged systemic administration of both streptomycin and I.N.A.H. is necessary. There is, however, great disagreement as to whether intrathecal medication is also required. Streptomycin, when given by intramuscular injection in the presence of active tuberculous meningitis, appears in the C.S.F. in amounts that exceed the required *in vitro* bacteriostatic concentration. Nevertheless, on streptomycin alone results are better with combined intrathecal and systemic administration than with systemic treatment alone (M.R.C. Report, 1948). This is presumably related to the very high concentration that persists in the C.S.F. for some hours after an intrathecal injection. Many authorities hold that the advent of I.N.A.H. has rendered intrathecal therapy unnecessary. There is no doubt that many patients recover on systemic chemotherapy alone and this form of treatment has the merits of simplicity and of avoidance of the risks inherent in intrathecal medication.

For several years, however, cases have been accumulating at Oxford in which systemic chemotherapy only was begun elsewhere and in which the patients steadily deteriorated, to improve and ultimately to recover when, after transfer, intrathecal therapy was added to the regime. As in several of these cases the systemic treatment was begun early in the illness, at a time when the prognosis should have been excellent, the conclusion is inescapable that not only is combined treatment more effective than systemic treatment alone, but that it should be used even in early and favourable cases (Fitzsimons and Smith, 1963).

The regime used at Oxford has been described in detail (Smith, Vollum, Taylor and Taylor, 1956) but may be summarised here: adults receive 50 mg of both streptomycin and I.N.A.H. daily by lumbar puncture unless there is a spinal block, when cisternal or ventricular punctures are substituted. These are continued until the patient's clinical condition is satisfactory, until he is apyrexial and gaining weight steadily, until the protein level in the C.S.F. is shewing a well sustained fall and the cell counts are below 100 per cu mm, and until at least 8 weeks have elapsed since *M. tuberculosis* were last identified in the C.S.F. This last criterion is only valid when daily specimens of C.S.F. are examined bacteriologically. At the same time 1G streptomycin by intramuscular injection and 300 mg I.N.A.H. by mouth are given daily. In the absence of chronic systemic disease the systemic treatment is continued for a minimum of two months after the intrathecal medication is concluded or for a total of six months, whichever period is the longer. Children receive a suitably reduced dose calculated on a rough weight for weight basis.

### Ethionamide

The place of ethionamide in treatment has not yet been fully assessed but it bids fair to prove a most useful line of defence. It has a powerful anti-tuberculous effect (Fouquet et al, 1958; Brocard et al, 1959) and when given by mouth passes freely from blood to C.S.F. (Hughes, Smith and Kane, 1962). It is, however, nauseating which is a serious drawback to its use in tuberculous meningitis. Nevertheless, it can be a useful addition to the systemic medication if, for any reason, intrathecal medication with streptomycin and I.N.A.H. has to be withdrawn prematurely, or if the organism is suspected of being resistant to streptomycin or I.N.A.H.

### P.A.S.

P.A.S. has a very limited place in treatment since the organism in the meninges seldom develops drug resistance. When given in effective doses it is nauseating and thus makes it even harder than usual to maintain the patient's nutrition. At Oxford it is only given in the rare case in which, for some reason, either streptomycin or I.N.A.H. are contraindicated.

### Adjuvants

The purpose of using and adjuvant is to combat the basal exudate and so increase the access of the antibiotics to the organisms. The two adjuvants chiefly used today are the corticosteroids and tuberculin.

### Corticosteroids

The corticosteroids are the most popular adjuvant in use at the present time. They are powerful anti-inflammatory agents, they can be given by mouth, and besides suppressing the abnormalities in the C.S.F. they often make the patient feel a good deal better at least for the time. But, although on theoretical grounds it is reasonable to suppose that, if given early enough in the illness, they might prevent the basal exudate from forming, there is no evidence whatever that once it has formed they can promote its resolution. On the contrary, gross exudates have been demonstrated after large doses of corticosteroids given for weeks. This seriously limits their usefulness since, in the majority of cases, significant amounts of exudate are already present at the time when treatment is begun. They appear, too, to be equally disappointing when used in the hope of preventing an extension of the arteritis. Moreover, they carry a real risk of promoting a serious spread of any secondary infection of, for example, infection of urinary tract or bronchial tree.

Before the place of corticosteroids as an adjuvant can be properly assessed, their effect on the blood-C.S.F. and blood-brain barriers must be considered. The efficacy of systemic medication depends on antibiotics appearing in the C.S.F. in therapeutic amounts. In active tuberculous meningitis, as in the intrathecal tuberculin

reaction, the permeability of the blood-C.S.F. barrier is greatly increased and the passage of substances from blood to C.S.F. facilitated. There is some evidence to shew that cortisone tends to restore the blood-C.S.F. barrier (Smith, Taylor, Hunter, 1955). If, therefore, corticosteroids are used in treatment the effect may well be to lessen the permeability of the barrier at the very time that maximal penetration of drugs is required (Smith, 1957). Cortisone appears to have the same effect on the passage of plasma constituants into brain substance, that is to say, on the blood-brain barrier (Sano, K., personal communication). It is, in all probability, for this reason that it has proved life-saving in the rare case in which the meningitis is complicated by acute cerebral oedema or, for that matter, by acute pulmonary oedema.

### Tuberculin

The purified protein derivative of tuberculin (P.P.D.) when given intrathecally to someone sensitised to tuberculin, provokes a brisk meningeal reaction (Swithinbanck, Smith, Vollum, 1955). In cases of tuberculous meningitis there is good evidence that these reactions promote the resolution of the basal exudate (Smith and Vollum, 1950; Smith, 1953; Acheson and Smith, 1958). There are, however, certain limitations to the usefulness of intrathecal P.P.D. No reactions, and therefore no benefit, can be obtained in patients who are tuberculin negative and this is not uncommon in tuberculous meningitis (Taylor, Smith, Vollum, 1953). The reactions are accompanied by an exacerbation of all the signs and symptoms of the meningitis including the increase in intracranial pressure. They are therefore potentially dangerous, especially as the effective dose often approaches the dangerous dose. Moreover, if the method is to be used safely and effectively generous laboratory and certain neurosurgical facilities are required. In spite of these drawbacks, however, the addition of intrathecal P.P.D. to a regime of combined intrathecal and systemic chemotherapy has, in a large number of cases, reversed a downhill course and ultimately controlled the hydrocephalus (Fitzsimons and Smith, 1963). With its use, the limits of recovery in any given case are really imposed by the amount of vascular damage that has already taken place when effective treatment is begun.

Details of this method of treatment have been published elsewhere (Smith, Vollum, Taylor and Taylor, 1957). The principle is to give a minute dose, usually 0.0075 ug in 1 ml saline, by lumbar puncture and to increase this every fourth day until a reaction is obtained, as shewn by an exacerbation of fever and other symptoms, accompanied by a sharp rise in the cell count and/or protein content of the C.S.F. This dose is then repeated weekly until the reaction begins to fade out when the dose is cautiously increased. The intensity of the reaction is the resultant of the dose and of the sensitivity of the patient, and the amount of P.P.D. that can safely be given is limited by the severity of the clinical disturbance accompanying the reaction. If any reaction should prove too severe it can be aborted with cortisone. The corticosteroids and P.P.D. are mutually antagonistic and if the corticosteroids have been used in treatment the use of P.P.D. is precluded until, after their withdrawal, the patient recovers his sensitivity to tuberculin as shewn by the Mantoux test becoming positive.

### General measures

These are of the utmost importance and must include the maintainance of proper hydration and nutrition, if necessary through an intragastric tube; care of the skin and chest by frequent turning and proper posturing with, where necessary, pharyngeal suction or tracheostomy. Intensive physiotherapy to prevent contractures of the limbs is needed. Frequent small blood transfusions are a valuable supportive measure and anticonvulsants should be exhibited routinely. Retention of urine is best treated by catheterisation in the acute stage of the illness with the usual precautions against infection. Secondary infection of

chest or urinary tract should be vigorously treated with appropriate chemotherapy.

### Treatment of systemic tuberculosis

In a large number of cases the systemic chemotherapy which is an integral part of the treatment of the meningitis, can be depended upon to control the concomitant systemic disease. Thus the common primary pulmonary complex and miliary tuberculosis are usually healing satisfactorily by the time the meningitis is under control. Chronic lesions, such as pulmonary phthisis or spinal caries, must be treated on their own merits. In the great majority of such cases, however, it is the meningitis that constitutes the immediate threat to life. If, therefore, measures required for optimal treatment of the systemic disease conflict with those required for control of the meningitis, the latter should be given priority. For example, we have found in cases of meningitis and spinal caries that the patient is best nursed free in bed until the intrathecal medication is finished and that only then should his spine be immobilised. Should, however, operation be required, as, for example, for relief of intestinal obstruction in cases of tuberculous peritonitis, the meningitis is no contraindication and general anaesthesiae is, on the whole, well tolerated.

### Prognosis

From the beginning of the Oxford study the cases have been divided into 2 series. The first, or "Main" series is composed of those in which all significant treatment was given at Oxford. The patients were of all ages and totally unselected in the sense that no patient was considered too ill to treat, while anyone who lived to receive even a single dose of streptomycin was included. Except in a few, early cases in which attempts were made to shorten or simplify treatment, a standard chemotherapeutic regime was used; and whenever the regime was changed, this was always done as a deliberate policy. A recovery rate of almost 50 % was achieved from the outset and this has steadily improved (Table I). Study of these cases, therefore, enables certain prognostic factors to be defined with some confidence.

The second, or "X" series, consists of cases in which the patients began their treatment elsewhere and were later transferred to Oxford for special reasons. Of these, by far the commonest was a disappointing response to treatment. Since the chemotherapeutic regimes used before transfer varied greatly, these cases provide valuable information on the effect of different methods of treatment on prognosis.

Finally, the survivors from both series have been followed up for periods varying from 2 to 14 years, and the quality of recovery assessed, not only in terms of the physical residua, but also in terms of the patient's capacity to return permanently to his normal life (Fitzsimons, 1963). This study, which has also given an accurate assessment of the relapse rate, shews that the prognosis for function is governed by the same factors as is the prognosis for life.

Of the different prognostic factors, by far the most important is the quality of the treatment given. Without effective antibiotics tuberculous meningitis was, and remains, a fatal disease. Even with the help of the modern antituberculous drugs, if these are not used to their fullest advantage, if general measures are neglected or the use of adjuvants misdirected, then some patients will die who might otherwise have lived. It is true that if the disease is allowed to progress unchecked it will reach an irreversible stage from which no treatment can effect recovery; but it is also true that there is no case, however favourable in other respects, in which the patient will not die if treatment is inadequate. Thus Lorber (1954), in his valuable study of the prognosis on streptomycin, found it necessary to limit his analysis to those centres where the recovery rate was at least 40 % in order to avoid the artefact of inadequate treatment. The progressive fall in mortality shewn in Table I is largely a reflection of improvements in methods of treatment.

Given adequate treatment, then the outstanding factor is undoubtedly the stage

reached by the disease at the time when treatment is begun. In the section on pathology the relationship between the extent of the pathological changes and both the prognosis and the clinical picture was discussed and a simple clinical classification set out. Experience has amply confirmed the prognostic validity of this classification for both life (Smith, Vollum, Taylor and Taylor, 1956) and quality of recovery (Fitzsimons, 1963). In summary, excluding accidents of treatment, or the development of some unusual complication either in the central nervous system or in the body as a whole, all patients classified as belonging to Group I should recover completely. Among those in Group II the survival rate should also be high (at Oxford 84 % as compared with 97 %) but the incidence of residua due to vascular occlusion, such as hemi— or paraparesis, defects of sight and epilepsy, is necessarily rather higher. Of those in Group III probably at least a half will die while the incidence of disabling residua among the survivors is also high.

The prognosis is also affected by the age of the patient, the concomitant systemic disease,and the development of certain complications.

The outlook is worst at the extremes of life. Among infants of under 3 years old results are often poor, but this is primarily because diagnosis is so frequently delayed that a high proportion of them fall into Group III. It is probably, however, that infants are more likely to become mentally retarded than are older children or adults. Thus of those patients in the Oxford series who survived as imbeciles, all but one were under 3 years old. The exception was a boy of 4 years in whom the meningitis was superimposed on a congenital hydrocephalus.

At the other extreme, elderly patients are at extra risk because they may be unable to support the strain of the long and difficult illness. They may die of cardiac or renal failure even though the meningitis is responding to treatment. Chronic phthisis or bronchitis and emphysema, hypertension and arteriosclerosis are all common among these older patients and all prejudice their chance of recovery.

Among the varieties of systemic disease, an overt miliary spread used to be thought to carry a bad prognosis. With streptomycin alone this was to some extent true (Lorber, 1954) and at Oxford a specially prolonged regime of treatment was used in such cases with good effect. The use of P.P.D. as an adjuvant, and of I.N.A.H., has made this unnecessary. More serious is widespread chronic pulmonary tuberculosis and tuberculous spinal caries: the former throws a considerable strain on the heart while the latter endangers the spinal cord. Moreover, both may cause chronic invalidism even when the meningitis is cured.

Of the complications affecting the prognosis, the commonest is spinal block. Sometimes it is already present when the patient is admitted to hospital but more commonly it develops during the first month of treatment. It increases the risks of intrathecal medication since the lumbar injections are rendered ineffective and resort must be had to the more hazardous intra-cisternal or intra-ventricular routes. It is caused by the deposition of tuberculous exudate throughout the spinal canal and its appearance is a sure sign that the infection has not been brought under control. If, therefore, it develops in the face of lumbar medication the added risks of the intracranial injections must be accepted, since to lessen the intensity of medication in the face of clear evidence that the disease is progressing is to invite disaster. Similarly the risk must be accepted when spinal block develops on systemic treatment alone, as it not infrequently does.

Other, rarer, complications that alter the prognosis for the worse are the development of a non-communicating hydrocephalus due to a tuberculoma from concomitant tuberculous peritonitis, paralytic ileus and acute dilatation of the stomach, and retention of urine from benign prostatic hypertrophy have also been encountered. Each of these conditions must be treated on its own merits.

Finally, while fits are fairly common early in the illness and have no special prognostic significance, it is our experience that fits coming on late in the illness, for

example, during the third or fourth month of treatment, carry a very bad prognosis. The reason for this is obscure but nevertheless they often appear to usher in the terminal phase of the illness.

## Discussion and Conclusions

An attempt has been made here to give a concise, overall account of the natural history of tuberculous meningitis. From this, it should be clear that the principles governing successful treatment are the same as in other varieties of bacterial meningitis, namely: early institution of appropriate chemotherapy; free access of the chosen antibiotics to all parts of the cerebro-spinal pathways; maintainance of an adequate concentration of the antibiotics in the C.S.F. for a sufficient length of time; and, finally, treatment of the systemic infection (Smith, Duthie and Cairns, 1946; Smith, 1956). Experience has shewn that in the overwhelming majority of unsuccessful cases failure can be attributed to neglect of one or more of these principles. It is, therefore, worth considering briefly the special difficulties that may be encountered in their application in tuberculous meningitis.

### Early institution of appropriate chemotherapy

Neglect of this principle is perhaps the most important single cause of failure. The cause for this neglect is twofold. Firstly, there is the difficulty of making the diagnosis in the early stages of the illness or even of recognising the presence of a meningitis. This difficulty is particularly great in infants in whom stiffness of the neck is a late and inconstant sign. Secondly, in cases in which a "lymphocytic" meningitis of undetermined aetiology has been found, there is a common reluctance to give antituberculous chemotherapy for fear that, on one hand, it may obscure the diagnosis and, on the other, may prove to be unnecessary. This attitude is unjustified since, provided corticosteroids are withheld, if in the doubtful case treatment is begun, both the clinical response and that of the C.S.F. have great diagnostic value while, at the same time, the patient's welfare is safeguarded should he ultimately prove to have tuberculous meningitis.

### Free access of the chosen antibiotics to all parts of the cerebrospinal pathways

It is the application of this principle that is so controversial, involving as it does the questions of whether intrathecal medication is required and of whether corticosteroids or P.P.D. should be used as an adjuvant. The objections to daily intrathecal medication are obvious: it throws a considerable burden on the nursing and medical staff and on the sterilisation service of the hospital, since it is time-consuming and demands some experience and the strictest aseptic technique on the part of the operator. More important, it is unpleasant and sometimes painful for the patient. Above all, it carries certain inherent risks, namely those of traumatic haemorrhage and secondary infection. Nevertheless, experience with those cases forming our "X Series" (see section on prognosis) has convinced us that it gives better results than does systemic treatment alone, and that though without it many patients will recover, some will die who might have lived while other will be left with disabling, and avoidable, residua. (Fitzsimons and Smith, 1963). Precisely the same arguments hold in favour of and against the use of P.P.D. as an adjuvant. We have seen too many failures on corticosteroids to be impressed with their value. In brief then, if circumstances are such that intrathecal chemotherapy and P.P.D. cannot be used safely, they are probably best not used at all. It must, however, be remembered that there is now good evidence to shew that although systemic chemotherapy, with or without added corticosteroids, is undoubtedly an effective form of treatment, it is not the optimal treatment. The attitude which we have heard expressed, that provided one gives systemic streptomycin and I.N.A.H. and, if the response is disappointing, corticosteroids, one at least has the sa-

tisfaction of knowing that everything possible has been done, is impermissible.

### Maintainance of an adequate concentration of the antibiotics in the C.S.F. for a sufficient length of time

It is the observance of this principle that governs the relapse rate. As in all forms of tuberculosis the lesions are slow to heal; and to allow the concentration of the antibiotics in the C.S.F. to fall before the lesions have either resolved or, at the least, have become firmly encapsulated, is to invite relapse. The problem therefore is to known when the meningeal infection is obsolete. Among the first 21 patients in the Oxford Main Series to survive their initial illness, 5 relapsed after discharge from hospital. It was study of their cases that enabled the criteria for stopping treatment to be defined, as set out above in the section on treatment. Experience has confirmed the validity of these criteria in that, among these cases in which they were strictly observed, the relapse rate has been negligible. (Fitzsimons, 1963). It must be realised, however, that it may be very many months before they are all fulfilled. Thus in certain successful cases *M. tuberculosis* have been identified in the C.S.F. after almost a year of continuous intrathecal and systemic medication. It follows that if the course of treatment is limited to a standard period, of, for example, so many weeks or months, some patients will almost inevitably relapse.

### Treatment of the systemic infection

Here there is little to add to what has already been said in the section on treatment beyond a reminder that streptomycin loses its antibacterial action in an acid medium. Since the presence of a miliary spread must be presumed in every case of tuberculous meningitis —whether or not it can be recognised on radiography or ophthalmoscopy— there is always the possibility of lesions seeding themselves in the renal tract, where they may persist unless the urine is kept alkaline. This probably explains why *M. Tuberculosis* have occasionally been cultured from the urine months, or even years, after the meningitis has been cured. Any such case merits full investigation of the renal tract.

From this discussion of the principles of treatment and their application, it emerges that the treatment of tuberculous meningitis, is never a matter of simple routine. Each separate case must be carefully studied and the details of treatment adapted to suit the needs of the individual patient. But provided this is done, then the great majority of patients may be expected to make a full and permanent recovery from what was once an almost universally fatal disease.

### Acknowledgements

The study of the chemotherapy of tuberculous meningitis at Oxford was begun on the initiative of the late Sir Hugh Cairns

| | | | *Aged 14 yrs and under* | | *Aged 30 yrs and over* | | | |
|---|---|---|---|---|---|---|---|---|
| | *N° of cases* | *Average age yrs* | *N°* | *% age* | *N°* | *% age* | *Died N°* | *Died % age* |
| Before Dec. 31st, 1948 | 37 | 11.5 | 23 | 62 % | 3 | 8 % | 19 | 51 % |
| Jan. 1st 1949 - Dec. 31st 1950 | 45 | 16.7 | 20 | 44 % | 7 | 16 % | 18 | 40 % |
| Jan. 1st 1951 - Dec. 31st 1952 | 39 | 19.4 | 16 | 41 % | 10 | 26 % | 14 | 36 % |
| Jan. 1st 1953 - Dec. 31st 1954 | 28 | 20.4 | 13 | 46 % | 7 | 25 % | 9 | 32 % |
| Jan. 1st 1955 - Dec. 31st 1956 | 25 | 23.6 | 8 | 32 % | 8 | 32 % | 2 | 8 % |
| Jan. 1st 1957 - Dec. 31st 1958 | 23 | 24.9 | 5 | 22 % | 6 | 26 % | 4 | 17 % |
| Jan. 1st 1959 - Dec. 31st 1960 | 13 | 19.5 | 3 | 23 % | 1 | 8 % | 0 | — |
| Totals . . . . | 210 | | 88 | 42 % | 42 | 20 % | 36 | 17.1% |

and, until his death in 1953, was carried out under his close, personal direction. My colleague, Dr. R. L. Vollum, from the first, has been in charge of the all-important bacteriological aspects of this work. I am also deeply grateful to the different research assistants, registrars and house physicians, and members of the nursing staff at the Meningitis Unit of the United Oxford Hospitals, and at the one-time Military Hospital for Head Injuries, Wheatley, without whom this study could never have been carried on.

## SUMMARY

The aim here has been to give a short, overall account of the natural history of tuberculous meningitis, with special emphasis on those aspects that most directly affect diagnosis, prognosis and treatment.

The incidence of tuberculous meningitis varies directly with that of tuberculosis as a whole. It may complicate any form of tuberculosis and may therefore occur at any age. Most commonly it arises in relation, immediate or remote, to the primary infection. In communities in which tuberculosis is being brought under control, primary infection is often delayed until adolescence or early adult life. In such communities, therefore, tuberculous meningitis is not only becoming rarer, but is no longer predominantly a disease of childhood. Failure to realise this may cause serious delay in diagnosis.

The meninges may be infected by direct spread from neighbouring structures, notably the spine, but much more commonly the infection is blood-born. Rich's hypothesis of the pathogenesis is outlined, and the place of possible precipitating factors is considered. Since at autopsy miliary tuberculosis and tuberculous meningitis have been found together in an overwhelming majority of untreated cases, the presence of a miliary spread must always be assumed, even when it cannot be detected.

The problem of treatment is defined by the pathology of the disease. Of paramount importance are the basal exudate and the obliterative arteritis. The former shields the organisms from the action of the antibiotics and causes the well known syndrome of ocular palsies, communicating hydrocephalus and, in all probability, mental confusion. The latter causes infarction of brain tissue, resulting in all degree of neurological deficit. Much rarer, but important in that they require special treatment, are diffuse cerebral oedema, the large tuberculomata, and occlusion of the aqueduct of Sylvius.

Given adequate treatment, it is the extent of these changes that determines the prognosis. Since this can be infered from the clinical condition, as confirmed by pneumoencephalography, there is a sound pathological basis for the simple clinical classification of severity that proved such a useful guide to prognosis, namely:

Group I Patients fully rational with no neurological signs other than those of meningitis.

Group II Patients confused and/or shewing focal neurological signs.

Group III Patients mentally inaccessible and/or with a complete hemi or paraplegia.

The characteristic changes in the C.S.F. including the increase in the permeability of the blood-C.S.F. barrier to bromide, are briefly described. These changes are, almost certainly, the expression of spontaneous intrathecal tuberculin reactions and may in certain cases, be either diminished or exagerated. Since these departures tend to obscure the diagnosis they are described more fully.

The changes in the C.S.F. commonly seen during the first weeks of chemotherapy are also described as they have great diagnostic value. They are not seen when corticosteroids are given. The relation of the C.S.F. findings to prognosis is discussed.

Ideally diagnosis should be made during the onset, which classically is insidious. The difficulty is to recognise the presence of the meningitis. The importance of the *persistance* of otherwise non-specific symptoms is stressed. It is once again pointed out that in young children stiffness of the neck is a late and inconstant sign. The onset may be either unusually prolonged or curtailed. Both these anomalies are described as they tend to obscure the diagnosis. The fully developed picture is briefly discussed.

The differential diagnosis during the onset is from other febrile illnesses. The critical investigation is examination of the C.S.F. Once the meningitis is recognised the differential diagnosis is from the other varieties of meningitis in which lymphocytes predominate in the C.S.F. The most important of these are listed. Two special investigations of proved value in diagnosis are discussed, namely the bromide test and pneumoencephalography. Finally, it is urged that in any really doubtful case chemotherapy should be begun. In this way the valuable test of treatment is applied while, at the same time, the patient's welfare is safeguarded.

Treatment is discussed under the headings of the chemotherapy, the adjuvants, general measures, and treatment of the systemic disease. Under the first of these the controversy between systemic chemotherapy alone and combined systemic and intrathecal chemotherapy is discussed. Similarly under the heading 'adjuvants' the relative merits of corticosteroids and intrathecal tuberculin are considered. From experience gained at Oxford it is concluded that, in spite of the obvious drawbacks, combined chemotherapy is superior to systemic treatment alone, and that intrathecal tuberculin remains the best weapon at present available for combating the basal exudate. The importance of the general measures is emphasized.

Among the different prognosis factors the quality of the treatment is overriding. Provided this is adequate, then the outstanding factor is the stage reached by the disease when treatment is begun, as defined in the section on pathology. The effect on prognosis of age, of the concomitant systemic disease and of certain complications such as spinal block, is also discussed.

The basic principles governing successful treatment are the same as for other varieties of bacterial meningitis, namely; early institution of appropriate chemotherapy; free access of the chosen antibiotics to all parts of the cerebro-spinal pathways; maintainance of an adequate concentration of the antibiotics in the C.S.F. for a sufficient length of time; and treatment of the systemic disease. The difficulties most likely to be encountered in the special application of these principles to the problem of tuberculous meningitis are considered; and it is concluded that there is now no valid reason why the great majority of patients should not make a full and permanent recovery.

## RESUMEN

La finalidad de este trabajo es abarcar en forma concisa la historia de la meningitis tuberculosa, señalando muy especialmente aquellos aspectos relacionados directamente con su diagnóstico, su pronóstico y su tratamiento.

Las condiciones en que sobreviene una meningitis tuberculosa son variables, al igual que en los casos de tuberculosis en general. Puede resultar como complicación de cualquier tipo de tuberculosis, lo que significa que puede aparecer a cualquier edad; en general su aparición está en relación remota o inmediata con la infección primaria. En algunas sociedades se controla el tratamiento de los tuberculosos, demorando en muchos casos la infección hasta la adolescencia o la juventud; allí no sólo ha bajado considerablemente el número de casos, sino que ha dejado de ser una enfermedad infantil por excelencia, y el hecho de perder de vista esta posibilidad puede causar demoras fatales en el diagnóstico.

Las meninges pueden ser contagiadas de

la infección por las estructuras circundantes, particularmente la columna, pero más comúnmente dicha infección es de origen sanguíneo. Se presenta a grandes rasgos la hipótesis de patogénesis de Rich, considerando además los posibles factores que provocan la precipitación de este tipo de meningitis. Habiéndose hallado al hacer la autopsia en una enorme cantidad de casos no tratados la tuberculosis miliar y la meningitis tuberculosa juntas, debe suponerse siempre la presencia de una siembra miliar, aún cuando no pueda ser comprobada.

El problema del tratamiento se define por la patología de la enfermedad. Son particularmente importantes 2 elementos: el exudado basal, que impide la acción de los antibióticos sobre el organismo, causando el conocido síndrome de parálisis oculares, hidrocéfalo comunicante y muy probablemente confusión mental; en segundo lugar está la arteritis obliterativa, que causa infarto del tejido cerebral, dando lugar a todo tipo de deficiencias de orden neurológico. Hay que considerar otros elementos, que si bien menos frecuentes, son importantes en la medida que exigen tratamiento especial: el edema cerebral difuso, el tuberculoma en placa y la oclusión del acueducto de Silvio.

Con un tratamiento adecuado la progresión de estos cambios determina el pronóstico. Dado que esto tiene un fundamento clínico, confirmado por la neumoencefalografía, una simple clasificación en base a la severidad resulta útil para el pronóstico.

Grupo I Pacientes en completo uso de razón y que no presentan más síntomas neurológicos que los que implica la meningitis.

Grupo II Pacientes confusos y/o evidenciando síntomas neurológicos focales.

Grupo III Pacientes mentalmente inaccesibles y/o presentando hemi- o paraplejia total.

Las modificaciones características del líquido cefalorraquídeo incluso el aumento de la permeabilidad de la barrera sangre-L.C.R. al bromuro, son brevemente descriptas. Estos cambios son casi seguramente la manifestación espontánea de la reacción intratecal de la tuberculina y pueden disminuir en algunos casos y aumentar en otros. Dado que estas modificaciones tienden a oscurecer el diagnóstico son descriptas con más detención.

También son descriptos los cambios del L.C.R. apreciables durante las primeras semanas de quimioterapia, ya que poseen gran valor a los efectos del diagnóstico. No aparecen en caso de ser suministrados corticoesteroides. Se discute la relación entre las observaciones del L.C.R. y el pronóstico.

El diagnóstico ideal debería ser hecho al comienzo, que en general es insidioso. La dificultad está en reconocer la presencia de una meningitis. Se subraya muy especialmente la importancia de la *persistencia* de síntomas no específicos en otras circunstancias. Una vez más se señala que la rigidez del cuello en los niños es un síntoma tardío e inconstante. El ataque puede prolongarse inusitadamente o detenerse; ambas anomalías tienden a oscurecer el diagnóstico y por lo tanto son descriptas. Es discutido brevemente el cuadro en su desarrollo total.

El diagnóstico diferencial durante el ataque se hace con otras enfermedades febriles. La investigación crítica es el examen del L.C.R. Una vez reconocida la meningitis el diagnóstico se hace con otras variedades de meningitis en las que predominan los linfocitos en el L.C.R. Se enumeran las más importantes. Se discuten dos investigaciones especiales de valor reconocido en el diagnóstico: el test de bromuro y la neumoencefalografía. Por último, se recomienda iniciar la quimioterapia en cualquier caso que resulte realmente dudoso, y de esa manera se aplica un test de tratamiento al paciente a la vez que se salvaguarda su bienestar.

Se discute el tratamiento bajo los títulos de quimioterapia, los coadyuvantes, medidas generales y tratamiento de la enfermedad sistémica.

Bajo el primer título se discute la posición de la quimioterapia sistémica exclusivamente y la de la quimioterapia sistémica e intratecal combinadas. Bajo "coadyuvantes" se consideran las ventajas del uso de

corticoesteroides o tuberculina. Se concluye a partir de la experiencia adquirida en Oxford que a pesar de todos los inconvenientes, la quimioterapia es superior al tratamiento sistémico exclusivo, y que la tuberculina intratecal sigue siendo en la actualidad el mejor medio para combatir el exudado basal. Se insiste en la importancia de las medidas generales.

De entre los diferentes factores pronósticos la calidad del tratamiento es fundamental. En caso de ser adecuado, el factor preponderante es la etapa que ha alcanzado la enfermedad al comenzar el tratamiento, de acuerdo a lo definido en la sección de patología. Se discute también el efecto sobre el pronóstico de la edad, de la enfermedad sistémica concomitante y de ciertas complicaciones como el bloqueo espinal.

Los principios que deben gobernar un tratamiento exitoso son los mismos que los empleados para otras variedades de meningitis bacteriana, a saber:

Iniciación inmediata de una quimioterapia apropiada; acceso de los antibióticos elegidos a las vías cerebro-medulares; mantenimiento de una concentración adecuada de los antibióticos en el L.C.R. por un tiempo suficientemente largo; y finalmente tratamiento de la enfermedad sistémica. Se consideran las probables dificultades a enfrentar durante la aplicación de estos principios al problema de la meningitis tuberculosa, y se concluye que no hay actualmente razones válidas que nieguen la posibilidad de una recuperación total y permanente a la gran mayoría de los pacientes.

## RÉSUMÉ

Le but de ce travail est de donner succintement l'histoire de la meningite tuberculeuse, en soulignant particulièrement les aspects ayant un rapport direct avec le diagnostic, le pronostic et son traitement.

Les conditions dans lesquelles survient une méningite tuberculeuse sont variables, de même que dans les cas de tuberculose en géneral. Elle peut survenir comme complication de n'importe quelle espèce de tuberculose, c'est à dire qu'elle peut apparaître à tous les âges; en géneral son apparition est en rapport immédiat ou lointain avec une infection primaire. Dans certaines sociétés, où la tuberculose est controlée, on attarde l'infection jusqu'à l'adolescence ou l'âge juvénile; de cette façon le nombre des cas est très inférieur, et la tuberculose a cessé d'être une maladie d'enfants par excellence. Ne pas considérer cette possibilité peut entrainer des délais fatals dans le diagnostic.

Les méninges peuvent se contagier de l'infection des régions voisines, particulièrement du rachis, mais l'infection d'origine sanguine est plus commune. On présente à grands traits l'hypothèse de pathogénèse de Rich, en considérant aussi les probables facteurs qui amènent cette espèce de méningite. Ayant trouvé pendant l'autopsie d'une grande quantité de cas non traités la tuberculose miliaire et la méningite tuberculeuse ensemble, on doit toujours supposer une dissémination miliaire même si on ne peut pas le prouver.

Le problème du traitement est défini par la pathologie de la maladie. 2 éléments sont particulièrement importants: l'exsudé basal et l'artérite oblitérative. Le premier empèche l'action des antibiotiques sur l'organisme et cause le syndrome bien connu de paralysie oculaire, l'hydrocéphalus communiquant et bien probablement, la confusion mentale.

Le deuxième cause l'infarctus du tissu cérebral, provoquant toute sorte de déficiences neurologiques.

On peut trouver d'autres éléments, moins fréquents mais etant importants, puisqu'ils ont besoin d'un traitement spécial, tels que l'oedème cerebral diffus, la grande tuberculomata et l'occlusion de l'aqueduc de Sylvius.

Si ces éléments sont correctement traités, leur progression détermine le pronostic. Ce dernier pouvant être inféré cliniquement et confirmé par la pneumoencephalographie, une classification basée sur la severité,

a démontré être très utile pour établir le pronostic:

Groupe I Patients lucides ne présentant d'autres signes neurologiques que ceux propres à la méningite.

Groupe II Patients confus et/ou montrant des signes neurologiques focaux.

Groupe III Patients mentalement inaccessibles et/ou avec une hémi- ou paraplexie totale.

Les changements caractéristiques du L.C.R. incluant l'acroissement de la perméabilité de la barrière sang-L.C.R. au bromide, sont brièvement décrits. Ces changements sont, presque sûrement, l'expression des réactions spontanées à la tuberculine intrathécale, et peuvent parfois être diminués dans certains cas, exagérés dans d'autres. Du moment que ces procès tendent à obscurcir le diagnostic ils sont plus complètement dècrits.

Les changements du L.C.R. qu'on peut apprécier facilement pendant les premières semaines de chémotherapie, sont aussi décrits puisqu'ils ont une grande valeur diagnostique. On ne les voit pas si on administre des corticosteroïdes au patient. La relation entre les découvertes du L.C.R. et le pronostic est discuté.

Le diagnostic idéal devrait être fait au commencement, quand l'attaque est insidieuse. Il y a des difficultés à reconnaître la présence de la méningite. On signale la persistance de quelques symptômes non-specifiques dans d'autres circonstances. On affirme que la regidité du cou est un signe tardif et inconstant chez de petits enfants. L'attaque initiale peut être très prolongée ou peut s'arrêter tout à coup. Ces deux anomalies sont décrites puisqu'elles aussi tendent à obscurcir le diagnostic. Le cadre entièrement développé est aussi brièvement discuté.

On fait le diagnostic différentiel des autres maladies fébriles pendant l'attaque. L'investigation critique est l'examen du L.C.R. Une fois reconnue, la méningite est soumise à un diagnostic différentiel des autres varietés de méningite, dans lesquelles dominent les lymphocites dans le L.C.R. On enumère les maladies les plus importantes. On discute deux investigations spéciales dont la valeur pour le diagnostic a été prouvé: le test bromurique et la pneumoencéphalographie. Finalement on insiste sur l'emploi de la chimiotherapie dans les cas vraiment douteux. De cette façon on applique un test de traitement d'une certaine valeur, à la fois qu'on sauvegarde la sécurité du patient.

Sous les titres de "chimiothérapie", "les coadjuvants", "mesures generales", et "traitement des maladies systémiques" on discute le traitement. Sous le premier de ces titres on présente la controverse entre la chimiothérapie systémique toute seule, et la chimiothérapie systémique combinée avec l'intrathécale.

Sous le titre de "coadjuvants" on considère les mérites des corticosteroïdes et de la tuberculine. Les resultats des expériences faites à Oxford font conclure que malgré tous les inconvénients, la chimiothérapie combinée est bien supérieure au traitement systémique tout seul, et que la tuberculine intrathécale continue à être jusqu'à présent le moyen le plus efficace pour combattre l'exsudé basal.

On insiste sur l'importance des mesures générales à adopter.

Parmi les différents facteurs pronostiques la qualité du traitement est fondamentale. Pourvu que celui-ci soit correct, le facteur décisif est l'étape atteinte par la maladie au commencement du traitement, selon la définition de la section se rapportant à la pathologie. On discute aussi l'effet sur le pronostic d'âge, des maladies systémiques concomitantes et de certaines complications telles que le blocage spinal.

Les principes basiques qui assurent du succès au traitement sont les mêmes qui gouvernent le traitement d'autres espèces de méningite bactérienne: l'institution de la chimiothérapie dès le commencement; l'arrivée des antibiotiques choisis, à toutes les voies cérébro-spinales; la manutention d'une concentration convenable d'antibiotiques pendant une période suffisamment longue; et finalement, le traitement de la

maladie systémique. On considère les difficultés qui peuvent apparaître au cours de l'application de ces principes au problème posé par la méningite tuberculeuse, et on arrive à la conclusion qu'il n'y a pas de raison valable pour nier une recupération totale et permanente dans la plupart des patients.

## ZUSAMMENFASSUNG

Der Zweck dieser Arbeit war, einen kurzen und panoramaartigen Bericht ueber die Naturgeschichte der tuberkuloesen Meningitis unter besonderer Beruecksichtigung jener Aspekte, die direkt mit Diagnose und Prognose und Behandlung zu tun haben, zu geben.

Die Haeufigkeit der tuberkuloesen Meningitis variiert direkt mit jener der Tuberkulose als Ganzes. Sie mag jedwede Form der Tuberkulose zu komplizieren und deshalb in jedem Lebensalter vorkommen. Meistens entsteht sie als unmittel- oder mittelbare Reaktion gegen die Primoinfektion. In Gemeinschaften, in denen die Tuberkulose unter Kontrolle gebracht worden ist, ereignet sich die Primoinfektion oft erst in der Pubertaet oder im Erwachsenenalter. In diesen Gemeinschaften ist die Tuberkuloese Meningitis deshalb nicht nur seltener geworden, sondern ist auch nicht mehr vorwiegend eine Kinderkrankheit. Dies zu vergessen kann die Ursache einer schwerwiegenden Verzoegerung der Diagnosestellung sein.

Die Hirnhaeute koennen durch direkte Streuung von den benachbarten Strukturen aus, besonders der Wirbelsaeule, infiziert werden; jedoch ist die hematogene Infektion die gewoehnlichere. Es wird die Hypothese der Pathogenese von Rich besprochen sowie die Rolle moeglicher praezipitierender Faktoren in Betracht gezogen. Da bei Autopsien miliare Tuberkulose und tuberkulose Meningitis in der ueberwaeltigenden Mehrheit der nicht behandelten Faelle, beieienander gefunden worden sind, muss das Vorhandensein einer miliaren Streuung immer angenommen werden, auch wenn sie nicht entdeckt werden kann.

Die Therapie ist durch die Pathologie bestimmt. Das basale Exsudat und die obliterierende Arteritis sind von groesster Wichtigkeit. Ersteres schirmt die Mikroben von der Wirkung der Antibiotika ab und verursacht das wohlbekannte Syndrom der Augenlaehmungen, des kommunizierenden Hydrozephalus und hoechst wahrscheinlich auch der Werwirrungszustaende. Letztere verursacht den Infarkt in der Gehirnsubstanz mit allen Stufen neurologischen Defizits. Viel seltener aber wichtig, weil sie eine besondere Therapie erfordern, sind das diffuse Hirnoedem, die grossen Tuberkulome und der Verschluss des Acqueductus Silvii. Bei entsprechender Behandlung wird die Prognose durch die Ausdehnung dieser Veraenderungen bestimmt. Da diese aus dem klinischen Zustand abgeleitet und durch die Pneumoenzephalographie bestaetigt werden kan, ist eine vernuenftige pathologische Basis fuer eine einfache klinische Klassifizierung des Schweregrades vorhanden, die sich nuetzlich fuer die Prognosestellung erwiesen hat, naemlich:

1. Gruppe: Voellig klare Patienten ohne neurologischen Befund, ausser dem der Meningitis.

2. Gruppe: Verwirrte Patienten und oder solche mit fokalen neurologischen Zeichen.

3. Gruppe: Patienten ohne Bewusstsein oder solche mit Hemi -oder Paraplegie mit oder ohne Bewusstseinsverlust.

Die charakteristischen Veraenderungen der Spinalfluessigkeit einschliesslich der Permeabilitaet der Blut-Liquor-Schranke fuer Brom, wird kurz beschrieben. Diese Veraenderungen sind sicherlich der Ausdruck spontaner intrathecaler Tuberkulin-

reaktionen und koennen in gewissen Faellen vermindert oder vermehrt sein. Da diese Abweichungen die Diagnose erschweren koennen, werden sie eingehender beschrieben.

Die Veraenderungen der Spinalfluessigkeit waehrend der ersten Wochen der Chemotherapie werden auch beschrieben weil sie von grossem diagnostischen Wert sind. Man beobachtet sie nicht wenn Kortikosteroide gegeben werden. Es wird das Verhaeltnis des Liquorbefundes zur Prognose auseinandergesetzt.

Die ideale Diagnose waere beim Beginn, welche klassischerweise schleichend ist. Die Schwierigkeit besteht darin, das Bestehen einer Meningitis zu erkennen. Die Wichtigkeit des *Weiterbestehens* von sonst nicht spezifischen Symptomen wird unterstrichen. Es wird nochmals hervorgehoben, dass bei kleinen Kindern die Nackenstarre ein spaetes und und nicht konstantes Zeichen ist. Der Beginn kann entweder ungewoehnlich langgezogen oder abgekuerzt sein. Beide Anomalien werden beschrieben weil sie die Diagnose erschweren koennen. Das vollentwickelte Krankheitsbild wird kurz beschrieben.

Die Differenzialdiagnose im Beginn muss mit anderen fieberhaften Krankheiten gemacht werden. Die kritische Untersuchung ist die der Spinalfluessigkeit. Sobald die Meningitis erkannt ist muss die Differenzialdiagnose mit den anderen Meningitisarten bei welchen Lymphocyten im Liquor dominieren, gemacht werden. Zwei besondere Untersuchungen von erprobtem Wert bei der Diagnose werden auseinandergesetzt, naemlich der Bromtest und die Pneumoenzephalographie. Schliesslich wird empfohlen, dass man in wirklich zweifelhaften Faellen die Chemotherapie starten sollte. Auf diese Weise wird der wertvolle therapeutische Test angewandt, waehrend gleichzeitig die Patienten Gesundheit des Patienten gewaehrleistet ist.

Die Behandlung wird in den Kapiteln "Chemotherapie", die "Koadjunvanten", "Allgemeine Massnahmen" und "Behandlung der Systemkrankheit" beschrieben. Im ersten Kapitel wird auf den Meinungs streit zwischen Systemchemotherapie allein oder der Kombination System— und intrathekaler Chemotherapie eingegangen. Ebenso im Kapitel "Koadjuvanten" werden die relativen Vorteile der Kortikosteroid und des intrathekalen Tuberkulins beschrieben. Aus seiner Erfahrung in Oxford schliesst der Autor, dass trotz zweifelloser Rueckschlaege, die kombinierte Chemotherapie besser ist als die Systembehandlung allein, und dass das intrathekale Tuberkulin vorlaeufig noch die staerkste Waffe gegen das basale Exsudat ist. Es wird ausdruecklich auf die Wichtigkeit der allgemeinen Massnahmen hingewiesen. Unter den verschiedenen prognostischen Faktoren ist die Qualitaet der Behandlung am Wichtigsten. Wenn diese richtig ist, dann ist der naechstwichtigste Faktor die Etappe der Krankheit, in der die Behandlung begonnen worden ist, wie im Kapitel ueber Pathologie auseinandergesetzt ist. Die prognostische Rolle des Alters, der gleischzeitigen Systemerkrankung und gewisser Komplikationen, wie z.B. der spinale Block, werden auch beschrieben.

Die basischen Prinzipien, die eine erfolgreiche Behandlung regieren sind dieselben wie bei anderen Arten der bakteriellen Meningitis, naemlich der rechtzeitige Beginn einer geeigneten Chemotherapie; die Moeglichkeit, dass das gewaehlte Antibiotikum an alle Teile der zerebro-spinalen Bahnen gelangt, das Unterhalten einer geeigneten Konzentration der Antibiotiken in der Spinalfluessigkeit waehrend einer genuegend langen Zeit und die Behandlung der Systemkrankheit. Es werden die am leichtesten zu treffenden Schwierigkeiten bei der besonderen Anwendung dieser Prinzipien beim problem der tuberkulosen Meningitis beschrieben; und man kommt zum Schluss, dass heutzutage bei den meisten Patienten kein Grund vorliegt, dass sie vollkommen und dauernd wiederhergestellt werden koennen.

## REFERENCES


*Acheson, R. M.*, 1958. Brit. J. Radiol. 31, 81.

*Acheson, R. M., Smith, H. V.*, 1958. Quart. J. Med. N. S. 23, 275.

*Blacklock, J. W. S., Griffen, W. A.*, 1935. J. Path. Bact. 40, 489.

*Brocard, H., Desvignes, P., Brincourt, J., Beust, M.*, 1959. Rev. Tuberc., Paris. 23, 106.

*Cairns, H.*, 1949. Brit. Med. J. 1, 969.

*Cairns H., Russell, D. S.*, 1946. J. Path. Bact. 58, 649.

*Cairns, H., Smith, H. V.*, 1952. Tuberculosis of the Central Nervous System. 'Modern Practise in Tuberculosis'. Butterworth and Co. London.

*Daniel, P. M.*, 1949. Proc. R. Soc. Med. 62, 169.

*Debré, R., Brissaud, H. E.*, 1953. 'Méningite Tuberculose et Tuberculose Miliare de l'Enfant; Masson et Cie, Paris.

*Ebert, R. H., Barclay, W. R.*, 1952. Ann. intern. Med. 37, 506.

*Fitzsimons, J. M.*, 1963. Tubercle 44, 87.

*Fitzsimons, J. M., Smith, H. V.*, 1963. Tubercle 44, 103.

*Fouquet, J., Heimann, V., Teyssier, L., Rist, N.,Grumbach, G., Liberman, C.*, 1958. Rev. Tuberc., Paris. 22, 490.

*Greenfield, J. G.*, 1958. 'Neuropathology', Arnold, London.

*Happ, W. M., Casparis, H. R.*, 1922. Amer. J. Dis. Childh. 23, 527.

*Hughes, I. E., Hume Adams, J., Ilbert, R. C.*, 1963. J. Neurol. Neurosurg. Psychiat 26, 83.

*Hughes, I. E., Smith, H. V.*, and *Kane, P. O.*, 1962. Lancet 1, 616.

*Lincoln, E. M.*, 1947. Amer. Rev. Tuberc. 56, 75.

*Lincoln, E. M., Sewell, E. M.*, 1963. Tuberculosis in Children. McGraw-Hill. N. Y.

*Lorber, J.*, 1951. Arch. Dis. Childh. 26, 28.

*Lorber, J.*, 1954. Amer. Rev. Tuberc. 69, 13.

*Macgreggor, A. R., Green, C. A.*, 1937. J. Path. Bact. 45, 613.

Medical Research Council Report, 1948. Streptomycin in Tuberculosis Trials Committee. Lancet 1, 582.

*Merritt, H. H., Fremont-Smith, F.*, 1938. The Cerebrospinal Fluid. W. B. Saunders and Co., Philadelphia.

Ministry of Health Report, 1961. Appendix B. H. M. Stationary Office. London.

*Muller, D.*, 1953. Rrsch. Z. Nervenheilk 170, 1.

*Osler, W.*, 1892. "The Principles and Practice of Medicine". Pentland, Edinburgh.

*Ounsted, C., Smith, H. V.*, 1955. Tuberculosis in the Commonwealth. Transactions of the N.A.P.T. 4th Commonwealth and Tuberculosis Conference, p 280.

*Rich, A. R.*, 1946. 'The Pathogenesis of Tuberculosis' 2nd Ed. C. C. Thomas, Springfield, Illinois.

*Rich, A. R., McCordock, H. A.*, 1933. Bull. Johns Hopkins Hosp. 52, 5.

*Salvaing, J.*, 1954. La Tuberculose méningée traitée par Streptomycine, Paris.

*Sano, K.*, Personal communication.

*Smith, H. V.*, 1953. Proc. R. Soc. Med. 46, 588.

*Smith, H. V.*, 1956. Tubercle. Colonial Supplement Nº 11, 1.

*Smith, H. V., Daniel, A. M.*, 1947. Tubercle 28, 64.

*Smith, H. V., Duthie, E. S., Cairns, H.*, 1946. Lancet. 1, 185.

*Smith, H. V., Norman, R. M.*, and *Urich, H.*, 1957. J. Neurol. Neurosurg. Psychiat. 20, 250.

*Smith, H. V., Taylor, L. M.*, and *Hunter, G.*, 1955. J. Neurol. Neurosurg. Psychiat. 18, 237.

*Smith, H. V., Vollum, R. L.*, 1950. Lancet 2, 275.

*Smith, H. V., Volum, R. L.*, 1954. Brit. Med. Bull. 10, 140.

*Smith, H. V., Vollum, R. L.*, and *Cairns, H.*, 1948. Lancet 1 627.

*Smith, H. V., Vollum, R. L., Taylor, L. M.*, and *Taylor, K. B.*, 1956. Tubercle 65, Nº 2, 585.

*Still, G.*, 1909. "Common Disorders and Diseases of Childhood". Frowde, London.

*Swithinbank, J., Smith, H. V., Vollum, R. L.*, 1953. J. Path. Bact. 65, 565.

*Taylor, K. B., Smith, H. V.*, and *Vollum, R. L.*, 1955. J. Neurol. Neurosurg. Psychiat. 20, 1.

*Taylor, L. M., Smith, H. V.*, and *Hunter, G.*, 1954. Lancet 1, 700.

*Taylor, L. M., Smith, H. V., Vollum, R. L.*, 1953. Tubercle 34, 296.

*Whytt, R.*, 1768. 'Observations on the Dropsy of the Brain'. Edinburgh. J. Balfour.

*Williams, M., Smith, H. V.*, 1954. J. Neurol. Neurosurg. Psychiat. 17, 173.

# Some Aspects of Aseptic Meningitis

**J. PARK BIEHL, M. D.**

From the Department of Neurology, University of Cincinnati College of Medicine and the Cincinnati General Hospital, Cincinnati, Ohio, U. S. A.

The causes of meningitis are diverse and include any agent capable of creating an inflammatory reaction in the leptomeninges. The more familiar forms are infectious, and one can usually recognize meningitis due to suppurative disease. The clinical picture is familiar. The patient becomes acutely and quickly ill, perhaps after a few days of prodromal symptoms, with fever and sepsis. He is usually severely ill when seen with a marked disturbance in consciousness, fever, and rigidity of the neck. The cerebro-spinal fluid usually contains thousands or tens of thousands of neutrophils with decreased sugar content and markedly elevated protein. In some cases, particularly those due to the pneumococcus, large numbers of organisms are seen in the stained smear, which completes the diagnosis.

Another group, generally caused by viruses, may also be fairly well characterized, but often with less certainty than the first group. Ordinarily there are relatively mild symptoms with headache and meningeal irritation, more often than not occurring in the summer months. The cerebro-spinal (CSF) may contain hundreds of cells, but early in the course will show little or not protein increase. The sugar content is rarely altered.

Frequently, however, one has difficulty in distinguishing such patients from those comprising a third group which is more heterogeneous in nature, and which requires careful diagnostic attention. This group, together with viral meningitis, comprises for this discussion what is called aseptic meningitis. The causes generally are infectious, chemical, physical, and neoplastic. Patients with this type of illness may be characterized as usually becoming ill in a way other than acutely, the onset being insidious or subacute most of the time. He may be severely ill, with stiffness of the neck, fever, and confusion. Examination of the CSF reveals increased pressure with fluid containing hundreds of cells which may either be predominately neutrophilic or lymphocytic. The protein is generally elevated above 100 mg. per cent. The sugar content in many cases is lowered. Smear of the fluid in most instances is negative for micro-organisms, except in the case of cryptococcal meningitis. When one is faced with such a patient one has one of the most pressing problems in all of medicine. Such a patient may have any one of a number of otherwise fatal diseases, most of which may be cured, however, by one of a number of completely different therapeutic approaches. Since these therapies are frequently traumatic, if not dangerous in themselves, it follows that the closer one comes to recognition of specific causes the more successful therapy mill be. The major causes of aseptic meningitis are listed in Table I. Those that are particularly important or common, or both, are underlined. Thus the usual considerations include viral disease, tuberculosis, cryptococcal meningitis, and suppurative disease

TABLE I

MORE IMPORTANT CAUSES OF ASEPTIC MENINGITIS

I. *Viral*
- Mumps
- ECHO
- Poliovirus
- Coxsachie
- Lymphocytic Choriomeningitis

II. *Rickettsiae*
- Typhus
- Rocky Mountain Spotted Fever

III. *Bacterial*
- syphilis
- *tubercle*
- Leptospira

IV. *Fungus*
- *Cryptococcus* (Torula)

V. *Miscellaneous*
- *Brain abscess*
- *Subdural abscess*
- chemical meningitis (blood, air, anesthetic, etc.)
- *malignancy invasion*
- cerebral infarction
- Staphylococcal sepsis

adjacent to the leptomeninges. In our experience the majority of such patients today who are critically ill with aseptic meningitis have tuberculous meningitis. Since this disease appears to have become progressively less frequent over the past 10 years, it is likely that the trend will continue and other possibilities will continue to become more and more important diagnostically.

With this in mind, the following three cases are presented with the suggestion that, while each is typical of tuberculous meningitis, other causes may have been responsible in certain of them. The reader is invited to decide which, if any, represents a patient with tuberculous meningitis.

## CASE I

A fifty-five-year-old white former coal miner entered the hospital because of headache. Five weeks earlier intermittent bitemporal headache appeared which later became constant and increasingly severe. There was a tendency to veer to the right on walking, impairment of memory, and increasing weakness. Two weeks before admission vomiting began which also became increasingly severe. By the time he entered the hospital he had lost 20 pounds.

For many years he had worked in soft coal mines and was told at the time he left the mines twelve years earlier that he had silicosis. A mild cough was usually present without any recent worsening.

Examination revealed a normal temperature. His blood pressure was 140/80. He appeared to be acutely ill though not remarkably so. There was evidence of recent weight loss. The patient was intermittently confused. Forward flexion of the neck produced a slight pain and resistance on extreme flexion. The Kernig and Brudzinski

signs were not present. He was generally weak without any specific loss of strength. The deep reflexes were all hyperactive, but symmetrically so. The plantar responses were flexor.

The white blood cells numbered 10,500 and the hemoglobin was 15.5 grams. His stools were repeatedly guaiac positive. The tuberculin test was positive. Roentgenograms of the chest revealed conglomerate silicosis. An electroencephalogram revealed a mild bifrontal fast dysrhythmia with a well developed alpha pattern elsewhere.

Lumbar puncture revealed slightly yellow fluid under a pressure of 118 mm. of water. Five-hundred white cells were present, all lymphocytes. The protein was 154 mg. per cent and the sugar concentration was 26 mg. per cent. Subsequent spinal taps yielded similar results.

## CASE II

A negro, about sixty years of age, was brought to the hospital by the police, having been found unconscious on the street.

It was later determined from friends that he had lived alone, and in recent months had been complaining of chest pain, shortness of breath, and swelling of the feet and abdomen. It was said that about one year earlier a "spot" was found in a chest film taken for survey purposes. His diet had been poor and he had drunk much wine for many years.

Examination revealed a confused restless man who could give his name but could not carry out simple requests. There was no speech defect when he could be made to speak. A two day growth of beard was noted on his face. There was evident weight loss. Forward flexion of the neck was resisted but was apparently not painful. The Kernig and Brudzinski signs were not present. The right arm wandered on forward extension, suggesting weakness of that limb.

The white cells of the blood numbered 5,200 and the hemoglobin was 9.5 grams per cent. The stool was negative for blood.

Lumbar puncture revealed clear, colorless fluid under a pressure of 300 mm. of water. The patient, however was not relaxed. Three-hundred and fifty-six white cells were present which consisted of lymphocytes and clusters of deeply staining cells. The protein level was 198 mg. per cent and the sugar 17 mg. per cent. Five subsequent lumbar punctures revealed findings not materially different from this.

Roentgenograms of the chest and of the skull were not contributory. The pineal gland was not calcified.

## CASE III

A sixteen-year-old negro boy had had cough, fever, and chilliness for four weeks. After one week severe right frontal headache developed, and he became anorexic and remained in bed. He got up to go to the bathroom on the night before admission to the hospital and fell because his leg was paralyzed. Weakness of the right upper limb was also noted at this time. Physical examination revealed a temperature of 102.2 degrees F. The patient was ill and letargic. There was a right hemianopia. The neck somewhat stiff to flexion, but not painfully so. The deep reflexes were difficult to obtain, but were absent in the ankles. The right abdominal skin reflex was absent. Plantar responses were flexor. The white blood cells numbered 23,500 with 84 % neutrophils and 16 % lymphocytes. Lumbar puncture revealed an initial pressure of 410 mm. of water. The fluid was turbid, containing 18,000 white blood cells per cubic millimeter, 90 % of which were lymphocytes and 10 % neutrophils. The protein level was 137 mg. per 100 cc., and the sugar 51 mg. per 100 cc. Roentgenograms of the chest and skull showed no abnormality. On arrival on the ward the patient had a right-sided seizure beginning in the right upper limb.

The similarities between these three cases are at once evident. The two who were able to relate their history described illnesses measured in weeks which were progressive and included headache and later neurologic symptoms of deficit. Two in fact indicated that a lung disease had been present. Each was acutely ill with frank signs

of meningeal irritation but two exhibited little or no signs of neurologic deficit.

The spinal pressure was elevated in two, and in all three lymphocytes were present numbering from 356 to 1,800. The protein was markedly elevated in all three, and the sugar was reduced in two. One could hardly avoid a decision to treat each of these patients as tuberculous meningitis at least temporarily until other data should reveal another diagnosis.

Each of the three was in fact treated for tuberculous meningitis, and in each, for at least a period of time this was considered the most likely diagnosis. The first patient was placed on isoniazid and streptomycin. Cortisone was withheld because of the evidence of gastrointestinal bleeding. He did poorly, and in the fifth week of treatment the fourth sample of spinal fluid sent for fungus culture was found to contain Cryptococcus neoformans. The treatment was changed to Amphotericin B, and made an uneventful recovery. The second patient was also started on isoniazid and streptomycin. He also did poorly and his mental status remained impaired. Fever never occurred. Subsequent spinal taps revealed pressures never in excess of 160 mm. of water, the protein level varied from 182 to 250 mg. per cent and the sugar from 17 to 50 mg. per cent. Gram stains, routine cultures, and concentrations for acid fast organisms were negative. India ink preparations for Cryptococcus were negative. He died after three weeks in the hospital. Autopsy revealed a large gastric ulcer with indurated edges. The meninges were diffusely thickened to a mild degree only. It was only on microscopic examination that it was found that the patient had an infiltrating signet ring carcinoma of the stomach with metastasis to the meninges and adrenal gland. There was no evidence of tuberculosis. The third patient received streptomycin, penicillin, and isoniazid. Six hours after admission another convulsion occurred, following which he was deeply comatose. He died 12 hours after admission to the ward. Autopsy revealed extensive subdural suppuration bilaterally. A 2 cm. extradural abscess was also seen behind the right frontal sinus which contained pus. Erosion of the bony plates of the sinus was not observed. Cultures revealed beta hemolytic streptococcus and an organism of the colon group.

## DIFFERENTIAL DIAGNOSIS

Tuberculous meningitis is the first possibility that comes to mind in most patients of the sort discussed here. This probably stems from the prevalence of this disease in previous years, but it of course remains equally important today because of the urgency of getting specific treatment under way. In our experience several features have stood out as being of diagnostic value in tuberculous meningitis which sets it aside from other condition in this group. In viral meningitis the cellular response in the CSF occurs first and usually only after its subsidance does an increase in protein occur. In contrast the elevation of the protein in tuberculosis may precede pleocytosis by several weeks. By the time the patient is seen there are characteristically, hundreds of cells in the CSF. The protein by this time is at a level of 200 mg. per cent or more. As a general rule, it is most unlikely that one could identify tuberculous meningitis with a protein less than 50 mg. p[er] cent.

In about half of our adult patients with tuberculous meningitis, there is no clinical evidence tuberculosis elsewhere. Miliary tuberculosis is most frequent in those showing lesions. Relatively few had fibrocaseous pulmonary tuberculosis or other extrapulmonary forms of the disease. Thus one cannot expect to see tuberculosis elsewhere to substantiate a suspicion of tuberculosis as the cause for meningitis. Occasionally, bilateral or unilateral sixth nerve paralysis will appear in tuberculous meningitis. This has a certain amount of specific significance since in our experience, it has never occurred in meningitis other than tuberculous.

With reasonably good bacteriologic technique the tubercle bacillus can be isolated from the CSF by culture in almost all cases of tuberculous meningitis. Since this takes

up to six weeks to complete, it is obvious that a positive culture is of confirmatory value only. Finally, in tuberculosis, a therapeutic response of anti-tuberculous drugs in itself has confirmatory value in the diagnosis of this disease. A patient becoming progressively worse in the face of an adequate drug therapy over a period of two or three weeks probably does not have tuberculous meningitis except in the patient who also has chronic pulmonary tuberculosis with cavity formation.

Carcinomatous disease involving the meninges manifests itself variably, due to the varied possible sites of involvement. We have had patients with diverse clinical pictures, having as their basic lesion meningeal infiltration with neoplastic cells, and others who have had only a pure meningeal reaction similar to Case I. For example, a 61-year-old man developed an essentially symmetrical painful peripheral neuropathy with weakness and atrophy of lower limbs and urinary frequency and dribbling. This neuritis ascended over a period of three months, culminating in flaccid paralysis of the lower limbs. Spinal taps revealed fourteen monunuclear cells on one occasion with protein levels of 160, 205, and 60 mg. per cent on three occasions. Disseminated fibrotic pulmonary disease was revealed by the chest films, but no discrete mass was identified. At autopsy a small bronchial carcinoma was found with extensive metastatic deposits in the lumbar nerve roots and a thin sheath of neoplastic cells within the subarachnoid space of the cord and posterior fossa. Patients resembling the more classical form of aseptic meningitis have been seen by us with primary cancerous lesions in the lungs, stomach, and uterine cervix. Such patients are not commonly encountered, but are more than a mere curiosity in a neurologic practice.

Cryptococcal meningitis may occur as a peculiarly chronic remitting disorder. It is probably the most indolent of all of these forms of meningitis. It is seen particularly in patients with lymphomas, a relationship which cannot be demonstrated between lymphomas and tuberculous meningitis. In our current experience it is almost as common as tuberculous meningitis. It is probably best detected by following the simple rule of having the CSF searched for Cryptococcus whenever it is to be examined for the tubercle bacillus. Some of these patients respond well to Amphotericin B.

Ordinarily, suppurative disease of the nervous system such as brain abscess or subdural abscess stand apart clearly from aseptic meningitis. All too often, however, patients presenting with meningeal irritation due to the proximity of such abscesses to the CSF are diagnosed as meningitis. It happens too often (case III) that a diagnosis of tuberculous meningitis is settled upon, when the presence of subdural abscess later becomes apparent. Frequently one must look further for the cause of the meningitis, since it may require a different treatment.

It is remarkable that the pial membrane forms such a firm barrier to infection. A virulent spreading infection such as subdural abscess is bordered by this membrane, and seldom is this barrier broached. The inflammatory response produced in the subarachnoid space in subdural abscess is almost invariable sterile. Subdural abscess characteristically arises from the frontal sinuses, usually produces seizures, hemiparesis or aphasia and usually presents evidence of sepsis. These features make the diagnosis of subdural abscess apparent enough, if one keeps them in mind. Intracerebral abscess poses a problem less often, but on occasion arteriography is required to rule such a mass lesion in a hemisphere.

Occasionally ischemic disease of the brain may lead to an inflammatory response in the CSF, usually mild in degree. The following case is considered an example of this.

A 72-year-old carpenter entered the hospital with a left-sided paralysis. On the day before admission he experienced sudden transient blindness in the right eye with right-sided headache. This cleared within an hour. On the morning of admission the left side of his mouth became weak followed quickly by left-sided weakness. On admission he showed flaccid paralysis of the left limbs and the lower portion of his face. His tongue deviated to the left on protrusion. There was decreased sensation on

the left with absent deep reflexes on that side. The plantar response was extensor on the left. Arteriography of both carotid and vertebral vessels revealed marked stenosis of the right internal carotid artery at its origin.

On the second day his temperature rose to 102 falling on the third day to 100 where it remained for 3 days, before returning to normal. The white cells numbered 5,100 on admission rising to 11,800 on the second day and faling to 7,800 on the fourth.

The initial lumbar puncture revealed a CSF pressure of 190 mm. of water. The fluid was cloudy and contained 3,670 cells of which 95 % were neutrophils, the protein level was 118 mg. per cent and the sugar 108 mg. per cent. Smear, cultures and india ink preparations were negative. On the third day the pressure had risen to 340 mm. The fluid was still cloudy, with 680 cells, 84 % neutrophils. The protein was 150 mg. per cent and the sugar 70 mg. per cent. On the sixth day the CSF was normal except for a protein level of 51 mg. per cent. The hemiplegia remained essentially the same over a period of six weeks.

In recent years it has been said that bacterial meningitis treated with effective antibiotics for a few days, results in a nonpurulent CSF. In the differential diagnosis of aseptic meningitis, such a possibility is sometimes put forward. It is admittedly difficult to eliminate this possibility in a patient with aseptic meningitis who has received one or several injections of penicillin a day or two previously. In our experience the problem has hardly ever occurred. Certainly patients with pneumococcal meningitis who have received penicillin earlier present with a somewhat modified form of the disease. Yet this modification does not eliminate the basically septic appearance of the disease, and the CSF does not resemble that of aseptic meningitis.

The concept of aseptic meningitis presented here is broader than that usually encountered. The miscellaneous causes cited in this discussion must, however, be considered in the instances of meningitis not frankly purulent. The distinctions between the various types are often blurred. Certainly a patient approximating the picture of tuberculous meningitis should be treated at least temporarily with anti-tuberculous drugs. The possibility of causes other than tuberculosis must be constantly considered.

## SUMMARY

The more familiar forms of meningitis are infectious and their clinical picture is familiar. There is another group, however, that requires careful diagnostic attention as it is more heterogenous in nature.

This group together with viral meningitis comprises what is called aseptic meningitis. The causes generally are infectious, chemical, physical, and neoplastic. The clinical picture shown by such patients presents one of the most pressing problems in all of medicine, as it may reveal one of a number of otherwise fatal diseases, most of which may be cured, however, by one of a number of completely different therapeutic approaches. Since these therapies are frequently traumatic, if not dangerous in themselves, it follows that the closer one comes to recognition of specific causes the more successful therapy will be. The major causes of aseptic meningitis are listed, and the author underlines among them, those being particularly important or common. In the authors' experience the majority of the patients critically ill with aseptic meningitis have tuberculous meningitis, but since this disease appears to have become progressively less frequent over the past 10 years, it may be expected that other possibilities will continue to become more and more important diagnostically.

The author presents three cases, with the suggestion that while each is typical of tuberculous meningitis, other causes may have been responsible in certain of them. One showed to be a case of fungal meningitis; the autopsy of the second revealed a large gastric ulcer with indurated edges and the meninges diffusely thickened to a

mild degree, and only on microscopic examination it was found that the patient had an infiltrating signet ring carcinoma of the stomach with metastasis to the meninges and adrenal gland. The autopsy of the third one revealed extensive subdural suppuration bilaterally, and also a 2 cm. extradural abscess behind the right frontal sinus containing pus.

The author states that in most of the patients discussed tuberculous meningitis is the first possibility that comes to mind. This probably stems from the prevalence of this disease in previous years, but it of course remains equally important today because of the urgency of getting specific treatment under way. Several features that have stood out as being of diagnostic value in tuberculous meningitis setting it aside from other condition in this group, are described.

In this paper the author is presenting a broader concept of aseptic meningitis than that usually encountered.

The distinctions between the various types are often blurred. Certainly a patient approximating the picture of tuberculous meningitis should be treated at least temporarily with anti-tuberculous drugs. The possibility of causes other than tuberculosis must be constantly considered.

## RESUMEN

Las formas más corrientes de meningitis son de origen infeccioso y configuran cuadros clínicos fácilmente identificables. Existe sin embargo un grupo de naturaleza más heterogénea que requiere particular atención en cuanto a su diagnóstico; es el grupo de las llamadas meningitis asépticas, que incluye las meningitis virósicas y cuyo origen es en general infeccioso, químico, físico y neoplástico. El cuadro clínico que presentan dichos pacientes constituye uno de los problemas médicos más urgentes a resolver, ya que puede llevar al diagnóstico de una serie de enfermedades mortales en casos en que en realidad se trata de enfermedades totalmente curables por diversos métodos terapénticos. Tratándose de terapéuticas frecuentemente traumáticas, aunque no peligrosas en sí, cuanto más ajustado sea el reconocimiento de las causas específicas tanto más exitoso resultará el tratamiento. Se enumeran las causas fundamentales de las meningitis asépticas, subrayando en especial las que se destacan por su importancia o por ser más corrientes. La experiencia del autor demuestra que la mayoría de los pacientes con graves meningitis asépticas tienen meningitis tuberculosa. Dado que esta enfermedad se ha hecho menos frecuente en los últimos 10 años puede esperarse que ganen importancia otras posibilidades en cuanto a su valor diagnóstico.

El autor presenta tres casos y hace notar que aunque todos parecen ser casos típicos de meningitis tuberculosa, otras causas pueden estar en juego. El primero demuestra ser un caso de meningitis fungosa; la autopsia del segundo reveló en primera instancia la existencia de una extensa úlcera gástrica con bordes indurados y leve engrosamiento de las meninges; un examen microscópico permitió descubrir un carcinoma estomacal en sello de anillo con metastasis en las meninges y glándula suprarenal. La autopsia del tercero reveló una extensa supuración subdural bilateral y un absceso extradural de 2 cm. de grosor conteniendo pus detrás del seno frontal derecho.

El autor sostiene que en la mayoría de los pacientes en cuestión se sospecha la posibilidad de una meningitis tuberculosa, debido a que en años anteriores la tuberculosis se daba con mucha frecuencia; a pesar de esto el problema planteado mantiene su importancia hoy en día porque es urgente la aplicación de tratamientos específicos. Se analizan una serie de aspectos que han demostrado valor diagnóstico en los casos de meningitis tuberculosa, distinguiéndola dentro del grupo. Cabe destacar que en este trabajo el autor presenta un concepto más amplio de meningitis asépticas que el corriente.

Si bien es cierto que a menudo son difíciles de distinguir los diversos grupos de meningitis, el paciente que presente un cuadro semejante al de la meningitis tuberculosa deberá ser sometido transitoriamente al tratamiento correspondiente, pero siempre debe considerarse la posibilidad de que pueda deberse a otras causas.

## RÉSUMÉ

Les formes les plus courantes de méningite sont d'origine infectieux et donnent des cadres cliniques faciles à identifier. Il existe cependant un groupe plus heterogène quant à sa nature, qui exige une attention particulière en ce qui concerne son diagnostique; c'est le groupe des ainsi dites méningites aseptiques, qui inclut les méningites à virus, et dont l'origine est en général infectieux, chimique, physique et néoplastique. Le cadre clinique presenté par ces patients constitue un probleme médical des plus urgents à résoudre, étant donné qu'il y a des cas de maladies graves qui sont guérissables seulement si on applique une thérapeutique convenable. Puisqu'il s'agit de thérapeutiques frequemment traumatiques, et pas dangereuses en elles-mêmes, le succès du traitement dépendra d'une reconnaissance aussi exacte que possible des causes specifiques. On énumère les causes fondamentales des méningites aseptiques, en soulignant particulièrement les plus courantes et les plus importantes. L'expérience de l'auteur prouve que la plupart des patients présentant des graves méningites aseptiques ont une méningite tuberculeuse. Comme cette maladie est devenue moins fréquente dans les derniers dix ans on peut espérer que d'autres possibilités deviennent importantes dans l'aspect diagnostique.

L'auteur présente trois cas en suggérant que même s'ils ont l'air d'être des cas typiques de méningite tuberculeuse, ils sont dûs à d'autres causes. Le premier se révèle comme un cas de méningite fongueuse; l'autopsie du deuxième paraissait d'abord dû à l'existence d'une large ulcère gastrique au bord durci et un léger grossissement des méninges; un examen microscopique permit la découverte d'un carcinome estomacal avec métastase dans les méninges et dans les capsules surrénales. L'autopsie du troisième cas révéla une large suppuration sousdurale bilatérale et un abscès extradural de 2 cm. d'épaisseur contenant du pus derrière le sinus frontal droit.

L'auteur affirme que dans la plupart des patients en question on soupçonne la possibilité d'une méningite tuberculeuse, ce qui est dû a la grande quantité de cas de cette maladie trouvés jadis.

Cependant le probleme posé continue à être important actuellement et il est nécessaire d'obtenir des traitements spécifiques pour chaque cas.

On analyse une série d'aspects ayant démontré posséder une valeur diagnostique dans les cas de méningite tuberculeuse, en la distinguant dans le groupe des autres possibilités. On doit signaler que l'auteur présente un concept de méningite aseptique plus ample que celui qu'on considère couramment.

Bien qu'il soit vrai que les différents groupes de méningites sont difficiles à distinguer, les patients présentant des cadres suggérant une méningite tuberculeuse devront être soumis, au moins transitoirement, à un traitement antituberculeux; on devra considérer cependant constamment la possibilité de l'existence d'autres causes.

## ZUSAMMENFASSUNG

Die bekanntesten Formen der Meningitis sind infektioes und das klinische Bild von ihnen ist allen vertraut. Es gibt jedoch noch eine andere Gruppe die eine besonders aufmerksame diagnostische Beachtung verlangt, da sie sehr heterogener Natur ist. Diese Gruppe bildet zusammen mit der Virusmeningitis die

Gruppe der sogenannten aseptischen Meningitiden. Sie sind gewoehnlich infektioesen, chemischen, physikalischen und neoplastichen Ursprunges. Das klinische Bild bei diesen Patienten stellt eines der dringlichsten Probleme in der Medizin dar, da es unter der Maske einer Anzahl sonst fataler Erkrankungen erscheinen kann, von denen jedoch die meisten geheilt werden koennen durch eines von vielen vollkommen verschiedener therapeutischer Mittel. Da diese nicht gefaehrliche Behandlungsmethoden haeufig traumatisierend sind, ergibt sich, dass je naeher man zur Erkennung der spezifischen Ursache kommt, umso erfolgsreicher die Behandlung sein wird. Es werden die hauptsaechlichen Ursachen der aseptischen Meningitis aufgezaehlt, wibei der Autor besonders diejenigen hervorhebt, die besonders wichtig oder haeufig sind. Der Autor hat die Erfahrung gemacht, dass die Mehrzall der Patienten die mit einer aseptischen Meningitis schwer darniederliegen, eine tuberkuloese Meningitis haben. Aber da diese Krankheit anscheinend immer weniger haeufig zu werden scheint, muss man annehmen, dass andere Moeglichkeiten weiter immer wichtiger werden vom Diagnostischen Standpunkt aus gesehen.

Der Autor praesentiert drei Faelle und bemerkt, dass obwohl alle drei eine typische tuberkuloese Meningitis darstellten, auch andere Ursachen bei einigen von ihnen verantwortlich sein koennen. Ein Fall wies sich als fungoese Meningitis; bei der Autopsie des zweiten Falles fand man ein grosses Magengeschwuer mit verhaerteten Raendern und die Meningen mit einer diffusen leichten Verdickung, und erst die mikroskopische Untersuchung zeigte, dass der Patient ein infiltrierendes Ringkarzinom des Magens mit Metastasen in den Meningen und den Nebennieren hatte. Die Autopsie des dritten Falles zeigte eine ausgedehnte bilaterale subdurale Eiterung und einen extraduralen Abscess hinter dem rechten sinus frontalis, mit Eiter. Der Autor stellt fest, dass bei den meisten besprochenen Patienten die tuberkuloese Meningitis die erste Moeglichkeit ist, die in Betracht gezogen wird. Diese Wahrscheinlichkeit kommt daher, dass diese Erkrankung in frueheren Jahren vorherrschend war, aber diese Wahrscheinlichkeit bleibt weiterhin wichtig, damit eine spezifische Behandlung schnellstens eingeleitet werden kann. Verschiedene Charakteristische Eigentuemlichkeiten, die bei der tuberkuloesen Meningitis als von diagnostischem Wert betrachtet wurden und die durch anderen Erkrankungen dieser Gruppe an Wert verloren haben, werden beschrieben.

In dieser Arbeit praesentiert der Autor einen weiteren Konzept der aseptischen Meningitis als man gewoehnlich antrifft.

Die Unterscheidung zwischen den verschiedenen Typen ist oft undeutlich. Gewiss sollte jeder Patient, der das angenaeherte klinische Bild einer tuberkuloesen Meningitis praesentiert wenigstens vorruebergehend als solche mit antituberkuloesen Mitteln behandelt werden. Aber die Moeglichkeit anderer, nicht tuberkuloeser Ursachen, muss staending in Betracht gezogen werden.

# The Diagnosis and Treatment of Bacterial and Fungal Meningitis

**N. JOEL EHRENKRANZ, M. D.; PERITZ SCHEINBERG, M. D.**
Departments of Medicine and Neurology
University of Miami School of Medicine
Miami, Florida.

The extraordinary discoveries in the chemotherapy of infectious diseases since 1933 have changed the treatment of meningitis from measures of limited efficacy and often empiric gesture, to a program of highly curative therapy with a great reduction in mortality and morbidity. Despite this, the mortality of meningitis is still appreciable and some instances of meningitis fail to respond to drug treatment even though the infecting organism is susceptible to drug *in vitro*. In some of these cases debilitation and overwhelming infection account for the poor outcome[1, 2, 3] and indicate the need for investigation to decrease further the mortality.

Meningitis is an inflammation of the leptomeninges due to infection by a micro-organism which enters the subarachnoid and ventricular spaces during bacteremia or from a contiguous area in the skull, mastoids, or para-nasal sinuses. Entrance may also take place as a consequence of penetration following head trauma, intracranial or spinal surgery or, rarely, lumbar puncture. Purulent meningitis is more than simple involvement of the meninges; there is often associated inflammation of the contigous brain parenchyma and cranial nerves. The inflammatory process often involves the superficial vessels and causes thrombosis of intracerebral arteries and veins which results in infarction of brain tissue. The extent of vascular and parenchymatous damage is related to the intensity and duration of the infection. It is generally recognized that the appearance of neurologic signs of localized parenchymal involvement, such as convulsive seizures or lateralizing motor signs, signifies a poor prognosis for complete recovery[3].

The clinical signs of meningitis are familiar to most clinicians, as are the accompanying findings which may suggest the identity of the infecting bacteria, such as widespread petechial hemorrhages and areas of skin infarction sometimes seen in meningococcal infection or evidence of lobar pneumonia in pneumococcal infection. The most important diagnostic aid is a careful and complete examination of the spinal fluid.

Demonstration of micro-organisms in the cerebrospinal fluid is a necessary condition for the diagnosis of infectious meningitis during life. Microscopic examination of stained cerebrospinal fluid sediment will often give presumptive evidence of the presence of bacteria or fungi; the final proof rests in culture of the micro-organism. Cerebrospinal fluid should be inoculated on to appropriate media and incubated without delay, otherwise effete microorganisms may fail to grow and the specimen may yield misleading results. If possible, media should be inoculated at the bedside. Blood agar generally will support growth of bacteria commonly causing meningitis, such

as the pneumococcus. In addition, chocolate agar incubated in an atmosphere of $CO_2$ will result in good growth of *Hemophilus influenzae* and meningococci. A thioglycollate tube should be inoculated for culture of anaerobic bacteria. In circumstances where infection with *Mycobacterium tuberculosis* is suspect, cerebrospinal fluid should be plated on egg yolk or oleic acid-albumen medium and a guinea pig injected with cerebrospinal fluid as well. The larger the volume of cerebrospinal fluid used, the greater the chance of recovery of the tubercle bacillus. In the diagnosis of tubercuolus meningitis, a prolonged and careful examination of acid-fast stained cerebrospinal fluid sediment is particularly important since growth of the organisms is slow. The sediment from five to ten ml. of cerebrospinal fluid obtained by centrifugation at high speed for 30 minutes should be examined from serial specimens. In an instance where fungus infection may be the cause of meningitis, Sabouraud's glucose agar is the medium for cultivation; again guinea pig inoculation of cerebrospinal fluid should be carried out. Microscopic examination of an India ink preparation of cerebrospinal fluid may suggest the presence of fungi.

Of the commonly performed biochemical measurements of cerebrospinal fluid, only a decrease in the level of sugar suggests the occurrence of bacterial or fungal meningitis. Alterations in concentration of electrolytes or protein may occur in a wide variety of diseases. Since the level of sugar in the cerebrospinal fluid is, in part, a function of the amount of sugar in the blood, both should be determined, particularly when hyperglycemia is present. The cerebrospinal fluid sugar is roughly 40 % to 65 % of that of the blood sugar[4, 5, 6]. Cerebrospinal fluid sugar determinations are usually decreased in pyogenic meningitis but rarely so in cases of brain abscess. Moreover, if the initial sugar level is normal, serial specimens of cerebrospinal fluid in untreated bacterial meningitis (including tuberculous meningitis) will soon show a fall in sugar to an abnormal level[6, 7]. In untreated brain abscesses in our experience, if a decrease of moderate degree occurs on one examination, it will generally not be present on serial determinations. Hence, the occurrence of low level of sugar in several specimens of cerebrospinal fluid points to an infectious meningitis, and if no organisms can be demonstrated by microscopic examination or by culture in a few days, the diagnosis of tuberculous or fungus meningitis becomes likely. It must be kept in mind that certain non-infectious diseases involving the meninges, such as sarcoidosis or malignancy, may also result in a persistently reduced level of cerebrospinal fluid sugar[8].

The mechanism of decrease in cerebrospinal fluid sugar in bacterial meningitis is not at all clear. Bacterial fermentation is a possible cause; however, the presence of bacteria in cerebrospinal fluid does not invariably result in decreased sugar levels[9]. Moreover, the low levels of sugar found in tuberculous meningitis are clearly out of proportion to the slow rate of growth and glycolysis of *M. tuberculosis* whose numbers are generally scanty. Even under the circumstances of growth in artificial media, the fastest rate of division of *M. tuberculosis* is every 18 hours[10] and measurable glycolysis is even slower[7]. Leucocytes in cebrospinal fluid do not account for the fall in sugar since a similar leucocytosis may be seen in viral meningitis without such a fall. There is no relation between the number of polymorphonuclear leucocytes in the cerebrospinal fluid and the amount of sugar in each specimen. Patients with pneumococcal meningitis and low white blood cell counts in cerebrospinal fluid may have low levels of sugar, although this is not necessarily the case in experimental animals. Petersdorf *et al*[11] found no reduction in the concentration of cerebrospinal fluid sugar in experimental pneumococcal meningitis in dogs made leucopenic by total body irradiation in which no cerebrospinal fluid pleocytosis occurred. By contrast, in our patients with pneumococcal meningitis characterized by only a few leucocytes in the cerebrospinal fluid on repeated examinations, there was a marked decrease in the amount of cerebrospinal

**TABLE I. Occurrence of both low cerebrospinal fluid sugar levels and low leucocyte counts in patients with pneumococcal meningitis ***

**Serial Dilutinations**

| *Pt. #* | *Age* | *CSF Sugar mg. %* | | *WBC mm³* | *NO. PMN* | *Blood Sugar mg. %* | *Comment* |
|---|---|---|---|---|---|---|---|
| 5 | 59 years | a) | 10 | 4 | 4/4 | 200 | Patient had recently received x-ray treatment for carcinoma of tonsil. Died in 24 hours; only slight exudate on meninges. |
| | F | b) | 10 | 7 | 7/7 | 246 | |
| 9 | 70 years | a) | 10 | 5 | 3/5 | 64 | Patient had hypersplenism and leucopenia. Died in 24 hours; no autopsy. |
| | F | b) | 15 | 13 | 2/13 | 114 | |
| | | c) | 10 | 4 | 2/4 | 105 | |

* Pneumococci recovered from the cerebrospinal fluid of all patients.

fluid sugar (Table I). Lincoln has also described decreased sugar levels in tuberculous meningitis[12] in the presence of only a few inflammatory cells.

One explanation that is consonant with all of the observed data is that the decrease in cerebrospinal fluid sugar levels in bacterial meningitis is due to altered activity of cells lining the pia-arachnoid, and, therefore, reflects the extent and intensity of the meningeal response. For example, although neither galactose nor sucrose are metabolized in the body[13] the rate of galactose disappearance from the cerebrospinal fluid after intrathecal injection is much more rapid than that of sucrose[14]; this indicates the active transport of the former from the meninges to the blood similar to the active transport of galactose by the intestine[15]. Moreover, intrathecal injection of glucose in children with untreated tuberculous meningitis resulted in an elevation in blood sugar similar to that found after intramuscular injection. By contrast, when the blood sugar was elevated in children with tuberculous meningitis by oral or intramuscular administration cerebrospinal fluid sugar levels showed little absolute increase, although in normal children such an increase did occur[7]. The foregoing points to an increase in transport of sugar from the meninges to the blood and/or a decrease in transport of sugar from blood to meninges in tuberculous meningitis. That a variety of non-infectious diseases that involve the meninges may also result in decreased cerebrospinal fluid sugar level[8], also suggests that an alteration in behavior of meningeal cells is responsible for the fall in sugar level. Hence, it may be inferred that altered activity of meningeal cells, as well as glycolysis by leucocytes and bacteria, accounts for the decrease in cerebrospinal fluid sugar in acute bacterial meningitis.

The significance of the extent of hypoglycorrhachia in the prognosis of clinical recovery in pneumococcal meningitis can be observed in Table II. Those patients in our series of pneumococcal meningitis with a finding of less than 15 mg. % of sugar in the cerebrospinal fluid on the first lumbar puncture had a much poorer prognosis than those with higher levels of sugar ($0.01 > P > 0.001$). Similar observations are described in at least one other report

of pneumococcal meningitis[2]. This correlation is also found in tuberculous meningitis[16]. In *H. influenza* and meningococcal meningitis, where mortality rates are low, no such relation has been found. The concept that a low level of sugar in the cerebrospinal fluid is due to extensive meningitis is not vitiated by the disparity in outcome between patients with a low cerebrospinal fluid sugar in pneumococcal and tuberculosis meningitis on the one hand, and meningococcal and *H. influenza* meningitis on the other. Tuberculous and pneumococcal meningitis often occur in debilitated or particularly susceptible persons[3, 7]; the more extensive their meningitis, the poorer the outcome of treatment is likely to be. On the other hand, meningococcal and *H. influenza* meningitis occur in those who are otherwise healthy but who lack type-specific immunity[9]. Here a good result, despite extensive meningitis, may be anticipated and these good results can be ascribed to the pre-infection healthy state of the host.

More than 2000 to 3000 leucocytes per $mm^3$ of cerebrospinal fluid, particularly granulocytes, almost always indicates bacterial infection. On occasions, however, counts of 1000 to 2000 leucocytes, predominantly granulocytes, may be seen in virus meningitis[18].

Fungi possess the enzyme alcohol dehydrogenase, which catalyzes the conversion of sugar to alcohol[19]. This enzyme is absent in bacteria. In the absence of ingestion of alcohol[20], the presence of alcohol in the cerebrospinal fluid is presumptive evidence of a fungus infection of the meninges.

## Treatment of bacterial and fungal meningitis

The management of patients with acute bacterial or fungal meningitis resolves itself into the rapid and proper use of antibiotics and the care of the neurologic and systemic complications of the disease. This discussion will not be concerned with the ordinary principles of management of disease, but rather with the management of the infection and its complications.

### Meningococcal Meningitis

The use of sulfonamides in the treatment of meningococcal meningitis brought a dramatic decrease in the mortality of this disease which has not been improved by the addition of various antibiotics. Indeed, sulfonamide therapy is at times so effective that the cure of meningococcal meningitis has been described following a single intravenous dose[21]. The usual course of sulfonamide treatment is 6 grams intravenously at the outset, after patient's fluid losses have been replaced, and one gram every six hours thereafter for seven days. Certain considerations, however, justify inquiry into the efficacy of antibiotic treatment in meningococcal infection. *In vitro,* some meningococci have been described to be moderately resistant to sulfonamide action[22]. More recently, meningococci markedly resistant to sulfonamides have been detected among some carriers in whom intensive prophylaxis with sulfonamides had no effect[23]. Treatment with penicillin G seems to be as efficacious as sulfonamide therapy. Large doses of penicillin G, in the order of 12 million units a day by a parenteral route, have been shown to give as good results in the treatment of meningococcal meningitis as do sulfonamides[24].

Meningococcal meningitis is at times associated with septicemia which may cause multiple embolic infarcts of the skin and these must receive appropriate surgical attention and care to avoid secondary infection. Cardiovascular collapse in meningococcemia is often profound and difficult to treat; because of the frequent observation of bilateral adrenal hemorrhage and necrosis at autopsy, it has been argued that acute adrenal insufficiency is responsible for the collapse. Little evidence exists to support this view *(vide infra).* The use of adrenal cortical steroids is justified if pressor amines fail to maintain the blood pressure in the normal range. The syndrome of rapid onset of shock in association with bacteremia and meningitis can also occur in pneumococcal and influenzal meningitis, but it is less common in these infections.

**TABLE II. The relation of the initial cerebrospinal fluid sugar levels to the outcome of treatment of pneumococcal meningitis* with massive doses of penicillin G**

| | CSF sugar less than 15 mg. %; blood sugar less than 250 mg. % | CSF sugar greater than 15 mg. %; blood sugar less than 250 mg. % |
|---|---|---|
| Number surviving treatment | 8 | 12 |
| Total number treated | 20 | 12 |
| Average age: | 31 years | 31 years |

$0.005 < P > 0.001$

* Pneumococci recovered from spinal fluid of both patients.

### Pneumococcal Meningitis

Pneumococcal meningitis poses a special problem in management, for though some cases develop as a complication of pneumococcal pneumonitis and bacteremia, some occur by extension from infected mastoids or paranasal sinuses, or from a skull fracture which has opened into the nasal cavity. It is essential, therefore, that patients with meningitis be carefully examined clinically and by x-ray for such parameningeal source of infection. Otitis, mastoiditis or sinusitis at times may require surgical treatment for proper drainage. In the past subarachnoid block due to accumulation of the thick exudate was a frequent complication, but this is uncommon now.

This disease has a high mortality with any form of treatment (Table II), despite the fact that the pneumococcus is extremely susceptible to a wide variety of antibiotics. The intrathecal injection of aqueous penicillin G, while technically somewhat more difficult to administer, offers the advantage of direct instillation of the antibiotic into the meninges, and reports of its use by others and our experience too, suggest a better outcome with intrathecal treatment than with massive penicillin therapy intravenously or intramuscularly[25]. The usual intrathecal dosage is 5000 units for infants and children up to 2 to 3 years, 10,000 to 15,000 units for older children and 30,000 to 50,000 units for adults. Aqueous penicillin G for intrathecal injection is freshly dissolved and the appropriate dose made up in 10 ml. of 0.85 % Na Cl. After 10 ml. of cerebrospinal fluid have been removed, the penicillin solution is slowly injected at a rate of 1 ml. per minute (by the clock!). If the dosage and rate of injection are correct no reactions to intrathecal penicillin will be observed. Three or four doses of intrathecal penicillin are generally sufficient and are administered at intervals of 12 hours; intramuscular aqueous penicillin G in dosage of 100,000 units every four hours is given concomitantly. It is most important *not* to administer larger doses of penicillin G intramuscularly during the course of intrathecal penicillin since convulsions and even death may result from excessive concentrations of the antibiotic in the central nervous system. To avoid dosage errors, it is wise to have at least two persons do the calculation for diluting penicillin for intrathecal injection.

Should antibiotic treatment in the first 24 to 48 hours fail to result in improvement, as manifested by a rise in the level of cerebrospinal fluid sugar, an intensive search for an area of contiguous infection in the mastoids or sinuses must be conducted, and surgical drainage promptly performed if it is found, even though the patient may be a poor surgical risk.

### H. Influenza Meningitis

This is almost always a disease of the infant or child under 10 year of age, although occasionally it may be seen in adults with agammaglobulinemia, cerebrospinal fluid rhinorrhea, or other conditions impairing host resistance[26, 27]. The usual treatment is chloramphenicol in dosage of 100 mg. per kg. of body weight per day, or 3 to 4 gm. a day for an adult. In infants, doses of 25 to 50 mg. per kg. per day are not to be exceeded lest respiratory dysfunction occur[28]. The intrathecal administration of 20 to 50 mg. of streptomycin in 10 ml. of 0.85 % saline, injected as is intrathecal penicillin *(vide supra)*, results in rapid sterilization of the cerebrospinal fluid[29].

### Ampicillin in acute bacteria meningitis

Promise of one drug for the treatment of meningococcal, pneumococcal or *H. influenza* meningitis is seen in the recent report of the efficacy of ampicillin, a semisynthetic penicillin, in treatment of all of these infections[30]. Should these results be confirmed and extended, and should bacterial resistance to ampicillin not occur, the treatment of meningitis will be greatly simplified.

### Tuberculous Meningitis

Isonicotinic acid hydrazine (INH) treatment has resulted in spectacular rates of cure in tuberculous meningitis[31]. The drug is well absorbed after oral administration and is distributed throughout the body water; substantial concentrations are found in the cerebrospinal fluid of normal persons and subjects with tuberculous meningitis. INH penetrates the caseous material of tuberculous infection and is retained there for long periods of time[31]. Treatment is usually started with 10 mg. per kg. of body weight for 2 to 4 weeks and the dose is decreased to 5 mg. per kg. thereafter. The total duration of INH therapy should be at least one year. Peripheral neuritis is frequently seen in adults receiving INH in dosage above 5 mg. per kg. This side effect of INH can be both obviated and cured with the administration of 50 to 100 mg. of pyridoxine per day. Pyridoxine does not appear to interfere with the antibacterial action of INH.

Along with INH, treatment with streptomycin is recommended. Streptomycin is administered in dosage of 0.5 gm. intramuscularly once or twice daily until a total dose of 60 grams has been reached, then 0.5 to 1.0 gm. twice a week for six months to one year. Streptomycin has a curariform effect and, in excessively large doses, respiratory distress and failure may occur[31]. In the neonatal infant the dose of streptomycin should not exceed 10 mg. per kg. of body weight.

The simultaneous administration of a third drug, paraaminosalicylic acid (PAS), is also advised by some authors. One of the major effects of PAS appears to be potentiation of INH by competitive inhibition of acetylation[31]. The usual daily dosage in adults is 12 to 15 mg. in four divided oral doses. Gastrointestinal irritation to PAS is not uncommon.

### Treatment of meningitis due to other bacteria, partially treated bacterial meningitis and treatment in absence of positive cultures

Occasionally, infection of the meninges due to one of a variety of other bacteria is reported[32]. Treatment is best carried out using the results of *in vitro* sensitivities to antibiotics as a guide. When no organism is present as a result of partial antibiotic treatment, or before the return of bacteriological results, intravenous therapy with penicillin G in dosage of 1 to 2 million units every 2 hours should be administered once appropriate cultures have been secured. This will deal with meningococcal as well as pneumococcal infections. In a child under the age of 10 years, chloramphenicol should be added to this program since *Hemophilus influenzae* meningitis may be present. Where bacteriological studies fail to indicate the cause of infection, diligent inves-

tigation for tuberculous and fungal infection and for brain abscess is mandatory.

### Fungus infection of the meninges

Meningeal infections due to a variety of fungi have been arrested by treatment with amphotericin B[33]. This drug is administered intravenously and treatment is begun with 0.25 mg. per kg. of body weight in 500 ml. of 5 % glucose in water. Dosage is increased by 5 mg. a day or every other day until a level of 1 mg. per kg. is reached, if toxicity and side-effects permit. A dose of 1.5 mg. per kg. is never exceeded. Each dose must be slowly administered over several hours as more rapid injection almost invariably results in pyrogenic reactions and chemical thrombophlebitis. Fever, chills, transient azotemia, hypokalemia and a variety of other side-effects occur in a majority of patients receiving amphotericin B[34]. A total dose of two to six grams of amphotericin B is given, depending upon the clinical and mycological response. If relapse occurs a second or third course may be administered. Amphotericin B may also be injected intrathecally[33].

### Corticosteroid treatment

Corticosteroid and corticotropic hormones have a theoretical role as adjunctive therapy in treatment of tuberculous meningitis to reduce the inflammatory response. Organization of the thick basal exudate of tuberculous meningitis may result in hydrocephalus or endarteritis[35]. Treatment with corticosteroids should be started promptly and continued for several weeks until marked improvement in clinical and laboratory findings have occurred. Daily dosage is started with 200 to 500 mg. of cortisone (or its equivalent) for several days and then is decreased to avoid hyperadrenal corticism. Bacterial superinfection at times results as a consequence of steroid therapy in tuberculous meningitis and this risk should be weighed against the benefits of corticosteroid use[36].

By contrast to their use in tuberculous meningitis[37], judicious evaluation indicates that adrenal steroids have no place in the treatment of meningeal infections due to other bacteria, despite an occasional paper to the contrary[38]. Not only do careful studies reveal no benefits in routine treatment of pneumococcal or meningococcal meningitis with corticosteroid[39, 40, 41], but harm can result from their use as evidenced by the occurrence of venous thrombosis and bilateral renal cortical necrosis[42], superinfection[36], gastrointestinal hemorrhage and increased incidence of subdural collections of fluid[43].

Studies rarely show failure of adrenal function as a cause of cardiovascular collapse in meningococcal meningitis[44, 45], although this is a commonly proposed explanation. The origin of the severe hypotension of meningococcemia is likely to be similar to the cause of shock in bacteremia due to enteric bacteria, in which no adrenal hemorrhage is found and endotoxic damage to the host is presumed. Pressor amines will generally maintain the blood pressure in these circumstances. Some consider that the concomitance of adrenal hemorrhage and necrosis is sufficient evidence to warrant the use of adrenal cortical steroids along with pressor amines. This problem has not yet been adequately settled.

### Subdural effusions, cerebral edema and seizures

Serous subdural effusions are a complication of meningitis in the infant. If fever, irritability or focal neurological signs in an infant appear or persist in the course of treatment, sterile subdural effusion or persistance of active meningitis should be suspected. Subdural tap will then be necessary. This is done by careful insertion of a needle through the lateral angle of the anterior fontanelle and if a subdural effusion is present fluid can easily be withdrawn. Daily aspiration should then be carried out while antibiotic therapy is continued; if the patient still does not respond properly it is likely that a subdural membrane is present and will require surgical

removal. The complications of meningitis in the infant and their management have been thoroughly reviewed by Nyhan and Richardson[43].

Another complication of the acute bacterial meningitides, particularly in children and especially in meningitis due to *H. influenza,* is the severe generalized brain edema which occasionally may result in fatal cerebellar or tentorial herniation. It is difficult to anticipate this problem in advance, and once herniation has occurred little of a constructive nature can be done. Autopsy reveals that some of these patients show little purulent exudate around the brain, and that the infection has been adequately treated and apparently controlled. In these patients cerebellar or occasionally tentorial herniation had occurred and was probably responsible for the demise. For this reason, it is unwise to perform repeated spinal taps once the diagnosis has been established, for removal of lumbar subarachnoid fluid increases the likelihood that a swollen brain will expand inferiorly with herniation. A patient who appears to be disproportionately obtunded, despite adequate treatment, should be suspected of having serious cerebral edema, and immediate steps undertaken to reduce the swelling by the use of hypothermia, osmotic diuretics, or perhaps by a 24 hour course of adrenal cortical steroids. Hypothermia can be achieved rapidly by surrounding the patient in ice contained in plastic bags or by use of a hypothermia unit with blanket and provides excellent reduction of brain volume, without the rebound sometimes seen following the use of osmotic diuretics, such as urea or mannitol[46]. A one day course of adrenal cortical steroids also reduces brain swelling and, in our opinion, their short-term use is not hazardous[47]. In any event, use of any of these agents is rarely necessary for longer than 24 to 36 hours, for the edema itself is temporary.

The occurrence of convulsive seizures in purulent meningitis is a serious prognostic sign, because it may indicate involvement of the brain parenchyma either directly or through arterial or venous thrombosis. It requires immediate reassessment of type and dosage of drug therapy, a consideration of immediate surgical treatment, if a parameningeal source of infection such as mastoiditis or sinusitis is present, and anticonvulsant treatment. This last should be prompt and vigorous, utilizing sodium phenobarbital primarily, with or without diphenylhydantoin. There is some evidence that frequently recurrent seizures may result in further brain edema and thereby complicate the original disease. The use of anticoagulants is not indicated even if cortical venous thrombosis is suspected, because the mechanism of inflammation producing vascular thrombosis does not appear to be amenable to anticoagulants, and also because such lesions often result in hemorrhagic brain infarction.

## SUMMARY

The clinical signs of meningitis are familiar to most clinicians as are the accompanying findings which may suggest the identity of the infecting bacteria. The most important diagnostic aid is a careful and complete examination of the spinal fluid.

Of the commonly performed biochemical measurements of cerebrospinal fluid, only a decrease in the level of sugar suggests the occurrence of bacterial or fungal meningitis. It may be inferred that altered activity of meningeal cells, as well as glycolysis by leucocytes and bacteria, account for the decrease in cerebrospinal fluid sugar in acute bacterial or fungal meningitis.

Demonstration of micro-organisms in the cerebrospinal fluid is a necessary condition for the diagnosis of infectious meningitis during life.

More than 2000 to 3000 leucocytes per $mm^3$ of cerebrospinal fluid, particularly granulocytes, almost always indicates bacterial infection: counts of 1000 to 2000 leucocytes, predominantly granulocytes, may be seen in virus meningitis.

In the absence of ingestion of alcohol,

the presence of alcohol in the CSF is presumptive evidence of a fungus infection of the meninges, as it is known that fungi possess the enzyme alcohol dehydrogenase, which catalyzes the conversion of sugar to alcohol.

Treatment of every one of the following types of meningitis is described in this paper: meningococcal, pneumococcal, H. influenza, and tuberculous meningitis.

Special attention is drawn to the efficacy of a new drug for the treatment of meningococcal, pneumococcal or H. influenza meningitis, a semi synthetic penicillin; should results be confirmed and extended and should bacterial resistance of ampicillin not occur, the treatment of meningitis will be greatly simplified. Finally the authors describe treatment of meningitis due to other bacteria, partially treated bacterial meningitis and treatment in absence of positive cultures.

Corticosteroid treatment may be used as an adjunctive therapy in tuberculous meningitis. Its use in the treatment of pneumococcal or meningococcal meningitis reveals no benefits, and it may cause serious harm.

Finally the authors describe three kinds of complications of meningitis —subdural effusions, cerebral edema and seizures— and the way to counter-act them.

## RESUMEN

La mayoría de los médicos están familiarizados con los síntomas clínicos de la meningitis así como con los hallazgos complementarios que pueden sugerir la identidad de la bacteria infectante. El examen completo y cuidadoso del líquido céfalorraquídeo es el elemento más importante para un buen diagnóstico.

Entre los dosages realizados en el L.C.R. solamente el descenso del nivel de azúcar sugiere la existencia de una meningitis bacteriana o fungosa. Puede inferirse que este descenso se debe a una alteración en la actividad de las células meníngeas así como a la glicólisis de leucocitos y bacterias.

La demostración de la existencia de microorganismos en el líquido céfalo-raquídeo constituye una condición necesaria para el diagnóstico en vida de meningitis infecciosas.

La presencia de más de 3000 leucocitos por $mm^3$ de líquido céfalorraquídeo conteniendo granulocitos en abundancia, casi siempre implica una infección bacteriana; en la meningitis virósica puede encontrarse entre 1000 y 2000 leucocitos por $mm^3$, observándose también un amplio predominio de granulocitos.

En los casos en que no hay ingestión previa de alcohol, su presencia en el LCR evidencia la posibilidad de una infección fungosa de las meninges, puesto que la enzima alcohol dehidrogenasa contenida en los hongos actúa como catalizador en la transformación del azúcar en alcohol.

Los autores analizan el tratamiento que corresponde a los siguientes tipos de meningitis: meningocóccica, neumocóccica, H. influenza y tuberculosa.

Se señala la eficacia de una nueva droga en el tratamiento de las meningitis meningocóccica, neumocóccica o H. influenza. Se trata de una penicilina artificial, la ampicilina; de confirmarse los resultados obtenidos, y siempre que las bacterias no desarrollen resistencia frente a ella, el tratamiento de las meningitis se vería muy simplificado. Por último, los autores analizan el tratamiento de las meningitis producidas por otras bacterias, las meningitis bacterianas parcialmente tratadas y el tratamiento en ausencia de cultivos positivos. En los casos de meningitis tuberculosa puede emplearse un tratamiento a base de corticosteroides como complemento. Debe prescindirse de su uso en los casos de meningitis neumocóccica o meningocóccica, ya que lejos de resultar beneficioso puede acarrear graves daños.

Para concluir, los autores analizan tres

tipos de complicaciones posibles y la forma en que deben ser combatidas: efusiones subdurales, edemas cerebrales y convulsiones.

## RÉSUMÉ

Les symptômes cliniques des méningites ainsi que les indices quant à la nature des bactéries infectieuses qui l'accompagnent, sont familiers pour la plupart des médecins. L'élément le plus important pour obtenir un bon diagnostique est une examination soigneuse et complète du liquide céphalorachidien.

Les mésurages biochimiques couramment effectués dans le LCR prouvent que la simple diminution de la proportion de sucre suggère l'existence d'une méningite bactérienne ou fongueuse, cette diminution pourrant être attribuée à une altération de l'activité des cellules méningées ainsi qu'à la glycolyse de leucocytes et bactéries.

L'évidence de microorganismes dans le liquide céphalorachidien est une condition nécessaire pour le diagnostique en vie des méningites infectieuses.

La présence de plus de 3000 leucocytes par $mm^3$ de liquide céphalorachidien contenant des granulocytes en abondance implique presque toujours une inféction bactérienne; 1000 à 2000 leucocytes par $mm^3$. peuvent se trouver dans les meningites à virus.

La présence d'alcool dans le liquide céphalorachidien sans ingestion préalable du même, fait penser à la possibilité d'une infection fongueuse des méninges, étant donné que l'enzyme alcool déhydrogénase des fungus agit comme catalysateur dans la transformation du sucre en alcool.

Les auteurs analysent le traitement indiqué pour les espèces de méningites qui suivent: méningococcique, pneumococcique, H. influenza et tuberculeuse.

On souligne l'efficacité d'une nouvelle drogue dans le traitement des méningites méningococcique, pneumococcique ou H. influenza. Il s'agit d'une penicilline artificielle; si les résultats obtenus sont confirmés et pourvu que les bactéries ne lui résistent pas, le traitement des méningites sera bien plus simplifié. A la fin les auteurs analysent le traitement des méningites produites par d'autres bactéries, les méningites bactériennes partiellement traitées et le traitement en absence de cultures positives. Dans les cas de méningites tuberculeuses on peut employer un traitement basé sur des corticosteroïdes comme complément. On doit éviter l'application de ce traitement aux méningites pneumococciques ou méningococciques, puisque loin d'être bénéficieux, il entraine des conséquences graves.

Pour conclure les auteurs analysent trois genres de complications possibles et la façon de les combattre: effusions sousdurales, oedèmes cérébraux et convulsions.

## ZUSAMMENFASSUNG

Die klinischen Zeichen der Meningitis sind den meisten Klinikern bekannt, ebenso wie de Begleitbefunde, die etwas ueber die Identitaet der infizierenden Bakterien aussagen koennen. Die wichtigste diagnostische Hilfe ist die sorgfaeltige und vollstaendige Untersuchung der Spinalfluessigkeit. Unter den gewoehnlichen biochemischen Untersuchungen der Spinalfluessigkeit ist es nur das Sinken des Zuckerspiegels, welches das Vorhandensein einer bakteriellen oder durch Fungi verursachte Meningitis nahelegt. Der Nachweis von Mikroorganismen in der Spinalfluessigkeit ist die notwendige Bedingung fuer die Diagnose einer infektioesen Meningitis. Mehr als 2000 bis 3000 Leukozyten pro $mm^3$ Spinalfluessigkeit, besonders Granulozyten, weisen fast immer auf eine bakterielle Infektion hin; 1000 bis 2000 Leu-

kozyten mit Vorherrschen der Granulozyten, werden bei der Virusmeningitis beobachtet.

Wenn kein Alkohol konsumiert worden ist, bedeutet die Anwesenheit von Alkohol in der Spinalfluessigkeit, dass es sich wahrscheinlich um eine Fungusinfektion der Meningen handelt; denn man weiss dass die Fungi das Enzym Alkohol-Dehidrogenase enthalten, welches die Umwandlung von Zucker in Alkohol katalysiert.

In dieser Arbeit wird die Behandlung der folgenden Meningitisarten beschrieben: M. meingoccica, pneumococcica, H. Influenzae, M., tuberkuloese M.. Es wird besonders auf die Wirksamkeit eines neuen Mittels fuer die Behandlung der Meningokokken, Pneumokokken oder H. influenzae Meningitis hingewiesen, Es handelt sich um ein halbsynthetisches Penicillin. Wenn die Resultate sich bestaetigen und noch weitere hinzukommen, und wenn sich keine Bakterienresistenz gegen Ampicillin entwickelt, wird die Meningitis behandlung sehr vereinfacht werden. Am Schluss beschreiben die Autoren die Behandlung der durch andere Bakterien verursachten M., besonders der schon behandelten bakteriellen M. und der Behandlung in Abwesenheit positiver Kulturen.

Die Behandlung mit Kortikosteroiden kann als beigeordnete Therapie bei der tuberkulosen Meningitis angewandt werden. Ihre Anwendung bei der Pneumokokken oder H. Influenzae M. hat keine Vorteile, und kann im Gegenteil ernsten Schaden verursachen.

Schliesslich beschreiben die Autoren drei Klassen von Komplikationen der Meningitis: subdurale Effusionen, Hirnoedem und Krampfzustaende, sowie die Art, sie zu bekaempfen.

## BIBLIOGRAPHY


(1) *Groover, R. B., Sutherland, J. M., and Landing, B. H.*: Purulent meningitis of newborn infants. - New Eng. J. Med., 264: 1115, 1961.

(2) *Quaade, F. and Kristensen, K. P.*: Purulent meningitis: A review of 658 cases. Acta Medica Scandinavica, 171: 543, 1962.

(3) *Carpenter, R. R., and Petersdorf, R. G.*: The clinical spectrum of bacterial meningitis. - Am. J. Med., 33: 262, 1962.

(4) *Fremont-Smith, F. and Dailey, M. E.*: Cerebrospinal fluid sugar. - Arch. Neurol. and Psych., 14: 390, 1925.

(5) *Otila, E.*: Studies on the cerebrospinal fluid in premature infants. - Acta Ped., 35: suppl. 8, 1948.

(6) *Goodwin, G. M. and Shelly, H. J.*: The sugar content of the cerebrospinal fluid and its relation to the blood sugar. - Arch. Int. Med., 35: 242, 1925.

(7) *Weichsel, M. and Herzger, G.*: Significance of the diminution of the spinal fluid sugar in tuberculous meningitis. J. Ped., 9: 763, 1936.

(8) *Levinsky, W. J.*: Hypoglycorrachia (low cerebrospinal-fluid sugar), in diffuse meningeal neoplasm. - New Eng. J. Med., 268: 198, 1963.

(9) *Harter, D. H. and Petersdorf, R. G.*: A consideration of the pathogenesis of bacterial meningitis: Review of experimental and clinical studies. - Yale J. Biol. and Med., 32: 280, 1960.

(10) *Middlebrook, G. and Dubos, R. J.*: Bacterial and Mycotic Infections of Man, 3d ed. edited by R. J. Dubos, page 277, pub. by J. B. Lippincott Co., Philadelphia, 1958.

(11) *Petersdorf, R. B., Garcia, M., and Swarner, D. R.*: The mechanism of hypoglycorrhachia in experimental pneumococcal meningitis. - Proc. Soc. Exp. Biol. (N. Y.), 102: 669, 1959.

(12) *Lincoln, E. M., Sordillo, S. V. R., and Davies, P. A.*: Tuberculous meningitis in children: A review of 167 untreated and 74 treated patients with special reference to early diagnosis. - J. Ped., 57: 807, 1960.

(13) *Hubbard, R. S. and Zoll, J.*: Entrance of intravenously injected sucrose into the cerebrospinal fluid. - Proc. Soc. Exp. Biol and Med., 70: 394, 1949.

(14) *Bernstein, A. O. and Gregersen, M. I.*: The diffusion of glucose and sucrose from the cerebrospinal fluid. - Amer. J. Physiol., 123: 747, 1938.

(15) *Crane, R. K. and Krane, M.*: On the mechanism of the intestinal absorption of sugars. - Biochem. Biophys. Acta 20: 568, 1956.

(16) *Wright, N. L.*: Observations on the diagnosis of tuberculous meningitis. - J. Lab. and Clin. Med., 52: 48, 1958.

(17) *Weinstein, L. and Meade, R. H.*: The treatment of tuberculous meningitis. - Med. Clinics of N. A. 39: 1331, 1955.

(18) *Jamieson, W. M., Kerr, M. and Sommerville, R. G.*: Echo type-9 meningitis in East Scotland. - Lancet, Mar., 15, 1958.

(19) *Dawson, D. M. and Taghavy, A.*: A test for spinal-fluid alcohol in torula meningitis. - New. Eng. J. Med., 269: 1424, 1963.

(20) *Goodman, L. S. and Gilman, A.*: The Pharmacological Basis Of Therapeutics. 2nd. ed., page 104, MacMillan Co., 1955, N.Y.

(21) *Winter, S. J.*: Treatment of meningococcic meningitis in children with a single intravenous dose of sodium sulphadiazine. - J. Ped., 26: 459, 1945.

(22) *Love, B. D. and Finland, M.*: In vitro susceptibility of meningococci to eleven antibiotics and sulfadiazine. - Am. J. Med. Sci., 228: 534, 1954.

(23) *Millar, J. W., Siess, E. E., Feldman, H. A., Silverman, C. and Frank, P.*: In vivo and in vitro resistance to sulfadiazine in strains of neisseria meningitidis. - JAMA 186: 139, 1963.

(24) *Lepper, M. H., Dowling, H. F., Wehrle, P. F., Blatt, N. H., Spies, H. W. and Brown, M.*: Meningococcic meningitis: Treatment with large doses of penicillin compared to treatment with gantrisin. - J. Lab. and Clin. Med., 40: 891, 1952.

(25) *Weinstein, L., Goldfield, M. and Adamis, D.*: A study of intrathecal chemotherapy in bacterial meningitis. - Med. Clinics of N.A., 37: 1363, 1953.

(26) *Merselis, J. G., Sellers, T. F., Johnson, J. E. and Hook, E. W.*: Hemophilus influenzae meningitis in adults. - Arch. Int. Med., 110: 837, 1962.

(27) *Jervey, L. P.*: Adult influenzal meningitis. - Arch. Int. Med., 111: 376, 1963.

(28) *Weiss, C. F., Glazko, A. J. and Weston, J. K.*: Chloramphenicol in the newborn infant, a physiological explanation of its toxicity when given in excessive doses. - New Eng. J. Med., 262: 787, 1960.

(29) *Meade, R. H. and Weinstein, L.*: The treatment of H. influenzae meningitis. - Boston Med. Quart., 7: 1, 1956.

(30) *Ivler, D., Thrupp, L. D., Leedom, J. M., Wehrle, P. F. and Portnoy, B.*: Ampicillin in the treatment of acute bacterial meningitis, presented at Third Interscience Conference on antimicrobial agents and chemotherapy. - 1963, Washington, D.C.

(31) *Robson, J. M. and Sullivan, F. M.*: Antituberculosis drugs. - Phar. Rev., 15: 169, 1963.

(32) *Lepper, M. H., Blatt, N. H., Wehrle, P. F. and Spies, H. W.*: Treatment of bacterial meningitis of unusual etiology and purulent meningitis of unknown origin. - Am. J. Dis. Child., 85: 295, 1953.

(33) *Seabury, H. J. and Dascomb, H. G.*: Experience with amphotericin B. - Ann. N. Y. Acad. Sc., 89: 202, 1960.

(34) *Newcomer, V. D., Sternberg, T. H., Wright, E. T., Reisner, R. M., McNall, E. G. and Sorenson, L. J.*: Second conference on medical mycology. The treatment of systemic fungus infections with amphotericin B. Ann. N. Y. Acad. Med., 89: 221, 1960.

(35) *Acheson, R. M. and Smith, H. V.*: Radiological techniques in the management of tuberculous meningitis. - Quart. J. Med., 27: 83, 1958.

(36) *Lepper, M. H.*: Prophylaxis in patients receiving adrenal steroid therapy. - J. Chronic Dis., 15: 691, 1962.

(37) *Voljavec, B. F. and Corpe, R. F.*: The influence of corticosteroid hormones in the treatment of tuberculous meningitis in negroes. - Am. Rev. Resp. Dis., 81: 539, 1960.

(38) *Ribble, J. C. and Braude, A. I.*: ACTH and adrenal steroids in the treatment of pneumococcal meningitis in adults. - Am. J. Med., 24: 68, 1958.

(39) *Lepper, M. H. and Spies, H. W.*: Treatment of pneumococcic meningitis. - Arch. Int. Med., 105: 253, 1959.

(40) *Wasz-Hockert, O.*: Steroid therapy in acute, life-threatening infections. - Acta. Ped., 140: 79, 1963.

(41) *Lepper, M. H. and Spies, H. J.*: The use of intravenous hydrocortisone as supplemental treatment in acute bacterial meningitis: An alternate case study. - Antibiotics Annual, 1957-1958, pg. 336, pub. by Medical Encyclopedia Inc. N. Y.

(42) *Margaretten, W. and McAdams, A. J.*: An appraisal of fulminant meningococcemia with reference to the Shwartzman phenomenon. - Am. J. Med., 25: 868, 1958.

(43) *Nyhan, W. L. and Richardson, M. B.*: Complications of meningitis. - Ann. Rev. Med., 14: 243, 1963.

(44) *Uhl, H. S. M.*: Nor-epinephrine in the treatment of acute meningococcemia with shock (Waterhouse-Friedrichsen syndrome) and an evaluation of adrenocortical function. - New Eng. J. Med., 249: 229, 1953.

(45) Discussion in Year Book of Pediatrics, 1955-56, pages 78-80, ed. by S. S. Gellis, Year Book Publishers, Chicago.

(46) *Langfilt, T. W.*: Possible mechanisms of action of hypertonic urea in reducing intracranial pressure. - Neur., 2: 196, 1961.

(47) *Galicich, J. H. and French, L.*: Use of dexamethasone in the treatment of cerebral edema resulting from brain tumor and brain surgery. - Am. Pract. and Dig. Treat., 12: 169, 1961.

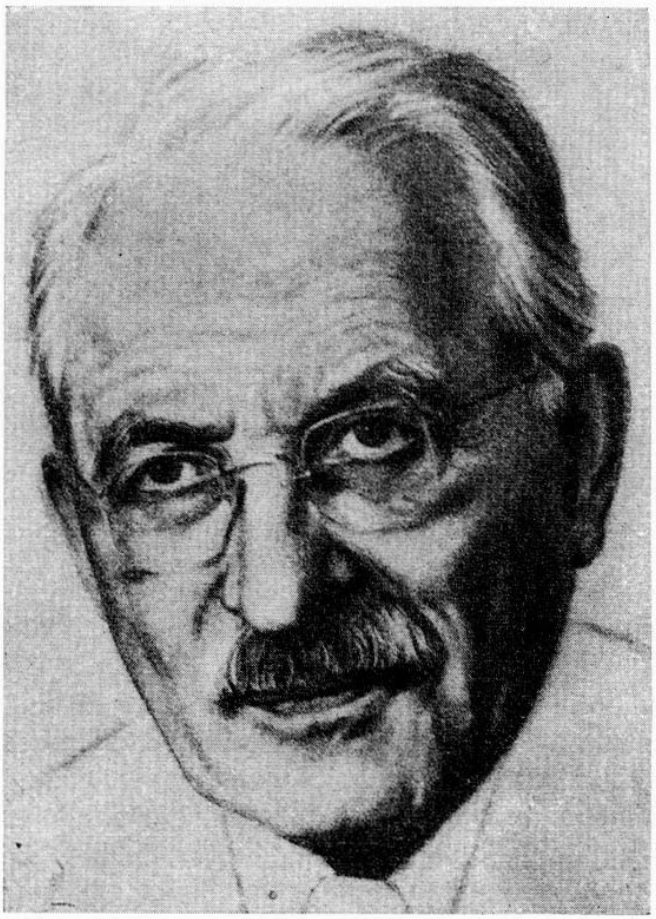
# Personality

## Prof. SELMAN A. WAKSMAN

August 10, 1963.

It was pouring rain that cold afternoon when we arrived at the private hospital where Dr. Waksman was convalescing.

A few days before we had welcomed him at the airport of Montevideo. He was on a scientific tour giving lectures in the east coast of South America, and for a week he was the center of attraction in the scientific circles. Lectures, banquets, receptions were given in his honor. He was ready to leave Montevideo to go to Buenos Aires where he had a heavy schedule of social and scientific events. Among them was the honor of closing a TB hospital. Dr. Waksman suddenly became ill and had to undergo an appendicitis operation in Montevideo.



The room was in half darkness. Dr. Waksman's silhouette was outlined against the wide window. From the cloudy sky a gray fog covered the city like a curtain, giving the panorama the artistic beauty of a "sfumato" painting. At the sound of our steps, Dr. Waksman turned slowly. A soft smile brightened his noble features. He welcomed us, and pointing to the chairs near the bed, said to us "Come nearer."

The atmosphere was propitious to reminiscent talking. Like a thread the sound of his voice began to evolve remembrances of old days, in Priluka, Russia. From them emerged the strong figure of his grandmother. "A woman of valor" to which the Bible refers to; decided, clever, though unschooled. She was the widow of a tanner of hides (his other grandfather was a manufacturer of copper ware). They belonged to a middle class that was to be placed

in between the rich landowner and the poor "mujick" who labored in the fields. They were the artizans.

They lived in a small adobe house. How his grandmother managed to raise a family of eight girls, run the business (upon the death of her husband, she moved to town and became a merchant), without even knowing how to make simple mathematical operations, clearly speaks of her ingeniousness, endurance, and will to succeed. It was not an unfamiliar sight to see her on the roads coming or going to different towns selling or taking orders for manufactured goods which she purchased in the large city. But even though she overcame the difficulties of her lack of education, she was aware of it and wanted her family to go to school and be better equipped to face life. Difficult times lay ahead of her. Competition was rapidly growing while she became handicapped by old age. So she retired from business. The youngest daughter Fradia (Dr. Waksman's mother), loved to study and used to read the Bible for the neighbors who couldn't do it themselves, and she also read them the sacred writings on the Holidays. When she married, her husband joined her in the business. But while Selman was growing, his mother wanted him to be a man of learning, which also suited the young man's reflexive nature.

The room was growing darker. Dr. Waksman spoke slowly and with certain fatigue as a person who was just recovering from an operation. We had to stretch our necks to follow him. "On those days", he went on: "How I loved and profited from the study. With a group of boys our own age, we founded a school to teach other children who were illiterate. This was performed as a labor of love, without seeking any kind of remuneration, but to give others, the poor ones, knowledge, which we thought we were lucky to have".

When the time arrived to enter the Gymnasium, he found it difficult to do so in Czarist Russia. The time was passing; he sent his papers to the Polytechnicum in Zurich and was accepted. But at the same time he received letters from his relatives in America who urged him to come there. Dr. Waksman recalled that he considered both opportunities and decided to try America and making a significant gesture, he said, "So, I shook the dust off my shoes and sailed to the United States".

## HIS STUDENT DAYS IN AMERICA

Young Waksman had a secret wish; he wanted to unveil the "mystery of life". Thus, in 1910, a new immigrant arrived in America with empty pockets and a mind full of golden illusions.

He settled down on a farm in New Jersey where his relatives lived. Then he proceeded to send his application for admission to Columbia University. While he was waiting for an answer, his cousin informed him that there was an Agricultural University nearby, whose Dean, Dr. Lipman, was also a Russian immigrant. Following their advice he decided to visit him. Dr. Lipman welcomed him, and, in the midst of their conversation, he suggested to him that the study of "life processes" for which he was so eager could be done at this University as well as in any other place. This assurance pleased him and shortly afterwards he entered Rutgers College, later the New Jersey State University, having obtained a scholarship.

The scholarship and 20 cents an hour, which he earned working in a botanical laboratory, were all the resources he had to keep up his studies and maintain himself.

Professor Byron Halsted, the Professor of Botany whose picture can be seen in Dr. Waksman's office, went to the University on Saturday afternoons and had long conversations with the newcomer. The subjects were various: sometimes they were about the differences in the organization of research work in Europe and the United States; at other times about the relationship between professor and student; or about the possibilities offered by small universities in relation to large ones. At the end of these dialogues, Dr. Halsted said emphatically: "If you don't report all this time as working time I'll never speak to you again". How well old Professor knew that the seventy cents earned in an afternoon represented to Waksman the next day's meals.

...''LE ROLE DES INFINIMENTS PETITS M'APPARAISSAIT INFINIMENT GRAND..." — Pasteur

The long story that followed this was one of faith, sacrifice, and unending effort.

As Dr. Lipman suggested, he didn't need to go any further to fulfil his wishes. Who doesn't remember the fable, retold many times, of the Indian farmer who, upon hearing about a wonderful land where it was possible to find acres of diamonds, sold his farm and made the long journey only to die alone in desperation; while the fellow who bought his farm found a lot of diamonds right there. Dr. Waksman found something more valuable than diamonds in a little pinch of soil right in the University backyard.

In that little universe his keen eyes discovered the drama of life with its fights for survival, victories, and disasters. In just one gram of soil he detected tens of thousands of fungi, hundreds of thousands of actinomycetes, tens of millions of bacteria. To decipher the meaning of their microscopic lives, to discover their secret weapons, brought Dr. Waksman the Nobel Prize, glory, and the good fortune to present to humanity something more appealing than diamonds-the hope of recovery to a large group of desperate sufferers.

His investigations led to the development of an industry worth many millions. It has helped to create in the very university, with which Dr. Waksman is associated, an Institute dedicated to the study of microbes. It has made possible the creation of a Foundation by Dr. Waksman to bring to reality many unfulfilled dreams of his fellow scientists. That all these miracles came from a pinch of soil seems to be a fairy tale, unless we remember that a spark of genius and long unending effort created the wonder.

Dr. Waksman affirms that there probably exists, a far greater number of all kinds of forms of life in the earth than upon it. Under the pavements of the streets, in mountains and valleys, exist millions and millions of microscopic organisms that carry on a silent and, for us, an unnoticed existence.

Nevertheless, they were the first inhabitants of the world. Maybe they hold the treasured secret of the vital spark starting from inorganic matter. Two thousand millions of years before man's arrival they shared the life of this planet. They were the unquenching laborers helping na-

ture to keep this world ship-shape. They destroyed dead matter in order that from them life might flourish again. It seems that they participate in the symbolic dance of Shiva, Hindu deity, whose meaning is the eternal destruction and restoration.

But Waksman saw further and deeper, more than the alchemist did, that those humble forms of life performed in the process of transformation of the earth's surface. He pondered the disturbing question. How do these organisms live together in the earth? Is it possible that a struggle like the one discovered by Darwin existed in this minute society? What effect has one upon the other? Many of these microorganisms called actinomycetes fluctuate between the higher forms of bacteria and the lower form of fungi. They, said Waksman, are so numerous that they are almost begging to be studied.

Observing them from backstage, playing the drama of existence, he realized that they enacted the repetitious libreto of Nature in their attempt of adaptation, agression, and defense. His attention was attracted by the tremendous destructive power that one group of actors, the actinomycetes, exerted upon others, the bacteria. In some mysterious way, every living system performing its life at different levels is serving some end that contributes its control to Mother Nature.

Every man, Renan affirms, is like the tapestry weaver who, working from the back can't see the design. We work, he said, for a God, like the bees that make honey for the use of man. How is this true for such a humble existence like the soil microbes? These creatures, devoid of chlorophyll and incapable of assimilating the solar energy, must depend for their nutrition on vegetable and animal waste that finds its way into the earth. Once Bergson, examining the eternal flow of nature, asked himself: What is there behind this stampede of animals and living things perpetuated through time? The plants grow ceaselessly, men and animals succeed without interruption, the gender exists but the individual, plant or animal, is increasingly renovated in the world.

Very rarely do we find vestiges of those animals, plants, or men that have preceded us thousands of years ago. If we imagine how it would be to find the earth full of traces of antidiluvian animals, intermixed with the waste of other living creatures, besides all the waste of the vegetation that could have accumulated, we would be sunk in a swamp that would result in a tragic, if not impossible, life. But, how has all this evidence of a long past life disappeared from the surface of the earth? We must turn our grateful eyes to the tiny microbes of the soil who made this miracle possible. Ignorant of their main purpose, they busied themselves preserving their own existence and carrying on terrific battles for survival.

## DOMESTICATION OF MICROORGANISMS FOR DISEASE CONTROL

And now men of science had found another task for them: to preserve and prolong human life. In 1940, Dr. Waksman stated: "There is increasing appreciation of the probability that nature harbors many unknown organisms, and that we still have quite incomplete knowledge of the activities, potentialities, and importance of many well-known microbes. We are at the beginnig of a period of domestication of a new type of organism, which may help in combating the deadly enemies of man".

Without the necessary funds to obtain the appropriate equipment, Professor Waksman carried on his research with the voluntary aid of his students, who helped to perform, control and repeat the experiments, to classify the cultures, and to try to isolate their products, etc. He realized that certain microbes had the ability to generate substances capable of inhibiting or destroying other kinds of microbes. Puzzled, he checked closer on their behavior and discovered the secret weapon. They carried on a kind of chemical warfare and generated substances with the aim of depressing or destroying the enemy. Moreover, they were particularly resistant to adverse conditions. This carried Dr. Waksman to the thought of how to profit by this ability for the benefit of mankind. This led to a lifelong research in the pursuit of knowledge of these almost invisible lives and to determine to what extent man could utilize these substances without risk to his own physical integrity.

Many years have elapsed since this investigator published his first work in 1915 about the actinomycetes and their role in relation to the other inhabitants of the soil. Since then he performed innumerable experiments that shed light on their biochemical activities and their influence in the natural processes in the soil. In 1940, Dr. Waksman isolated the first chemical substance produced by a culture of an actinomycete. He designated it Actinomycin A. However, this powerful chemical weapon could not be used in laboratory animals due to its high toxicity which invalidated it as a possible therapeutic agent. Nevertheless, years later it found application in the treatment of certain tumors. Those who feel dazzled by the final results of this investigation which led to the discovery of streptomycin should know the endless efforts which led to success. The affirmation that genius equals long patience could never be more properly applied than in his case. Ten thousand microbes were studied. Of these, only ten per cent were capable of carrying on bactericidal warfare. Then he concentrated on the study of these thousand microbes, and only ten per cent of them could be grown under conditions where they could be analyzed. From this group of a hundred microbes he extracted the secret weapons from only ten. One of these ten compounds gave rise to the famous antibiotic that was called streptomycin.

How easy it is to compress in a handful of words the innumerable hours of labor expended. How alluring is the success that makes deception and disheartening experiences fade. Not only do conditions conspire against the men of science, as the evasive way which Nature deludes those who seek to disclose her enigma, but also the impatience and incomprehension of those results that are rendered in due time, as if results in science were something to be ready at our command.

However, in 1940, one of the executive at Rutgers University thought that Dr. Waksman's salary should be reduced, saying that he didn't see any future in his endeavor; therefore, for economical reasons the salary of $ 4,620 per year for his investigation should be suppressed.

## NOBEL PRIZE IN PHYSIOLOGY AND MEDICINE

Happily this opinion wasn't shared by the authorities of the University and, three years later, in 1943, streptomycin was discovered. In 1952, a parade of torches celebrated the honor that was bestowed upon the University when one of its members, Professor Waksman, was awarded the Nobel Prize in Physiology and Medicine.

In 1952, Harold Cramer, Member of the Swedish Academy of Sciences made a toast to the Nobel Prize Winner: "You have discovered a new and powerful weapon in the deadly battle against one of the oldest foes of mankind, tuberculosis. This battle is as old as medical science and now we have a definite impression that at last the enemy is beginning to yield. If, as we may hope, your discovery will show the way to decisive victory, the gratitude due to you is of the kind that cannot be expressed in words".

## THE BLACK DEATH

But not only the White Plague was vanquished by this man of science. The Black Death also finished its reign of terror. How soon man forgets those sinister words. The new generation knows them only by name; what were some of the most horrible experiences in the past. Let us hear through Boccacio words of how human life was threatened in those days when this modern therapeutic weapon wasn't even dreamed of to become an aid for people.

"In the year of our Lord 1348, at Florence, the finest city in all Italy, a most terrible plague befell this city, which, whether owing to the influence of the planets, or be it sent from God as a just punishment for our sins..." After relating the apocalyptic vision of death and disaster everywhere, he concluded, "... hundreds of thousands of souls perished in the city only, whereas, before the calamity, it was not supposed to have contained so many inhabitants. What magnificent dwellings, what noble palaces were then depopulated to the last person. What families became extinct. What riches and vast possessions were left and unknown heirs to inherit. What a vast number of both sexes in the prime and vigour of youth, whom in the morning neither Galen, Hippocrates or Asclepious himself, but would have declared in perfect health, after dining heartily with their friends here, have supped with the departed friends in the other world!" This wailing of Boccacio came to us from the past as a testimony of how much humanity owes to a man like Dr. Waksman.

## OUT OF THE EARTH SHALL COME THY SALVATION

While others busied themselves in searching for hidden treasures on the earth he found it in the earth itself. Thus began the fabulous reign of the "mycins". Some 500 preparations are now known to have been obtained from this group of microbes, belonging to the genus *Streptomyces*. Man, animals, and plants have benefited from about 50 compounds selected from them.

Dr. Waksman could have collected millions from his discovery, but he preferred to transfer all his rights to Rutgers University. One of his concerns was to protect himself from the paralyzing effect of fame. He collected caricatures which represented the scientist as he sees himself and how he appears to others. "I don't know what could happen to some scientists when people begin to tell them they are great men. This is a dangerous thing if they don't take it with a sense of humor. I can't see how they could return to work". But Professor Waksman is a scientist at heart. He is always seeking to broaden the scope of knowledge, and this helps to keep the humble attitude of a real man of science. Moreover, there is his faithful wife, Mrs. Deborah Mitnik Waksman, "Bobili"

(little grandmother in Russian) as he affectionately calls her. And if you open one of the books written by Professor Waksman on "Microbial Associations and Antibiotic Substances", it is dedicated "My constant associate and antagonist Bobili". Professor Waksman affirms that this is the way a wife should be. A man must have somebody to tell him that not all he does seems perfect to the rest of the world. A wife has to put one in contact with reality once in awhile.

## STREPTOMYCIN — 1944 - 1964

Last June, a celebration was held at Rutgers University to honor the 20th anniversary of the discovery of streptomycin. Among the persons who contributed to a booklet commemorating this event were the first physician to use this drug in tuberculosis patients, Professor H. Corwin Hinshaw (Professor of Clinical Medicine at the University of California medical Center), who wrote about "Treatment of tuberculosis twenty years after the discovery of streptomycin"; Professor Chester Scott Keefer, (Wade Professor of Medicine Emeritus, Boston University) who was Chairman of the Chemotherapy and other agencies of the National Research Council during the period that streptomycin was tested for clinical investigation, who wrote about "Two decades of therapeutic achievement". Professor Robert Debre (famous pediatrician) of Paris attended the event and delivered a lecture entitled "Tuberculous meningitis cured for the first time". Professor Waksman's lecture for this occasion was headed by the Biblical choice as a symbol for his discovery "Out of the earth shall come thy salvation".

This is the wonderful story of a man who saw in nature a spectacle far more interesting than any fiction, who came closer to the frontier of life and could say with justice like Linneous observing a leaf: "I am speechless with fright; like another Moses, I have seen God from the back".

VICTOR SORIANO.