THE CEREBRO-SPINAL FLUID
in MENINGITIS

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Of recent years, many shorter and longer descriptions of the cerebro-spinal fluid have appeared in journals and textbooks, and it is difficult to avoid repetition of already well-known facts or to say anything particularly new about it. Readers specially interested in the subject should refer to the Presidential Address given to the Neurological Section of the Royal Society of Medicine by the late Professor Halliburton¹ in 1916, as in it are foreshadowed most of the essential facts which have since been repeated by subsequent writers. In his Address, Halliburton pointed out that normal cerebro-spinal fluid is "the perfect physiological medium" for the protection of the tissues of the central nervous system—more especially its nerve-cell elements—and, as he expresses it from the physiologist's point of view, it is the ideal "Ringer-Locke" solution, with its component chlorides, trace of sugar, and dissolved oxygen: and with, in addition, small quantities of protein and urea, and traces of other less important substances.

The following résumé, modified from a previous article by the present writer,² gives an outline of the characters of the normal fluid—with which the findings in the various forms of meningitis can be compared and contrasted.

In health, it is a water-clear, colourless, limpid fluid, secreted by the "choroid glands" of the cerebral ventricles, at a pressure, with the patient in the horizontal position, of about 80 to 120 mm. (Merritt and Fremont-Smith give 70 to 180 mm.) of the fluid itself—faintly alkaline in reaction, and with a specific gravity of about 1.006 to 1.008 or 1.009.³

Cells, from 0 to 3 "small lymphocytes" per c.mm., according to the patient's age and the level at which the fluid is drawn off—there being usually no cells at all, or occasionally one cell,

¹ "An Address on the Possible Functions of the Cerebro-Spinal Fluid," by W. D. Halliburton, M.D., F.R.S., Professor of Physiology, King's College, London, British Medical Journal, 1916, ii, 609. Halliburton ends his Address with a plea for a closer rapprochement "between those who pursue their investigations by the bedside and those who work in the laboratory," for the pathologist can do his work intelligently and effectively only if he is supplied with full clinical information as to the age and sex of the patient, the period and mode of onset of the disease, and other relevant details—for he has to plan his examination of an often too scanty specimen of fluid with the greatest economy and discrimination, and his interpretation of his own findings will often in no small measure depend upon the nature of the information supplied by his clinical colleagues.


³ There has been, of late, considerable discussion in the journals as to the exact specific gravity of the fluid, a point of some importance in connection with the giving of spinal-anaesthetic and other intra-thecal injections. At the West End Hospital, our own average normal figure, estimated by weighing, at a room-temperature of 21° C., in a specific-gravity bottle—the only accurate method—is 1.007.
in a child’s fluid at any level, and in an adult ventricular specimen: and not more than 2, or at most 3, cells in the lumbar-puncture fluid of middle-aged, or even of elderly persons. No red corpuscles should be found (if the first few drops from the needle are, as they should be, discarded). The reader will be familiar with the advisability of collecting such specimens of cerebro-spinal fluid in two (or more) successive fractions, as valuable information can often be obtained by the comparison of these with one another both on naked-eye and on microscopical examination. With the accidental access of blood at the time of puncture, the faintest visible trace of colourless "ground-glass" opacity may be taken as indicating the presence of about 500 red corpuscles per c.mm., a very faint pinkish tint appearing with about 1,000, and a definite pink with 2,000 corpuscles—and, with these degrees of contamination with blood, the specimen is still usable for a fairly accurate examination by the ordinary clinical methods of testing. Along with 500 red corpuscles, there is no appreciable increase of coagulable protein (including globulin) from the accompanying blood-plasma; whilst, with from 1,000 to 4,000 corpuscles, the increase in total protein, though just detectable, is under 0.005 (or 5 mgr.) per cent, and of globulin alone it is still not appreciable with even higher figures (e.g. up to some 40,000 to 50,000 erythrocytes, with which the total protein from the plasma, however, would show an increase of 40 and 50 mgr. per cent respectively). (See "A Further Note," by Dickson and Ottewill, Medical Press and Circular (1937), 194, p. 597.)

The total coagulable protein also varies with age and site. In the ventricular fluid it is only about 0·01 (or 10 mgr.) in the adult (in the young child it may be even less); whilst in the lumbar-puncture fluid of the young adult it is about 0·02 to 0·025: in the middle-aged, about 0·025 to 0·03: and in the elderly often a trifle more, though as much as 0·04 (40 mgr.) usually means (other causes being absent) some degree of vascular degeneration.

Globulin, no excess with the ordinary clinical tests (see above).

Lange's colloidal-gold curve is "negative." At the W.E.H., we aim at graduating our gold-sol so as to give a completely negative finding with the ventricular fluid of a child (0000000000), which will usually mean, with normal lumbar-puncture fluids from healthy young and middle-aged adults, readings of 0010000000 and 0011000000 respectively.

The Wassermann, Meinicke clarification (M.K.R. II) and Kahn tests (named in order of importance) are, in non-syphilitic cases, negative.

Chlorides (estimated as NaCl) vary from 700 or 720 to 750 or 760 mgr. per 100 c.cm. (in infants, a range of 650 to 750 mgr. is given): as compared with the fasting value of only 270 to 620 mgr. in the adult blood-plasma.

In this connection, it should be emphasised that specimens of blood must be collected under optimum conditions, particularly the avoidance of any venous stasis which, by producing "increased acidity" (i.e. a decreased alkalinity), drives some of the chlorides back into the erythrocytes. An analogous "increased acidity," follows from the glycolysis which supervenes if the specimens of blood or fluid are kept for any length of time after collection, lactic acid being produced from the breaking-down glucose.

Sugar (glucose) in the fluid (estimated by MacLean’s method) varies from 0·04 to 0·08 (40 to 80 mgr.) per cent., as compared with, say, 80 to 100 mgr. per 100 c.cm. in the "fasting" blood-plasma; or by Folin and Wu’s method, using capillary blood, 90–120 mgm. per 100 c.cm. For the reason given in the preceding paragraph, both the cerebro-spinal fluid and the blood must be examined for sugar reasonably soon, preferably immediately, after collection, before any appreciable degree of glycolysis has had time to occur.

(Examinations for substances such as urea, uric acid, cholesterol, and various vitamins are usually merely of "scientific," rather than of any practical, interest. If there should be any valid reason for their estimation, this is better and more conveniently carried out in the blood than in the cerebro-spinal fluid.)

Films and cultures for bacteria are negative.

The term "meningitis," when used without qualification, is usually taken to signify inflammation affecting more especially the leptomeninges, which comes to mean practically the same thing as "inflammation of the subarachnoid space"; and the cerebro-spinal fluid within this space tends to undergo varying degrees of ascertainable change, the characters of which will depend partly upon the nature of the causal irritant itself, and partly on the period, early or late, the intensity and virulence of its action, and also on the mode of its access to the subarachnoid space, its rate of spread therein, and whether it remains localised by adhesions or becomes generalised over brain and cord.
Fig. 2.—Exudate in epidemic cerebro-spinal meningitis, showing breaking-down pus-cells crowded with meningococci. (Leishman's stain, × 1,250).

Fig. 3.—Meningococcal meningitis in a man aged twenty-three: fresh-wet toluidin-blue preparations of typical early and late exudates:

(1) First lumbar-puncture fluid on second day of illness, before commencement of treatment. Film made and photographed immediately: exudate predominantly polymorphonuclear, the unstained cells being still alive, and the stained cells dying or dead. The background consists of the fluid still containing excess of stain.

(1A) The same preparation photographed next day. The cells are now dead, and their nuclei have taken up the available remaining toluidin-blue stain.

(2) Fourth lumbar-puncture fluid on seventh day of illness—The patient, under treatment with M. & B.’s "soluseptasine," was now convalescent, and the exudate almost entirely mononuclear. For details of the transition from a polymorphonuclear exudate, to one consisting of larger, and then of smaller, endothelial and finally of small lymphocyte-like cells, see Fig. 4. (W.E.H. case.) × 400.
FIG. 4.—Meningococcal meningitis: fresh-wet films from three W.E.H. cases:
(1) A girl aged ten years; (2) a baby aged six months; and (3) and (4) a man aged twenty-three years, all of whom recovered under chemotherapy with "soluseptasine."

A series of films from these cases showed, in the earlier stages, larger, and, in the later, smaller, endothelial cells in mitotic division, with the formation of progressively smaller "daughter-mononuclears." The smallest cells of the series are indistinguishable from "small lymphocytes." Fresh-wet toluidin-blue preparations of centrifuged deposits. (X 1,000.)

FIG. 5.—Polymorphonuclear exudate in a case of acute purulent meningitis due to Streptococcus mucosus, a not uncommon organism of middle-ear and sinus-infection. (Leishman's stain, X 1,250.)

FIG. 6.—Unusual Cells in centrifuged deposits of cerebro-spinal fluids, the result of over-energetic puncture:
(A) Group of myelocytes and nucleated red corpuscles in a fresh-wet toluidin-blue film the presence of which, in previously-examined unstained films, had been "puzzling."
(B) A similar film showing, in addition, a bone-corpuscle, and fat-globules evidently derived from bone-marrow.
(C) Experimental lumbar puncture in cadaver. The needle was intentionally thrust through the theca into an intervertebral disc and then withdrawn slowly and the cerebro-spinal fluid obtained by suction with a syringe. This small group of cartilage-cells was found in a fresh-wet toluidin-blue film of the centrifuged deposit. (All X 400.)
Meningitis may be suppurative, and is then practically always due to infection with bacteria, especially the pyogenic cocci (strepto-, pneumo-, staphylo-, or meningo-cocci): less frequently one of the Gram-negative bacilli of the coli-typhoid-paratyphoid group: or Pfeiffer's "Haemophilus" and the allied "Leptothrix" group: whilst for our present purpose we merely mention the infrequent occurrence of the Gonococcus, B. anthracis, and various monilia- and yeast-like organisms.

In some of the granulomatous diseases, such as tuberculosis, syphilis, and actinomycosis, and other streptothricial infections, descriptions of the organisms concerned, and the special methods for their identification, are given in bacteriological textbooks.

In the important group of the viral infections in which meningitis may occur, the lesion in the meninges is characteristically non-suppurative—though in a few instances, at the earliest stage of the infection, polymorphs are found in the cerebro-spinal fluid, and may then even predominate, for example in acute lymphocytic choriomeningitis ("L.C.M."); although this may be regarded as only a passing phase, and the exudate during the height and subsequent course of the disease is mononuclear and chiefly lymphocytic in character—as is also the case with the occurrence of meningitis as a complication in viral diseases in general. The various causal viruses themselves can be demonstrated only by special methods, and sometimes only by the inoculation of a susceptible animal. Viral meningitis of varying degrees of severity, from mild and transitory up to grave and severe, may accompany or supervene in certain forms of viral encephalitis, myelitis, and encephalomyelitis (e.g. epidemic and other types of encephalitis, poliomyelitis, mumps, true viral influenza, etc.).

For the understanding of the phenomena occurring in the cerebro-spinal fluid, more especially in the earliest phases of an attack of meningitis, the route by which the infection reaches the meninges is of importance. This may be by way of the blood-stream, and the organisms may be carried directly to the leptomeninges in the region over the vertex or elsewhere, as in many infections with streptococci or pneumococci; and it may then spread and give rise to a generalised meningitis. Another important route, however, is seen in many, perhaps in most, cases of meningococcal infection, namely by way of the choroid plexuses and ventricles, i.e. commencing in the brain as a chorio-endoventriculitis: a method of infection also found in many cases of tuber-

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**Fig. 7.—Diagrammatic representation of a mesial sagittal section, through the corpus callosum and hindbrain, to show:**

1. Septum pellucidum between lateral ventricles: 2. third ventricle with foramen of Monro (F) opening into it: 3. cerebral aqueduct of Sylvius: 4. fourth ventricle, opening into 5. the cerebello-medullary cistern by the median foramen of Magendie: 6. central canal of the spinal cord. (After E. B. Jamieson.)
culous meningitis, in which the acute spread in the subarachnoid space is preceded by the formation of perhaps a single, or sometimes several scattered, subacute tuberculous lesions in the choroids or ventricular walls; whilst, as its name implies, this is also the usual route of infection in acute viral lymphocytic choriomeningitis. A reference to Fig. 7, in which the "cerebrospinal pathway" is illustrated, will elucidate how an infection, starting, say, in the choroids of the lateral ventricles, will spread downwards until it reaches and infects the posterior basal region of the brain around the cisterna magna or great cerebello-medullary cistern, from which it then spreads to the under aspect of the cerebellum and around the medulla and pons. As the infection passes downwards in the ventricular chain within the brain, it can very easily penetrate outwards through the thinnest parts of the containing-walls, i.e. as shown in Fig. 7, in the region of the infundibulum, and so produce meningitis around the pituitary stalk and in the interpeduncular space; or through the thin roof-plates of the mid-brain and fourth ventricle to involve the adjacent upper surface of the cerebellum. If the anatomical facts in connection with this route of infection are kept in mind, the "posterior basal," or so-called "post-basic," distribution of the exudate characteristic of meningococcal and of tuberculous meningitis, at the stage before there is the general spread throughout the whole subarachnoid space, is adequately explained; as is also the sequence of events in consecutive samples of fluid drawn off by lumbar-puncture. Take, for example, a case of meningococcal infection. In its earliest stage, the infection is "blood-borne," as may be demonstrated by blood-culture. During the very earliest phase of intracranial involvement, the onset of which may be gradual or abrupt, with restlessness, headache and rise of temperature, lumbar puncture may still give a perfectly clear and colourless fluid, and even chemically and microscopically there may as yet be little or no appreciable change in its composition, though a ventricular puncture (if such should be deemed justifiable) may already show meningococci in the fluid, with increasing numbers of inflammatory cells, chiefly polymorphs, within the cytoplasm of which the organisms may be found, sometimes in small, sometimes in large, numbers (Fig. 2)—hence its name Neisseria intracellularis—though some, or (especially in the more acute and virulent types of infection) many, of the cocci may remain or become free in the fluid. The lumbar-puncture fluid then becomes progressively more purulent, with at first only a whitish "ground-glass" opacity and then an increasingly thick yellowish fibrino-purulent and perhaps clotted fluid, often tinged with a varying amount of blood. The condition is now a chorio-endoventriculo-meningitis—an empyema of the ventriculo-subarachnoid space. In these days of chemotherapy, the course and prognosis of such an infection are infinitely more favourable than in the time, say, of the First World War, when intrathecal injections of the specific serum and the repeated drawing off of fluid gave the main hope of recovery. Appropriate treatment with sulpha-thiazole (M. & B. 760) or thiaamide sodium must be instituted at the earliest possible moment, and a study of the character of the cells in Fig. 3 will indicate how rapidly a case, which previously might have gone on to a fatal termination, may improve. The meningococci disappear; the polymorphonuclear pus-cells diminish in number and are replaced by mononuclears, first by larger monocytes, some probably from the blood, but most of them derived from the endothelial lining-cells of the leptomeninges, and these in turn being replaced by mononuclear cells, or, more accurately, themselves becoming progressively diminished in size as they undergo mitotic division, until only a few "small lymphocytes" are left, and then these, too, finally disappear (Figs. 3 and 4).

In those cases in which the meningococci are scanty, or perhaps cannot be detected microscopically, in addition to making the usual cultures on blood-agar, etc., part of the specimen of the fluid itself (with or without the addition of some glucose-broth) should be incubated overnight and re-examined for organisms by film and subculture.

Whilst the infection is in process of spreading downwards within the neuraxis as a chorio-endoventriculitis, other phenomena are taking place in the cerebro-spinal fluid. As already noted, owing to damage to the "blood-brain barrier," free complement, and increasing amounts of coagulable protein, (most commonly from 100 to 500, but sometimes up to 1,000 mgr. or more per 100 c.c.m.), including globulin, pass into and are found in it.

Chlorides, which, as we have seen, are normally in greater concentration in the fluid than in the blood-plasma, become diminished in the fluid, perhaps from 750 to 600 mgr. per cent in acute meningitis, due to strepto-, staphylo-, pneumo- or mening-cocci, to typhoid or para-typhoid or to Pfeiffer's Hemophilus: or to 580 mgr. or even less in tuberculous cases: whilst,

1 Penicillin has now been successfully employed for the treatment of pneumococcal, as well as of staphylo-coccal, streptococcal, and other forms of meningitis (see p. 82).
on the other hand, in acute lymphocytic choriomeningitis and other viral affections and in syphilitic meningo-vascular cases, the chlorides (and also the sugar) are not appreciably diminished.

Sugar (glucose) in the fluid becomes progressively diminished in amount in bacterial meningitis, and the corresponding increase in the amount of lactic acid (a substance not normally present) suggests that this diminution is due to the actual breaking-down of the sugar, for example, by the ferments of the cells of the exudate, especially the polymorphs, and by any sugar-splitting bacteria present—and in this connection it must be emphasised that this process of glycolysis continues to take place in the fluid after it has been withdrawn, and the estimation of the quantity of sugar present, to be of any value, must therefore be carried out without delay. In tuberculous meningitis cases, the glucose may become diminished to below 30 mgr., perhaps to 20 or 15 mgr. per cent; whilst, in acute bacterial suppurative conditions, it may completely disappear. In viral and syphilitic infections, on the other hand, the percentage of sugar tends to remain comparatively unaffected. The quantitative estimations of chlorides and sugar are, therefore, of importance, not only in the diagnosis of meningitis and its varieties, but for prognosis and treatment, and their gradual return to normal indicates the favourable progress of the patient. For more detailed accounts of the cytology, chemistry, and bacteriology of the fluid in other forms of meningitis, recourse must be had to the textbooks.

In connection with the subject of purulent meningitis, we have, however, to consider, from the point of view of both diagnosis and treatment, its differentiation from certain other conditions in which polymorphs are found in varying, and sometimes in large, numbers in the subarachnoid space and cerebro-spinal fluid. Reference will be found on page 91 to the considerable number of polymorphs that may occur in the earliest stage of lymphocytic choriomeningitis, before the cells in the fluid have "steadied down" to a mononuclear, and particularly to the characteristic "small-lymphocytic," exudate. Also, in very acute cases of tuberculous meningitis, polymorphs are sometimes numerous, and may even come to outnumber the "small lymphocytes," which are usually regarded as the cells most characteristic of the tuberculous infection; and similarly, in the severest types of acute meningo-vascular syphilis, an analogous polymorphonuclear increase may be observed. The diagnosis, however, in these two infections is cleared up by the finding of tubercle bacilli in the former: and by positive Wassermann, Meinicke, and Kahn reactions in the latter.

Greater difficulty may be encountered in differentiating from meningitis some cases of cerebral abscess, in which the lesion is approaching or has actually reached the surface of the brain: and also in certain examples of cerebral tumour when complicated by the occurrence of degenerative and necrotic changes, and by an associated emigration of leucocytes into and from the affected parts of the tumour into the subarachnoid space and cerebro-spinal fluid.

I have myself also drawn attention to the remarkably rapid emigration of polymorphs into and from the tissues, healthy or diseased, for example of the brain, during the course of a surgical operation in which the electro-cautery or diathermy-needle or knife has been used—the appearance of the tissues coming to simulate purulent infiltration or even abscess-formation. In cerebral abscess, as well as in supplicative conditions of the middle ear, mastoid and paranasal sinuses, etc., as these spread through the dura towards the leptomeninges, and before the invading organisms reach the subarachnoid space, a few, and then increasing numbers of, polymorphs find their way into the fluid; and, when viable and perhaps still virulent bacteria also gain entrance, the condition may develop into a frankly purulent meningitis, though this may be prevented by appropriate early treatment (p. 82). In both cerebral abscess and purulent meningitis, the pressure of the fluid may rise to between 300 and 550 mm., but in the latter the rise tends to continue to a still higher figure—perhaps 1,000 mm. or more.

Successive samples of fluid obtained by lumbar-puncture from these progressive cases of abscess may show a fairly definite series of changes. At the commencement, the fluid may be clear and normal-looking, containing perhaps only a few lymphocytes, and the total cell-count then rising to 50 or 100 cells per c.mm., with a 20 or 30 per cent. proportion of polymorphs; and later, as the cells increase still more in number, the chlorides, at first normal in amount, undergo a gradual decrease until, if the lesion becomes a frankly purulent meningitis, the cellular and chemical findings approach and then become indistinguishable from those of that condition.

In abscess cases, the Lange reaction is variable, but usually gives a "mid-" to "end-zone" curve, the height of which depends largely on the amount of total protein (especially globulin) and the number of cells present.

1 Beattie and Dickson's Textbook of Pathology, Fourth Edition, 1943, pp. 1058-9, and Fig. 646.
A polymorphonuclear leucocytosis in the blood is usually found in cases of cerebral abscess, but this, too, is apt to be variable—sometimes slight in cases in which one might expect it to be more pronounced, depending upon factors such as the rate of increase of the abscess in size and its spread, its degree of encapsulation, and the nature of the infecting organisms.

A note may be added here as to certain findings not usually recorded in "official" descriptions of examinations of the cerebro-spinal fluid. In the centrifuged deposits of lumbar-puncture specimens, I have not infrequently encountered squamous cells from the skin-surface, together with their accompanying staphylococci, etc., and occasionally even a little cylindrical fragment of skin punched out by the exploring needle—an argument in favour (1) of the thorough preliminary sterilisation of the skin, e.g. with 1 in 500 biniiodide spirit, and not a mere rapid and perfunctory "dab" with spirit or ether, or even tincture of iodine: and (2) of rejecting the first few drops of fluid flowing from the needle, as these usually also contain contaminating red blood-corpuscles.

On one occasion several years ago, whilst examining a specimen of fluid, I was puzzled to find, in the preliminary fresh-wet films from the centrifuged deposit, certain "unusual" cells, until, in toluidin-blue and Leishman-stained films, I recognised them as myelocytes, accompanied by nucleated red corpuscles from the bone-marrow, due evidently to the over-enthusiastic penetration of one of the vertebral bodies (Fig. 6A).

In a similar "over-energetic" specimen I once found a bone-corpuscle along with myelocytes and erythroblasts (Fig. 6B); and, as a complementary experimental investigation, at my next autopsy, I passed a lumbar-puncture needle, attached to a syringe, through the fourth lumbar interspace, pushing it well forward (!) into the intervertebral disc, and then slowly withdrawing it under negative pressure, collecting some cerebro-spinal fluid on its backward journey—with the interesting result of finding several little groups of cartilage-cells in the centrifuged deposit of the specimen so obtained (Fig. 6C).

THE ANATOMY OF THE MENINGES

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The meninges constitute the coverings of the brain and spinal cord, and, unlike the central nervous system itself, they are mesodermal in origin. They are usually described in three layers, of which the outer or dura mater is mainly protective in function and relatively avascular, whereas the inner two layers, comprising the leptomeninges or pia-arachnoid, are mainly nutritive in function and are highly vascular. It is the leptomeninges which are the site of generalised meningitis or leptomenigitis.

Pachymentinx or Dura Mater.

This is a strong fibrous sheet which lines the skull and vertebral canal, in which it extends down to the second sacral vertebra.

Embryologically it arises as two layers which fuse in the vertebral canal and become closely united in the cranial region. The layers are only distinct at the sutures and where they separate to form the venous sinuses.

The dura mater is continuous with the orbital periosteum and, through the sutures, with the pericranium. It also accompanies most of the cranial nerves and all the spinal nerves a short distance, fusing with their respective sheaths. Inside the skull the dura forms the peristium, encloses the intracranial venous sinuses between its layers, and gives rise to four septa:—

(1) One of these, the falx cerebri, separates the cerebral hemispheres.

(2) The tentorium cerebelli intervenes between the cerebellum and the occipital lobes of the cerebrum, and is supported in the midline by its attachment to the falx cerebri. From the under surface of the tentorium (3) the falx cerebelli descends to separate the cerebellar hemispheres.