OTOGENIC MENINGITIS

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Introduction

UNTIL the introduction of sulphanilamide the fight to reduce the overwhelming mortality rate that attended otogenic bacterial meningitis usually ended in defeat. Whilst some hope could be held out to those patients whose cerebrospinal fluid reaction had not progressed beyond the cellular stage, the discovery of live bacteria in the fluid meant, with but rare exceptions, death. No method of treatment was rewarded by many successes, and the principal reason for the occasional recovery probably lay in the exceptional vitality of the patient. Nevertheless, the occasional recoveries were so dramatic and so complete that workers in all parts of the world devoted much time to the solution of this great problem.

Not many years ago one of the most indefatigable workers in the field of meningitis, J. A. Kolmer, said that the key to success would be chemotherapy. His prophecy has come true. Since the introduction of prontosil into clinical practice by Domagk in 1935 I have collected records of 194 recoveries from otogenic bacterial meningitis. The first case to respond to chemotherapy was recorded by Caussé *et al.* (1936), whilst up to the end of June 1939, the largest group reported was that by E. Appelbaum (1939) in which there were twenty-seven recoveries from otogenic streptococcal meningitis and three recoveries from otogenic pneumococcal meningitis.

During the first thirty-four years of the present century Gray (1936) was only able to find in the literature records of twenty-seven recoveries from otogenic streptococcal meningitis.

Thus it would seem that the introduction of the sulphanilamide group of drugs into the management of otogenic meningitis has entirely altered the gloomy prospect that this disease formerly presented. But, of course, chemotherapy cannot produce the best results unaided. A study of the extensive literature on the subject reveals a variety of opinions as to what constitutes meningitis, how the infection reaches

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the meninges, how the meninges react, and how the disease should be treated. There is nothing that I can add to what has already been written but in this article I would like to review the whole disease and to suggest methods of management, based on the pathways of infection, which may be necessary to supplement chemotherapy.

Ætiology

As may be seen in the report of Neal, Jackson and Appelbaum (1932) on 2,674 cases of bacterial meningitis, 67 per cent. occurred under the age of 10 years. This report included all forms of bacterial meningitis, but the age incidence was approximately the same for all types. In the earlier years of life meningitis is more likely to follow an acute aural infection, whilst in later life it is more often seen as a terminal event in a long-standing suppurative otitis media. Fraser and Halliday (1936) noted forty-three cases of meningitis in 2,731 cases of acute suppurative otitis media, an incidence of 1·8 per cent.; whilst in 8,905 cases of suppurative ear disease, both acute and chronic, meningitis was noted in sixty-four cases, an incidence of 0·7 per cent. (statistical tables from the Throat and Ear Department Royal Infirmary, Edinburgh, 1919-26).

When coming to meningitis as a cause of death we find that in a series of 15,000 autopsies at a general hospital there were records of 337 cases of septic meningitis, of which 175 were secondary to ear disease (Courville, 1937). At a special hospital an analysis of the total deaths over an eight-year period, A. A. Eggston (1934) showed that of 363, 124 had meningitis, and of these 124 cases ninety were caused by aural disease. Thus we see that the ear is the commonest source of infection in septic meningitis which is the most frequent cause of death in diseases of the ear, nose and throat.

Pathology

The train of events that is initiated by the extension of infection from the ear to the meninges has been fully dealt with by MacEwen (1893), Turner and Reynolds (1931), Eagleton (1932), Kopetsky (1935), Eggston (1934), Gaston (1935), and others. Their writings deserve careful study because a thorough knowledge of the route taken by the disease and of the effects

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produced should be the principal factor in deciding what method of treatment is to be adopted. That this is not always fully appreciated is apparent from a study of some of the cases reported in the literature, in which the treatment advised has borne little relationship to the state of affairs that it has been expected to remedy.

BACTERIOLOGY.

The bacteriology of otogenic meningitis follows that of otitis media. Neumann (1925) found that in 101 cases of otogenic bacterial meningitis forty-five were streptococcal, twenty-two streptococcus mucosus (pneumococcus III), sixteen pneumococcal, and four staphylococcal. Neal, Jackson and Appelbaum (1934) made the following observations in 623 cases of bacterial meningitis due to organisms other than the tubercle bacillus and the meningococcus :

Organism.	*Number.*	*Ear or nose infection.*	*Per cent.*
Pneumococcal	214	75	35
Streptococcal	205	121	59
B. Influenza	118	20	17
Staphylococcus . .	30	4	13

NOMENCLATURE.

There exists a variety of views on the subject of the classification and nomenclature of the meningeal complications of ear disease. Nobody disputes the title Meningitis when live organisms can be recovered from the cerebrospinal fluid, but for anything less than this, no matter how " meningeal " the clinical picture may be, it is held by many that the term Meningitis should not be applied. Instead such variations as Meningism, Meningeal Reaction, Sympathetic Meningitis, and Méningite de Voisinage have been used. Surely it would be in keeping with the pathological findings to use the word Meningitis for all cases showing clinical signs of meningitis and in which there are inflammatory changes in the cerebrospinal fluid. The terms Localized and Diffuse meningitis have been used extensively, and the criterion for a diffuse meningitis has again been the presence of organisms in the cerebrospinal fluid. It is true that many otitic cases begin as a localized infection of that part of the dura that is in direct contact with diseased bone. If this is not dealt with surgically the disease may become as diffuse as the fulminating cases that rush

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through the temporal bone before it has time to react to the disease.

Again, the term Primary meningitis is sometimes used to indicate meningitis without other intracranial complications, whilst Secondary meningitis is used when some other intracranial complication such as a brain abscess or lateral sinus thrombosis is present.

I think that it would be simpler to call all these cases Meningitis, but to use a qualifying adjective such as Serous, Cellular, or Bacterial, depending upon the findings in the cerebrospinal fluid. This would go far to clarify the subject, and would possibly help to stress the importance of the ear as an ætiological feature in meningitis.

Only too often has one been asked to see in its terminal stage a meningitis that has been under observation and treatment for some time as meningococcal meningitis, on the grounds that the absence of organisms pointed to a meningococcal infection. In the absence of any possible primary focus this may be the case, but it sometimes happens that the search for a primary focus is inadequate.

Method of Spread.

The temporal bone contains spaces for those organs of special sense that it houses, together with their nervous connections. It also is canalized by, or comes into direct contact with, numerous blood-vessels. An infection of the middle-ear cleft can spread through the temporal bone to reach the meninges by one of three routes: by the spaces already present naturally or formed by injury, long-standing disease or previous operation; along vascular channels; or by actual destruction of intervening bone.

These methods of spread have been well described by Tylor (1912) in a monograph based on the post-mortem observations in cases that had died of otitic meningitis, and by Turner and Reynolds (1931) in their detailed study of *Intracranial Pyogenic Diseases*, although their work was concerned more with the spread of infection from the nose than from the ears.

In order to examine these methods of spread in more detail, it will simplify matters to divide the petro-mastoid part of the temporal bone into three zones—an outer or tympano-mastoid, an intermediate or labyrinthine, and an inner or apical.

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The Tympano-mastoid zone contains the middle-ear cleft and the mastoid air-cells, and extends from the surface to the level of the labyrinth. The size and distribution of the cells varies enormously, and Cheatle (1907) has described the variations that may occur.

Even in acellular bones there will be found some small air-spaces in relationship with the antrum and the semi-circular canals.

The middle-ear cleft and associated cells are lined with mucous membrane which is continuous with that of the upper respiratory tract. It is this mucous membrane that is first attacked in acute otitis media, and if it is unable to check the onslaught of a virulent infection, extension may occur through the only natural preformed space in the tympano-mastoid zone, namely the petro-squamosal suture. Normally this suture closes in the second year but Cheatle (1907) noted that it remained patent throughout life in some of the temporal bones that he examined. It is difficult to say how often this route is responsible for the spread of infection, but it may account for some of those cases that pursue a very rapid course.

In a severe infection many of the small veins in the mucous membrane of the middle ear next become thrombosed. This is in the nature of a protective mechanism, but in some unfortunate cases the thrombophlebitic process may, failing as a barrier, actually guide the infection to the meninges. Such a process may develop quickly, and this mode of spread can account for those cases of meningitis that follow within the first few days of an otitic infection.

Ballance (1919) has pointed out in one of his essays on the *Surgery of the Temporal Bone* that the mucous membrane lining the mastoid air-cells acts as an internal periosteum. Infection of the mucous membrane will interfere with the nourishment of the underlying bone and favour necrosis, and this, combined with the action of the products of suppuration, may lead to extensive destruction of bone. Such destruction takes time and is not likely to be seen within the first week of an otitic infection. If an acute mastoid infection is left untreated, the disease may spread by destroying the bony barrier between the middle-ear cleft and the meninges. The shortest route would be upwards through the tegmen tympani to the middle fossa, and curiously enough this short route is more frequently taken in the cases of long-standing chronic

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suppurative otitis media than in the acute cases. Another and probably commoner route is backwards and inwards to the neighbourhood of the lateral sinus or the dura lying between it and the middle fossa, and a third is inwards in the direction of the apical zone cells. This last route is more particularly seen after a mastoid operation, and is probably a much commoner cause of meningitis than is generally realized.

The Labyrinthine zone. This is a block of dense ivory bone, canalized by labyrinthine and other channels, that acts as a barrier and hinders (but does not always prevent) the spread of infection from the outer to the inner zone. The labyrinthine fluids are in direct communication with the sub-arachnoid space, of which they may be said to be a backwater. Any infection that reaches these fluids can therefore easily be transmitted to the sub-arachnoid space. A very virulent infection may spread from the middle ear through one of the labyrinthine windows without hindrance. This is probably the commonest route taken in the fulminating cases of meningitis that follow within a few hours of the onset of an aural infection.

It would not be so easy for infection to spread through the labyrinthine zone by the venous route, but the veins draining the labyrinth certainly connect with meningeal veins through the internal auditory meatus, the fossa sub-arcuata, and the slit that transmits the ductus endolymphaticus. (Siebenmann, 1894.)

The erosion of any part of the labyrinthine capsule does occur, but, because of the density of the bone, it takes time. It is most commonly seen in cases of long-standing chronic suppurative otitis media and the prominence of the external canal is a favourite site for a fistula. The fistula may be present for some time and give rise to but few symptoms, until an acute infection supervenes and finds a preformed path to the labyrinth.

The Apical zone, like the tympano-mastoid zone, shows a variable cellularity, but probably not more than 25 per cent. of temporal bones have air-spaces communicating with those of the tympano-mastoid zone. It is only within the last few years that the significance of the petrous apex as a seat of infection has really been appreciated, and the original observations of Gradenigo (1904) have been amplified by those of Kopetsky and Almour (1930), Eagleton (1931), Ramadier (1933)

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and others. Infection of this zone takes place by the osseous route, and the number of pathways is strictly limited by the dense labyrinthine block. Broadly speaking, infection may track behind the labyrinth either above or below the external canal, in front of the labyrinth, that is, in front or through the superior canal, or above or in front of the cochlea. Petrositis does not develop quickly and in fact is usually seen some weeks after a simple mastoid operation. It is likely that the attention that is being paid to this complication will reveal it as one of the commoner causes of delayed meningitis that follows some time after an apparently successful mastoid operation.

To put it briefly : acute suppurative otitis media may cause meningitis within hours by spread through certain preformed spaces, within days by spread through veins, and within weeks by direct destruction of intervening bone.

The danger from chronic suppurative otitis media lies in the fact that gradual erosion of bone may have enlarged or have increased the number of preformed pathways, so that the patient is at the mercy of any acute flare-up. Therefore meningitis following chronic suppurative otitis media is likely to arise with so little warning that there is always the possibility of the smouldering ear being overlooked. Any injury such as a basal skull fracture running across the middle-ear cleft may invite extension by this route, either because of pre-existing otitis media or because injudicious management has allowed infection to creep in from outside.

The Cerebrospinal Fluid.

The cerebrospinal fluid may be looked upon as a mirror of meningeal behaviour, and as such it offers more information than anything else about the state of these membranes both in health and in disease. Meningitis produces both physical and chemical changes in this fluid, and it has been the custom to depend upon an examination of the cerebrospinal fluid before making a diagnosis of meningitis.

With but few exceptions otogenic meningitis will provoke the following sequence of reactions in the cerebrospinal fluid, and these reactions, serous, cellular and bacterial, correspond more or less to the clinical stages of the disease.

Serous stage.—The initial reaction of the cerebrospinal system to infection is an outpouring of fluid. This causes an

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increase in pressure above the normal 100-150 mm. of water. In this stage there may be no demonstrable change in the mineral constitution of the fluid, and neither increase in cells nor the presence of organisms may be noted. Kopetsky (1932) has pointed out that increased pressure may result in deficient oxygenation which causes an increase in the lactic acid content of the fluid. The lactic acid combines with the available carbonates, causing a reduction of the CO_2 content and a lowering of the pH. Kopetsky feels that these changes must interfere with the normal metabolism of the central nervous system and thus make it less able to resist infection.

This stage corresponds to the earliest clinical stage of meningeal irritation, the so-called Meningismus of some writers.

Cellular stage.—The next event in the development of an otogenic meningitis is as a rule an increase in the cellular content of the fluid above the normal five lymphocytes per cubic millimetre. The cells are almost always polymorphonuclears and they may be as numerous as 10,000 per c.mm. A fluid containing 1,000 cells per c.mm. will appear somewhat cloudy, whilst one with two or three thousand cells, a usual count in otogenic meningitis, will be turbid, giving a so-called " stone ginger-beer " appearance. When some of the cells are lymphocytes, the process of infection has usually been gradual, by the osseous route, and it may be looked upon as a favourable prognostic sign. Co-existent with the increase in cells there is an increase in the protein content of the fluid, due to interference with the hæmato-cephalic barrier that in health does not allow the passage of protein into the cerebrospinal fluid.

There is often a reduction in the chloride content of the cerebrospinal fluid. This runs parallel to the reduction of the chloride content of the blood and is in inverse proportion to the protein content of the cerebrospinal fluid. The sugar content should not be reduced unless bacteria or broken-down leucocytes are present, in which case they may have absorbed or altered the available sugar.

Bacterial stage.—The demonstration of bacteria in the cerebrospinal fluid of a suspected case of meningitis establishes an exact diagnosis. It indicates an advanced stage of the disease, especially if the bacteria can be cultured as well as seen on a direct smear. In occasional cases in which the resistance to the infection is said to be very low, large numbers of bacteria

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may be found in a fluid that contains but few, if any, cells. Such a case was under my care recently when no cells could be seen at all, but the fluid was faintly yellow and opalescent, due to the presence of masses of pneumococci.

In the bacterial stage the proteins remain high and the chlorides low, whilst the sugar will have disappeared. The sugar content has been taken as an indication of the severity of the disease, and its return after absence is looked upon as a favourable prognostic sign.

In order to obtain accurate results, the cerebrospinal fluid should be examined as soon as possible after it has been drawn off. Any undue delay may modify the findings, especially as regards the cellular content (J. G. Greenfield, 1926). Generally speaking, the pressure, cellular content and bacteriological examination are the findings that afford the greatest help, and these correspond to the serous, cellular and bacterial stages.

Clinical Features

The course of otogenic meningitis, and for that matter other forms of meningitis, can be divided into three clinical stages—the stage of onset, the stage of the established disease, and finally the stage of paralysis. In fulminating cases the sequence of events may be so rapid that it is not possible to distinguish the separate stages, but when the disease pursues a gentler course it is more easy to recognize them. The speed with which these stages follow one another depends partly upon the route taken by the infection and partly upon the condition of the infecting source in the middle-ear cleft. If the disease occurs within the first few days, or even hours, of an acute otitis media, it is likely to be of a fulminating type and the infection will have spread to the meninges by the vascular route or by preformed spaces. If, on the other hand, it follows upon a suppurative otitis media of long standing, it will have spread by the osseous route or by spaces preformed by long-standing disease. It may still be fulminating, especially if it is preceded by an acute upper respiratory infection, but this is less common than in the very acute cases. If the meningeal infection appears after the first week of an acute suppurative otitis media, it usually takes a less rapid course and the spread is almost certain to be by the osseous route or possibly by thrombophlebitis of one of the larger veins in contact with the temporal bone.

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The importance of recognizing these different clinical types will be evident when the question of treatment is considered.

Stage of onset.—Headache is the earliest and most constant symptom of meningeal invasion. Localized pain, often worse at night, is seen when there is infected bone in contact with the dura causing a localized patch of inflammation or collection of pus. A general invasion of the meninges causes a very severe headache that is not localized to any particular part.

Vomiting is a common symptom in the early stage of the disease. It varies in frequency, being possibly more noticeable in children, and like vomiting in other affections of the central nervous system it is not preceded by nausea and is unrelated to meals.

Photophobia is often not severe at the onset. A certain dislike of strong light is a fairly early symptom but it is not so marked or constant as in the later stages.

Fever. A rise of temperature is usual at the onset and it may be heralded by a rigor or convulsion. The temperature continues to rise and shows but little diurnal variation, except when there is a localized extradural collection of pus.

Mentality. There is an increase in mental activity that in the very earliest stages, especially in adults, may show itself as an unnatural brightness. This is accompanied by restlessness and in some cases is followed by a feeling of apprehension and general distress. In children it shows itself in the shape of fretfulness. This increased mental activity is not present all the time but occurs in bouts that are interspaced with drowsy periods. As the disease progresses the drowsiness becomes more apparent.

Reflexes are for a short time increased.

Neck. Stiffness of the neck and a dislike for flexion is the earliest and most valuable sign of meningitis (Layton, 1937). I remember one patient in whom the first warning of an approaching meningitis following a mastoid operation was the complaint that a draught from an open window behind the bed had caused neck stiffness.

Stage of the established disease.—As the disease progresses the symptoms and signs become more marked so that the true state of affairs is only too obvious. The headache becomes almost unbearable and photophobia may be so severe as to require a darkened room. Although the patient is mentally active, there are periods of noisy delirium; he dislikes being disturbed

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and may be very intolerant of any examination. The neck stiffness increases to rigidity and in children there may even at this stage be a tendency towards neck retraction. The reflexes will be less active and the superficial abdominal reflexes may be absent. The temperature will continue high and it may tend to rise. Kernig's and Brudzinski's signs are usually positive and are mainly of value as confirmatory tests.

Stage of Paralysis.—At the onset of this stage there is still a noisy and active delirium that alternates with periods of sleep. As the disease progresses the periods of sleep become longer, until eventually the patient passes into coma that precedes death. Tendon reflexes gradually disappear and cranial nerve palsies are seen, especially of those nerves supplying the eye muscles. Neck rigidity is extreme, and in children there may be marked head retraction and opisthotonos. Incontinence, especially in adults, is a late and serious sign indicating an advanced stage of the disease. Thus the terminal paralytic stage is characterized by delirium, gradually passing into coma, cranial nerve palsies, absent reflexes and incontinence. These signs are the result of increasing intracranial pressure, combined with the toxic effects of the disease on the central nervous system.

Diagnosis

A diagnosis of meningitis can only be established with certainty by an examination of the cerebrospinal fluid. Therefore if any of the symptoms or signs mentioned appear during the course of an otitis media, lumbar puncture should be performed without delay. It has been suggested that removal of cerebrospinal fluid by lumbar puncture may favour the dissemination of the disease by aspirating infection from the primary focus into the sub-arachnoid system. By the time that lumbar puncture is considered necessary, the disease has usually involved the sub-arachnoid system, and any possibility of further dissemination is of less consequence than the information to be obtained from the examination of a few cubic centimetres of cerebrospinal fluid that have been cautiously withdrawn from the lumbar region.

The three phases of the cerebrospinal reaction, serous, cellular and bacterial, correspond nearly to, although they are somewhat in advance of, the clinical stages of onset, established disease and paralysis.

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Otogenic Meningitis

Prophylaxis

On examining my own and other case records of otogenic meningitis, there are very few that could not have been prevented, and it will not be out of place to mention some of the avoidable factors that lead to meningitis.

Premature surgery.—Neumann (1932) has shown that mastoid operations in the early stages of an acute aural infection are more frequently followed by meningitis than if the operation is delayed until the second or even third week of the ear disease. It is now generally recognized that extensive surgical procedures in the earliest stages of acute aural suppuration favour dissemination of the disease. It is felt that this is because some days elapse before adequate protective barriers can be established. Another factor may be that the upper respiratory tract infection that was the original cause of the ear disease has not had time to settle down, and opening up fresh tissue-spaces will encourage the primary infection to spread even farther.

Incomplete surgery.—Neglect to exenterate all diseased cells in the Schwartze operation for acute mastoiditis may leave a focus of disease that will eventually spread to the meninges. This is all the more likely to happen if inadequate drainage has been afforded to the suppurating mastoid cavity. A thorough exenteration of all accessible cells should be the rule in the Schwartze operation, and adequate drainage should be provided afterwards. In this way the likelihood of extension to the meninges either directly, by way of venous channels or *viâ* the petrous apex will be reduced to a minimum.

Excessive surgery.—Accidental injury of the dura during a mastoid operation, especially in the posterior fossa in the region of Trautmann's triangle, where there is no brain tissue to dam up the tear, may lead to meningitis. Accidental luxation of the stapes or opening of a semi-circular canal in an infected area may be dangerous. Deliberate opening of the labyrinth in the early stages of acute labyrinthitis is very dangerous, and should never be undertaken.

Neglected aural suppuration.

(*a*) Acute. Untreated acute suppurative otitis media is, in these days, an unlikely cause of meningitis, but it has of recent years been made evident that despite a complete Schwartze operation it sometimes happens that disease tracks

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into the petrous apex from which it may, if not drained, infect the meninges. Every Schwartze operation that shows persistence of discharge from the mastoid or meatus associated with pain behind the eye and a low-grade fever should be looked upon as a possible case of petrositis, and investigated and treated accordingly.

(*b*) Chronic. Every case of chronic suppurative otitis media that does not respond to conservative treatment and in which there is evidence of disease of the lining, contents or boundaries of the middle-ear cleft requires an operation that will remove such disease and offer adequate drainage. Any mastoid in which aural discharge persists should be kept under regular observation and treatment so long as the ear remains moist. From time to time the otologist is asked to see an advanced case of otogenic meningitis that has been under medical supervision for some time, possibly several days, without a proper investigation of the auditory apparatus. In such patients there will not infrequently be a history of repeated headaches and attacks of vertigo over a long period. Careful attention to ear disease in the presence of these symptoms will lessen the frequency of otogenic meningitis.

Acute upper respiratory infection.—The use of nasal douches, or the aspiration of water whilst bathing, during the early stages of an acute upper respiratory infection sometimes leads to a particularly virulent form of otitis media that may end in a fulminating meningitis.

Treatment

Introduction.—The eradication of the primary focus in the ear has been looked upon as an essential part of the treatment of otogenic meningitis. It was felt, and is still felt by many, that a surgical attack upon the temporal bone should be instituted at the earliest possible moment.

As recently as six months ago no less an authority than Ersner (1938) said in a discussion on meningitis: "The most modern therapeusis is to attack the primary focus, and secondarily to institute an anti-meningitic regime." For some time I have felt that major surgery was only required when there was diseased bone in contact with the meninges (Cawthorne, 1938). To open the mastoid or, even worse, the labyrinth, in the cases of meningitis that have followed rapidly on the heels of an acute and possibly transient aural infection

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will not check the disease. Rather will it encourage further spread by opening up fresh tissue spaces.

The help afforded by chemotherapy has confirmed this view, and since stressing this point previously I have seen several cases that bear this out and I have noted reports of successful results by many writers where no attempt was made to eradicate the primary focus other than paracentesis. Layton, always a staunch advocate of early surgery in otogenic meningitis, recently said that he was beginning to wonder whether in the future they would treat the meningitis first with the sulphanilamides and attack the mastoid later (1939).

I believe that chemotherapy plays the predominant part in the management of otogenic meningitis (Cawthorne, 1939). Surgical eradication of the primary focus is called for when, and only when, there is reason to suspect diseased bone in contact with the meninges to be the method of spread. Such cases will be found when the meningitis follows after some weeks of aural suppuration or is seen in the course of long-standing ear disease. To omit surgery in these cases is dangerous, and is placing too great a burden on chemotherapy. I would therefore say that the first consideration is to check the meningitis by means of chemotherapy and other means, whilst surgical eradication of the primary focus will be called for if and when there is something to eradicate.

I will deal with the various aspects of treatment more or less in order of merit, and naturally chemotherapy will come first.

Chemotherapy.—Now that the value of the sulphanilamide group of drugs in the treatment of meningitis is well established, it will not be necessary to consider any other method of chemotherapy.

The original chemical compound Prontosil was synthesized by Mietzch and Klarer in 1932 (Holman and Duff, 1938), and in 1935 Domagk published the results he had obtained by treating streptococcal infections in mice with prontosil. Within a short time it was evident that prontosil had a profound effect on infections in man due to the beta-hæmolytic streptococcus, and it was thought that the active principle was sulphanilamide, a breakdown product of the original prontosil. Numerous preparations containing or giving rise to sulphanilamide appeared, and their use was attended by success in a variety of infections. Whitby (1937) described the effect upon

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pneumococcal infections in mice of a new compound prepared by Ewins and Phillips, which they called M & B 693. This drug has since been shown to be more effective in experimental streptococcal infections than sulphanilamide (Fleming, 1938), (Whitby, 1938). These experimental findings have been confirmed in clinical practice, and in addition to streptococcal and pneumococcal infections, M & B 693 has been found to be of value in the treatment of meningococcal, gonococcal, staphylococcal, B. coli and B. Welchii infections.

This group of drugs seems to act in virtue of its bacteriostatic properties which, according to McIntosh and Whitby (1939) is brought about by the neutralization of some metabolic function of certain bacteria so as to interfere with their food supply. The same authors have found no evidence to suggest that these drugs either stimulate phagocytosis or in any way influence the production of specific immune bodies.

The sulphanilamides are easily absorbed from the stomach and they travel in the blood-stream to permeate all the tissues and fluids of the body, and they are finally excreted in the urine (Marshall, Emerson and Cutting, 1937). In order to get the full benefit of chemotherapy it is necessary that the concentration of the drug in the blood-stream should reach an adequate level, and that this level should be maintained until the infection is overcome. For severe infections the optimum level is said to be from 10 to 15 milligrammes of the drug per 100 cubic centimetres of blood. In order to reach and maintain this level, regular administration of the drug in doses based on the body-weight is required. Long, Bliss and Feinstone (1939) have worked out exact tables showing the initial and maintenance doses required for different weights. They insist upon regular four-hourly administration, and it is interesting to note that children require higher doses in proportion to their weight than adults. This is because the more fluid diet of a child hastens the excretion of the drug. Arising out of this is their observation that fluids should not be given too liberally when it is desired to keep the concentration of sulphanilamides in the blood at a high level. Many toxic effects have been noted during the course of chemotherapy, some of them trivial and a few severe. The more serious effects appear to be on the hæmopoietic system, so frequent blood examinations should be the rule when giving large doses of sulphanilamide or M & B 693. Long *et al* (1939) have noted that the more serious

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complications are usually preceded by a bout of unexplained fever.

In dealing with a dangerous disease such as meningitis, the only justification for discontinuing the drug before the patient is cured would be the onset of a complication that might prove fatal unless the drug were stopped. In two recent papers (Maclean, Rogers and Fleming, 1939, and Ross, 1939) it has been shown that the pneumococcus can acquire tolerance to M & B 693, and it is suggested that the initial doses of the drug should be large when dealing with pneumococcal infections and that additional methods of increasing resistance to the infection should be employed whenever possible. The desired concentration of sulphanilamide or M & B 693 in the blood can be attained by oral administration. If this is out of the question, parenteral administration will be necessary. For this purpose the more concentrated solutions such as prontosil soluble, proseptasine, and the recently introduced soluble sodium salt of M & B 693 are available as an alternative to a 1 per cent. solution of sulphanilamide.

Drainage of cerebrospinal fluid.—Nearly every writer has stressed the importance of relieving the increased intracranial pressure that accompanies meningitis. Hassin (1932) says: "The phenomena of stasis and rarefaction of brain tissues are, in my opinion, the most important and dangerous cerebral complications of meningitis, for the stagnant fluids of the distended tissue spaces, surcharged with catabolic substances, cause degenerative changes in the ganglion cells and nerve fibres."

The increased intracranial pressure can be relieved by lumbar puncture and the withdrawal of excess fluid. This may have to be done two or even three times in the twenty-four hours for the first few days of the disease. In any case it should be done at least once a day until the pressure becomes normal. If a block develops in the spinal sub-arachnoid space, drainage will have to be by cisternal, or in the case of tiny children, by ventricular puncture. None of the methods suggested for continuous drainage of cerebrospinal fluid appear to offer any advantage over repeated lumbar puncture. It must be admitted, however, that repeated lumbar puncture can be very trying for the patient, and for this reason it is possible that in some instances the number of lumbar punctures carried out may be insufficient to relieve the increased intracranial pressure.

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Fortunately chemotherapy, by checking the disease, has helped to reduce the amount of drainage required in many cases.

It has been the custom of many writers to take advantage of the opportunity afforded by lumbar puncture to introduce serum, drugs, and even gas into the sub-arachnoid space. I think that in the light of our present knowledge intrathecal medication is rarely necessary, and it may often do harm. The introduction of drugs, with the possible exception of a 0·8 per cent. solution of sulphanilamide (Neal and Appelbaum, 1938), or serum into a sub-arachnoid space, the lining membrane of which is likely to be irritable and inflamed, will cause an increased outpouring of fluid and cells. This is the last thing to be desired, and as both drugs (Marshall *et al*, 1937) and serum (Thompson, 1937; Banks, 1938) can reach the sub-arachnoid space in effective concentrations *viâ* the bloodstream, there is no need to run the risk of provoking a meningeal reaction by intrathecal medication. The possible exception to this rule is in pneumococcal infections, in which, according to Finland, Brown and Rauh (1938) the anti-body necessary to attack pneumococci does not appear to reach the cerebrospinal fluid. They feel that the least harmful procedure is to inject intrathecally 10 c.c. of the patient's own serum after he has been given specific anti-serum by the intravenous route.

Eradication of the primary focus.—If there is reason to suspect diseased bone in contact with the dura, or a space preformed by bony disease, then with as little delay as possible the affected ear should be laid open and as much diseased bone removed as may seem necessary. The procedure suggested by Neumann (1932) is suitable and serves as a preliminary in the case of suspected infection of the petrous apex. The various approaches to the petrous apex have been described by Kopetsky and Almour (1920), Eagleton (1931), Frenckner (1932), Ramadier (1933) and Lempert (1937), and there is an excellent review of the whole subject by Almour (1938). When there is suppurative labyrinthitis secondary to chronic suppurative otitis media, translabyrinthine drainage of the lateral cistern as suggested by West and Scott (1909) is indicated. Naturally any localized area of disease within the skull such as an abscess of the brain or an infected thrombus in the lateral sinus or jugular bulb will also require attention.

Uninterrupted drainage for the cavity caused by any operation is, of course, essential, especially when there is a wide

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exposure of dura, and in this connection I would like to mention the value of oil-silk as a means of protecting the dura from the inevitable trauma that is caused by gauze when it adheres to an inflamed dural surface. A problem that arises in cases that have had an extensive exposure of dura is how to prevent them from being attacked at a later date by a casual otitis media. I have recently had three cases under my care in which a second attack of meningitis followed some time after an operation for otogenic meningitis where large areas of dura had been exposed and were in direct contact with the middle-ear cleft. I do not in any way wish to suggest that such exposure is not necessary, because I am sure that it is essential. I think that the wisest course to adopt is to try and form a barrier between the middle-ear cleft and the meninges by means of a secondary muscle-flap operation.

Anti-sera and Vaccines.—The use of specific anti-sera and vaccines in the treatment of otogenic meningitis has been advocated for many years by Kolmer (1926), and it has been shown by Neal, Jackson and Appelbaum (1937) that when meningitis follows scarlet fever good results can be expected from using anti-scarlatinal serum. These authors have also used bacteriophage and autogenous vaccine. As it is not thought that sulphanilamide or M & B 693 have any influence on the production of anti-bodies, it would certainly seem wise to supplement chemotherapy with specific serotherapy wherever possible. In certain cases, notably those caused by the pneumococcus, the artificial introduction of anti-bodies into the sub-arachnoid space may be desirable (Finland *et al*, 1938).

The question of intrathecal administration of anti-sera has already been dealt with, and it is only necessary to quote Banks (1938) and Hoyne (1936), who advocate the intravenous route, as the method of choice.

Blood Transfusions.—Whenever an examination of the blood reveals a deficiency in the red cell count or hæmoglobin content, transfusion of blood is required. Many authorities, notably in America, advocate repeated small transfusions, and Kopetsky (1938) feels that this is the best way to combat the chemical changes that the infection has caused in the cerebrospinal fluid. In some, but by no means all, of the cases of otogenic bacterial meningitis there may be a co-existing septicæmia. This is likely to cause anæmia and one or more blood transfusions may be of great service. Again, prolonged

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chemotherapy not infrequently causes an alteration in the blood picture that can easily be remedied by transfusion of blood.

General Treatment

The general management and nursing of the patient who is suffering from otogenic meningitis are naturally important, and I have found that the following points require particular attention.

Rest.—A characteristic feature of meningitis is the mental and physical activity that it causes. The periods of restlessness and delirium must be controlled as far as possible, because they may prove to be a great drain on the resources of the patient. A room that is both dark and quiet should be provided and if necessary, and I have usually found that it is, sedative drugs should be given. Sometimes nothing less than morphia will calm the patient, but I have found barbiturates such as luminal and seconal most helpful.

I think the patient should rest quietly in bed for some time after he has apparently recovered. I have been impressed by the relapses that do occur from time to time, and I think they are less likely to be seen if a long period of rest in bed is ensured.

Diet.—It has been the custom to encourage a large fluid intake, but during the period of intensive chemotherapy I think it is wiser not to do this, otherwise it may be difficult to maintain an adequate concentration of sulphanilamide in the blood. This does not mean that fluids should be restricted, but rather that they should not be forced. More often than not the diet has to be a liquid one and then it is important to see that, after the first few days, it has a high protein content. A prominent feature of the more protracted type of meningitis, such as the tuberculous form, is the wasting, and this is caused by under-nourishment. Vomiting may, of course, partly be the cause, and if this prevents adequate feeding, rectal or even subcutaneous infusions will be called for.

Bowels.—There is often a tendency to constipation and this can be conveniently dealt with by daily enemas.

Drugs.—Alkalis are always said to be good in febrile cases, and Long *et al.* (1939) recommend sodium bicarbonate to combat the clinical acidosis that may be seen with intensive chemotherapy.

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Conservative treatment of the ear.—When a surgical excursion into the temporal bone is not considered advisable I think that the ear canal should be kept free from any discharge by frequent mopping and, of course, the ear must be protected from outside infection by a sterile dressing. It will be wise to have an X-ray picture taken of the affected temporal bone at the earliest moment, and to have further pictures taken at intervals. This will give the surgeon a serial view of the effect of the infection on the temporal bone, and when taken in conjunction with the clinical signs it will strengthen his decision as to the right course that he should adopt.

Cases

The table that follows contains details of all the cases of otogenic meningitis that I have treated with one or other of the sulphanilamide group of drugs. It will be seen that there were six fatal cases, and it is only fair to chemotherapy to point out that three of them died within twelve hours of treatment being instituted, whilst two of the other fatalities occurred in the early days of chemotherapy and did not receive what I now believe to be adequate doses of the drug.

Conclusions

That meningitis is no longer such a fatal complication of ear disease may be largely attributed to the sulphanilamide group of drugs.

A knowledge of the condition of the infecting ear with special reference to whether it be acute or chronic, together with an understanding of the possible pathways that the disease may take to reach the meninges, are important factors in determining the line of treatment that should be adopted to supplement chemotherapy. The responsibility of the aural surgeon in a case of otogenic meningitis is great, because it is for him to decide upon the method of treatment most suitable for combating the primary source of infection, namely the ear.

Much of the experience I have had of otogenic meningitis has been in the London County Council's General Hospitals service and it gives me great pleasure to acknowledge my indebtedness to the Medical Officer of Health, Sir Frederick Menzies, for allowing me to publish details of those cases I have seen in the Council's Hospitals, and to the

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Date.	Name and Age.	History.	Cerebrospinal Fluid.	Treatment.	Progress.
15.1.37. Case No. I.	George S. 9.	Discharging right ear 5 weeks. Never before. Right Schwartze mastoid 9 days. Meningeal signs 2 days. Conscious on examination.	Turbid. Numerous pus cells. Direct film; no organisms. Culture, Hæmolytic Streptococci.	Neumann's mastoidectomy. Repeated lumbar puncture. Prontosil, Oral, Parenteral, Intrathecal. Blood transfusion.	Cerebrospinal fluid infected for 23 days. Discharged as cured in 3½ months.
4.2.37. Case No. II.	Louisa L. 47.	Discharging right ear many years. Meningeal signs 5 days. Drowsy on examination.	Turbid. 3,000 cells. Chiefly Polymorphs. No organisms in direct film or on culture.	Radical mastoidectomy and drainage of temporal lobe abscess. Prontosil, Oral and Parenteral. Repeated lumbar puncture.	Organisms never found in cerebrospinal fluid. Discharged as cured in 4½ months.
10.9.37. Case No. III.	Mary P. 17.	Discharging right ear 4 weeks. Never before, Right Schwartze mastoid 10 days. Meningeal signs 1 day. Drowsy and irritable on examination.	Turbid. 11,000 cells. 70% Polymorphs. Direct film, numerous organisms. Culture, H. Streptococci.	Neumann's mastoidectomy and drainage of lateral cistern. Repeated lumbar puncture. Prontosil, Oral.	Cerebrospinal fluid infected for 3 days. Discharged as cured in 3½ months.
20.10.37. Case No. IV.	Reg. H. 4½.	Discharging left ear 10 days. Left Schwartze mastoid 2 years previously. Dry till present attack. Meningeal signs 2 days. Delirious on examination.	Turbid. 1,400 cells. Direct film, organisms. Culture, Pneumococci (untyped).	Neumann's mastoidectomy. Repeated lumbar puncture. Prontosil, Oral, Parenteral.	Died on 4th day. No post-mortem.
16.2.38. Case No. V.	Willie A. 18.	Discharging left ear, probably for 5 days. Previous ear discharge right. Meningeal signs 3 days. Drowsy on examination.	Cloudy. 1,100 cells. 70% Polymorphs. No organisms in direct film or on culture.	Schwartze mastoidectomy after 12 days. Repeated lumbar punctures. Prontosil, Oral.	Ear dry in 1 month. Discharged as cured in 2 months.
21.4.38. Case No. VI.	Phyllis H. 10.	Discharging left ear 3 weeks. Left Schwartze mastoid and drainage of petrous apex one year previously. Meningeal signs 2 days. Conscious on examination.	Turbid. Numerous pus cells. No organisms in direct film. Culture, H. Streptococci.	Reopening mastoid and drainage of petrous apex posteriorly. Repeated lumbar puncture. Prontosil, Oral. Parenteral.	Died on 4th day. Post-mortem. *Diffuse meningitis.* Necrosis of left petrous apex.

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Date.	Name and Age.	History.	Cerebrospinal Fluid.	Treatment.	Progress.
4.5.38. Case No. VII.	Albert P. 19.	Discharge from both ears for many years. Left ear pain and more discharge for 1 week. Meningeal signs 4 days. Delirious on examination.	Turbid. Many pus cells. Direct film organisms. Culture, H. Streptococci.	Lumbar puncture. Soluseptasine, Parenteral, Intrathecal.	Died a few hours later. No post-mortem.
26.7.38. Case No. VIII.	Audrey H. 3.	Right ear discharge 1 week, now almost dry. Left ear discharge 1 day. Meningeal signs 12 hours.	Opalescent. 250 cells. 98% Polymorphs. Direct film organisms. Culture, Pneumococci.	Bilateral Neumann's mastoidectomy after 4 days. Repeated lumbar puncture. M & B 693, Oral, Parenteral.	Died 1 week later. Post-mortem. Diffuse meningitis. No evidence of osseous spread.
13.8.38. Case No. Va.	Willie A. 18. (See No. V.)	Left radical mastoid 1 month. Meningeal signs 2 days. Drowsy on examination.	Turbid. 1,800 cells 70% Polymorphs. No organisms in direct film or on culture.	Reopening of mastoid and drainage of petrous apex 2 weeks later. Repeated lumbar puncture. Prontosil, Oral.	Cerebrospinal fluid cleared after second operation. Discharged as cured in 4 months.
13.8.38. Case No. IX.	Fred C. 14.	Left ear discharge 3 weeks. Never before. Meningeal signs 3 days. Conscious on examination.	Turbid. 4,000 cells. 85% Polymorphs. Direct film organisms. Culture, Staphylococcus Aureus.	Neumann's mastoidectomy. Repeated lumbar puncture. M & B 693, Oral.	Cerebrospinal fluid infected for 16 days. Discharged as cured in 2½ months.
14.8.38. Case No. X.	Donald T. 18.	Left earache 2 days. No ear discharge. Left mastoid operations with exploration of temporal lobe 2 years before. Conscious on examination.	Turbid. 2,240 cells. No organisms in direct film or on culture.	Prontosil, Oral. Repeated lumbar puncture.	Cerebrospinal fluid clear in 5 days. Discharged as cured in 1 month.
23.8.38. Case No. XI.	Francis G. 69.	Left ear discharge several months. Meningeal signs 3 days. Comatose on examination.	Turbid. 4,600 cells. Mostly Polymorphs. Direct film organisms. Culture, H. Streptococci.	Neumann's mastoidectomy. Lumbar puncture. M & B 693, Parenteral.	Died 12 hours later.

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Date.	Name and Age.	History.	Cerebrospinal Fluid.	Treatment.	Progress.
26.9.38. Case No. XII.	Eileen McG. 10.	Left earache 3 days. Right ear discharge for a few weeks only following tonsillectomy 1 year ago. Conscious on examination.	Opalescent. 600 cells. 80% Polymorphs. No organisms in direct film or on culture.	Myringotomy (pneumococcal pus). Repeated lumbar puncture. M & B 693, Oral, Parenteral.	Cerebrospinal fluid clear in 3 days. Ear dry in 5 days. Discharged as cured in 20 days.
11.11.38. Case No. XIII.	James B. 6.	Discharging right ear 2 weeks. Never before. Meningeal signs 3 days. Delirious on examination.	Turbid. 4,500 cells. 70% Polymorphs. Direct film organisms. Culture, H. Streptococci.	Neumann's mastoidectomy. Repeated lumbar puncture. M & B 693, Oral, Parenteral. Anti-streptococcal serum. Blood transfusion.	Cerebrospinal fluid infected for 14 days. Discharged as cured in 3 months.
8.12.38. Case No. XIV.	Charles Y. 21.	Discharge from both ears since childhood, much increased for 1 week. Meningeal signs 4 days. Semi-delirious on examination.	Turbid. 2,000 cells. Direct film gram positive cocci. Culture, sterile.	Bilateral radical mastoidectomy and drainage of left temporal lobe abscess. Repeated lumbar puncture. M & B 693, Oral.	Organisms in cerebrospinal fluid for 1 week. Discharged as cured in 5 months.
2.3.39. Case No. XV.	Esther B. 19.	Right ear discharge 3 weeks. Never before. Meningeal signs 1 day. Conscious on examination.	Cloudy. 1,000 cells. Nearly all Polymorphs. No organisms in direct film or on culture.	Neumann's mastoidectomy. Repeated lumbar puncture. M & B 693, Oral.	Cerebrospinal fluid clear in 6 days. Discharged as cured in 6 weeks.
3.3.39. Case No. XVI.	Violet F. 24.	Right ear discharge off and on for years. Meningeal signs 1 week. Delirious on examination.	Turbid. Many pus cells. Direct film organisms. Culture, Pneumococci (untyped).	Neumann's mastoidectomy. Lumbar puncture. M & B 693, Parenteral.	Died 11 hours later. No post-mortem.
14.5.39. Case No. IIIa.	Mary P. 19.	Right earache 36 hours. Right mastoidectomy 1½ years ago for otogenic streptococcal meningitis. Meningeal signs 12 hours. Delirious on examination.	Opalescent, yellow. No cells in smear. Direct film teeming with organisms. Culture, Pneumococci, Type E XVII.	Repeated lumbar puncture. M & B 693, Oral, Parenteral. Anti-pneumococcal serum.	Cerebrospinal fluid sterile in 1 day. Symptom free in 1 month. Still in Hospital July 1939.

Medical Superintendents and Staff of St. Giles' Hospital, Dulwich Hospital, The Downs Hospital for Children, and St. Charles' Hospital for their willing help and co-operation in the management of these cases. I should also like to thank Dr. Hinds Howell for kindly allowing me to mention case No. X.

Finally I should like to pay tribute to the memory of my old chief, Mr. G. J. Jenkins, whose enthusiasm was largely responsible for arousing my interest in the many problems presented by otogenic meningitis.

Messrs. May & Baker kindly furnished me with supplies of M & B 693, and I have used this in some of the cases that I have reported.

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. . . .

Der Autor schlägt vor die Bezeichnung "Meningitis" für alle jene Fälle zu verwenden, bei denen die Cerebrospinalflüssigkeit Zeichen entzündlicher Reaktion aufweist. Je nach dem Ergebnis

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der Liquoruntersuchung würde das Adjektiv serös, cellulär oder bakteriell voranzusetzen sein.

Der Weg auf dem sich die Erkrankung vom Schläfenbein zu den Meningen fortsetzen kann, sowie die dadurch bedingte Behandlung wird beschrieben. Die klinischen Erscheinungen der otogenen Meningitis und Vorschläge zur Verhinderung dieser Komplikation werden besprochen. Es wird vermutet, dass die Chemotherapie in der Behandlung der Meningitis die Hauptrolle spielen wird. Die chirurgische Ausschaltung des primären Herdes ist immer angezeigt, sobald das Gewebe des Felsenbeins erkrankt ist.

. . . .

L'auteur propose que le terme " méningite " soit employé dans tous les cas où le liquide cérébro-spinal présente une réaction inflammatoire, et que le terme " séreux ", " cellulaire " ou " bactérien " soit ajouté, selon l'état du liquide cérébro-spinal.

Il indique le mode de propagation de la maladie, de l'os temporal aux méninges et montre l'importance de ce fait par le traitement.

Il décrit les aspects cliniques de la méningite d'origine otique, et indique les moyens les plus efficaces pour éviter cette complication.

Il suggère que dans le traitement de la méningite, la chimiothérapie devrait jouer le rôle prédominant et que l'indication de l'exérèse du foyer primitif se pose si et quand le tissu de l'os temporal est malade.

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