CLINICAL PATHOLOGY IN GENERAL PRACTICE

THE CEREBROSPINAL FLUID IN DIAGNOSIS

BY

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The examination of the cerebrospinal fluid (C.S.F.) constitutes a very valuable method in the investigation of many diseases of the nervous system, and even in some general disorders. It often enables a firm diagnosis to be made, even while the patient is still at home, and this cannot but be of immense satisfaction to both practitioner and patient. The process of recovery in diseases hitherto fatal, but now yielding to treatment by antibiotics, can be followed with a fair degree of scientific accuracy by means of the examination of frequent samples of C.S.F.

The C.S.F. is nearly always obtained by lumbar puncture. It can also be collected from the lateral ventricles of the brain and from the cisterna magna, but these two sites should be punctured only when the patient is in hospital, where such facilities as an x-ray department and operating theatre are readily available. Discussion of such procedures has accordingly been omitted from this article.

The technique of lumbar puncture,* while relatively simple, does require practice and should be performed only after due consideration has been given to the benefits likely to accrue from this method of examination. Should the specimen be collected by the patient's own doctor it should be dispatched to the pathologist at once, as examination of the fluid should always be made without any undue delay. This is particularly important in a suspected case of meningitis, for both the cell count and the sugar content of the fluid will fall after a few hours. The C.S.F. pressure, the result of the Queckenstedt test, and the suspected clinical diagnosis should in such cases always accompany the specimen. This will help the pathologist to decide what examinations will yield the most satisfactory answers to the problem concerned.

Normal Cerebrospinal Fluid

It is necessary to know, first of all, exactly what constitutes a normal fluid. Table I shows the range of figures that can

TABLE I.—Normal Cerebrospinal Fluid

Pressure	125 mm. of water
Appearance	Clear and colourless
Cells	Up to 4 lymphocytes per c.mm.
Protein	Up to 30 mg. per 100 ml.
Globulin (e.g., Nonne-Apelt reaction)	Negative
Chlorides	700–760 mg. per 100 ml.
Sugar	50–70 mg. per 100 ml.
Lange test	No change
Wassermann reaction	Negative

be regarded as normal for an adult. A few additional comments may be made. The cells are always lymphocytes in a fluid uncontaminated by blood, but if contamination has occurred one can assume that one polymorph may be present for every 500 red cells per c.mm.; never more than 4 and usually fewer than 4 cells per c.mm. are found. The level of the protein content—which is composed almost entirely of albumin and with only a trace of globulin—varies with age. A child should have 10 to 15 mg. of protein per 100 ml., while in an elderly adult a figure of 50–60 mg. per

100 ml. can still be regarded as normal. Similarly, prolonged immobility in bed will tend to raise the protein level. The chloride content may vary a little with the blood chloride, but the sugar level is fairly constant throughout the day, and it is not necessary therefore to collect the specimen while the patient is fasting.

The Lange colloidal gold test is empirical, and normally colour changes do not occur in any of the 10 tubes containing dilutions of C.S.F. Varying degrees of precipitation of the colloidal gold may occur, resulting in changes of colour, and these are recorded numerically from 1 to 5, the latter figure representing a complete loss of all colour in the supernatant fluid. There are two main types of abnormal curve: (1) the paretic, in which the maximum degree of colour change occurs in the first tubes—that is, in those of the strongest concentration of C.S.F.; and (2) the mid-zone or luetic curve, which shows a maximum change in the middle of the curve. Examples of each of these are described below. The C.S.F. pressure is normally about 125 mm. of water when the patient is in the recumbent position, and an increase takes place in cases of infection and when there is some space-occupying lesion inside the cranium. When the jugular veins are compressed in a healthy subject there is a rapid rise in C.S.F. pressure as recorded in the manometer, followed on release of the jugular pressure by a drop to the initial figure. This is known as the Queckenstedt phenomenon or test.

The clinical diagnosis and the results of the pathological examinations have always to be correlated, so that it would seem to be easiest to describe the results of the examinations under the headings of various disease processes.

Meningitis

There are three main types of meningitis—pyogenic, tuberculous, and virus. Table II shows the types of results that can be expected in each group. Naturally, the actual figures depend upon the stage of the disease reached when lumbar puncture is performed.

TABLE II.—The C.S.F. in Meningitis

	Pyogenic	Tuberculous	Virus
Pressure ..	Raised ++	Raised ++	Slight increase
Appearance	Turbid in varying degree	Clear or slightly opalescent	Usually clear
Cells ..	Hundreds or thousands	Tens or hundreds	4–200/c.mm.
Type of cell	Polymorphs	Usually more lymphocytes than polymorphs (2 or 3 to 1)	Lymphocytes
Protein ..	100+ mg./100 ml.	100+ mg./100 ml.	Up to 150 mg./100 ml.
Globulin ..	Positive	Positive	Positive
Chlorides ..	Decreased to about 650 mg./100 ml.	600 to 650 mg./100 ml.	Slight decrease—680 mg./100 ml.
Sugar ..	Absent	Decreased to 20 to 35 mg./100 ml.	Normal or only very slightly reduced
Direct smear	Causal organism	T.B. present	None
Culture ..	" "	" "	Sterile

In pyogenic infections, such as meningococcal or pneumococcal meningitis, the fluid which is turbid shows a considerable increase of cells, all of which are polymorphs. The chloride content is often reduced, although not to such a low level as in tuberculous meningitis, but this must not be regarded as a diagnostic feature. The reduction in the sugar content is of the utmost importance, and an accurate estima-

*See the article on this subject by Dr. William Goody earlier in this series (*British Medical Journal*, November 7, 1953, p. 1040).

tion should always be obtained. The fluid from cases of pyogenic meningitis shows a great reduction and often a complete absence of sugar. Effective treatment will always be reflected by a rise in sugar content, in fact this may precede the clinical improvement. The finding of the causal organism is vital, for it will indicate which antibiotic should be used. Prompt treatment is essential in all cases and is of special importance in pneumococcal meningitis.

The C.S.F. is less turbid in tuberculous meningitis than in the pyogenic group. There is an increase in cells, which are largely lymphocytes, although a small number of polymorphs are present in most cases. The chloride level is reduced in well-established cases, but may be almost normal in the early stages. The sugar content is early reduced, but this decrease never becomes a complete loss. Tubercle bacilli in the smears confirm the diagnosis. There is little doubt that they can be found in practically every case given enough care and time by the pathologist. Cultures or animal inoculation will confirm the smear findings after four or more weeks, but this delay is not permissible before initiating treatment. Again, a rise in the sugar level is the best guide to effective treatment, as intrathecal streptomycin will cause an increase in the cells and protein in the fluid, but does not affect the sugar level.

There are numerous viruses that are now known to affect the central nervous system, but all yield a somewhat similar C.S.F. picture. It is often difficult to distinguish between tuberculous meningitis, poliomyelitis, and lymphocytic meningitis in the early stages, but, by paying particular attention to the sugar and the results of the smear examinations, diagnosis should be possible. There are a few other conditions, such as sarcoidosis of the meninges and torulosis, both of which are very rare, that give rise to great difficulty in diagnosis.

Poliomyelitis

The C.S.F. varies with the stage of the disease, and in Table III are given the findings at the three most important stages. The noticeable feature in the pre-paralytic period is

TABLE III.—*The C.S.F. in Poliomyelitis*

	Before Paralysis	1st Week of Paralysis	Subsequent Weeks
Appearance	Clear and colourless	Clear and colourless	Clear and colourless, or with a coagulum
Cells	Can be up to 2,000/c.mm. (May be 25% polymorphs)	5-10 lymphocytes/c.mm.	Up to 4 per c.mm.
Protein	Normal or only slightly raised	Raised about 100 mg./100 ml.	Up to 300 mg./100 ml.
Globulin	Negative	Positive (+)	Positive (+)
Chlorides and sugar	Normal	Normal	Normal
Lange test	No change	0011210000	Normal or slightly mid-zone

the resemblance of the fluid, especially as regards the pleocytosis, to that found in tuberculous meningitis, except that the chlorides and sugar are normal. When paralysis occurs the cells decrease but the protein increases, and this increase may persist for some months. A fluid with a protein level of 150 mg. per 100 ml. or more may show a fibrin clot of the "spider web" type seen in tuberculous meningitis. Another point of importance is that, while polymorphs are commonly found in poliomyelitis, they are not seen in encephalitis.

Cerebral Abscess

The most characteristic features are to find a raised pressure, a pleocytosis of both lymphocytes and polymorphs, with normal sugar and perhaps normal or slightly reduced chloride levels, in a patient with infection of ear, frontal sinus, or lung. However, a deep-seated abscess may yield a C.S.F. similar to that found in a cerebral tumour in a similar site.

Encephalitis

The C.S.F. in the acute stage is under pressure, it is clear, and there is never a coagulum. A small lymphocytic pleocytosis with a slightly raised protein and a normal chloride content are found. The sugar level may be somewhat raised.

Syphilis

Primary.—A small proportion of patients with primary syphilis show a slight increase in the number of lymphocytes, together with a positive Wassermann reaction in the fluid before treatment. Few cases continue to give these findings after a normal course of treatment, but if these changes persist treatment should be continued, as in most instances the fluid will return to normal.

Secondary.—The C.S.F. shows an increase of cells up to about 50 per c.mm. composed almost entirely of lymphocytes, a slight increase in protein content, and a positive Wassermann reaction. The Lange test shows a mid-zone curve of the type 0012332100, but it is of no special significance. Rarely a spinal block caused by an inflammation of the meninges—an arachnoiditis—may be found, and give results similar to those seen in a spinal tumour, together with a pleocytosis and a positive Wassermann.

Tertiary.—There are three common types of disorder—namely, meningo-vascular syphilis, tabes, and general paralysis of the insane (G.P.I.). Table IV shows the results that

TABLE IV.—*The C.S.F. in Syphilis*

	Meningo-vascular	Tabes	G.P.I.
Pressure	Normal or slightly raised	Normal or slightly raised	Normal or slightly raised
Appearance	Clear and colourless	Clear and colourless	Clear and colourless
Cells	20-150/c.mm.	10-50 c.mm.	10-50/c.mm.
Type of cell	Mostly lymphocytes, few large mononuclears	Lymphocytes, a few large mononuclears	Usually lymphocytes and large mononuclears
Protein	Usually up to 100 mg./100 ml.	Usually up to 100 mg./100 ml.	50-150 mg./100 ml.
Globulin	Positive (+)	Positive (+ +)	Positive (+ +)
Lange test	Variable but usually mid-zone	Leutic, i.e., mid-zone (0012332100)	Paretic, i.e., 1st stage (5544322110)
Wassermann reaction:			
C.S.F.	+	++ (in 70%)	+++ (in 100%)
Blood	+++	+++ (in 65%)	+++

may be found in each of these conditions. It must be remembered that it is not always possible to place a patient in one of these categories with absolute accuracy following the first lumbar puncture, and it may be only after treatment or after a period of time that the correct diagnosis can be determined. The Lange test in particular does not always conform to pattern, and paretic curves such as 5544322110 may be found in meningo-vascular disease. Should, however, such a curve persist despite treatment a revision of the original diagnosis may be advisable. It is also noteworthy that a positive Lange curve of any pattern will change much more readily as a result of treatment in a patient with meningo-vascular syphilis than in either of the other two forms of this disease. The strength of the Wassermann reaction is indicated by the number of positive signs. Here again, treatment in meningo-vascular disease will reduce the strength of the Wassermann reaction faster in the C.S.F. than in the blood, and both will respond much more quickly in this type of disorder than in tabes or G.P.I. Fluids from these last two types of case may retain a positive Wassermann reaction in the blood or in blood and fluid, and an abnormal Lange test long after the patient improves clinically. The Wassermann reaction in the C.S.F. is positive in syphilitic conditions only, but a negative test does not exclude syphilis except for G.P.I. The other abnormal findings in the fluid in syphilis may be seen in some other conditions such as disseminated sclerosis, meningeal spread of a secondary carcinoma, sarcoidosis, and torulosis.

Congenital.—No alterations from the normal may be found in the fluid from some patients. Cases of clinical

tabes or G.P.I. will often show findings comparable to those found in acquired syphilis. Treatment only results in slow improvement in the pathological findings.

Disseminated Sclerosis

Characteristic changes may be found in this condition, one of which is a raised cell count of up to about 50 per c.mm. While lymphocytes largely predominate, a few fluids will also contain polymorphs in small numbers. The protein is rarely raised above 100 mg. per 100 ml., but the globulin test (Nonne-Apelt reaction) is almost always positive. The Lange test is abnormal in some 40-50% of cases and shows either a mid-zone or a paretic curve, the former occurring twice as often as the latter. The Wassermann reaction is always negative.

A paretic curve in the absence of a positive Wassermann reaction occurs only in disseminated sclerosis, inclusion-body encephalitis, and a few cases of encephalitis lethargica.

Cerebral Tumour

Lumbar puncture in cases of cerebral tumour is open to certain obvious dangers. Before removing C.S.F. it is essential to measure the fluid pressure, and to ensure by jugular compression, with a consequent rapid rise in pressure, that there is no herniation of the cerebellum into the foramen magnum. Great care must always be exercised in performing lumbar puncture in patients with a suspected cerebral tumour, and in general it is probably wiser to delay making this examination until the patient is in hospital, where operation can follow lumbar puncture should the need arise. Frequently the fluid pressure is raised, and any pressure above 200 mm. can be regarded as pathological. Examination of the fluid may show it to be quite normal. There is a raised cell count in some 5% of cases, which may be due to polymorphs as well as lymphocytes, and in a few cases even tumour cells may be found. The protein content is raised in some 75% of cases. On the whole the more innocent tumours tend to show a lower protein level, but there are exceptions to this rule. A glioma of the pons gives rise to a low protein, whereas a neurofibroma of the eighth cranial nerve is always associated with a raised protein content. Fluids from cases of tumours near the lateral ventricle have a higher protein content than do those associated with tumours above the tentorium and near the surface of the brain.

Spinal Tumour

The measurement of the C.S.F. pressure and the result of the Queckenstedt test are very important in this condition. There is no rise in pressure after jugular compression in a complete spinal block, while should the block be partial the rise will be slow, and the fall to the original level will also be slow. The initial pressure may, in fact, be low, figures of 40 mm. being not uncommon. The fluid, while it may be clear and colourless, is on some occasions straw-coloured and may clot spontaneously. Cells are not increased except in such conditions as meningeal sarcomatosis. The protein content is always raised in complete block, with figures even as high as 2,000 mg. per 100 ml. In partial block the protein content is raised, but rarely above 300-400 mg. per 100 ml. The Wassermann reaction is always negative, except in cases of syphilitic spinal arachnoiditis.

Other Conditions

There are numerous other disorders in which the examination of the C.S.F. may yield instructive results. For instance, in subarachnoid haemorrhage a fluid intimately mixed with blood will be obtained and, should the bleeding have occurred three days or more prior to lumbar puncture, the fluid after centrifugation will show a yellow coloration and a positive indirect van den Bergh reaction.

The examination of the C.S.F. for barbiturates in cases of poisoning by these drugs, and for urea and sugar in cases of coma from uraemia or diabetes, may also be mentioned as examples of some of the less common investigations that can be carried out.

The pathologist, provided he is aware of the possible clinical diagnosis, should be able, as a result of his examination of the C.S.F., to express a reasonably confident opinion on the nature of the disease process. There are, however, some neurological conditions which may still baffle both the practitioner and the pathologist, but these will probably be seen only at very infrequent intervals by any one practitioner.

Next article on Clinical Pathology.—"Simple Skin Pathology," by Dr. John O. Oliver.

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APPROVED NAMES

The General Medical Council has authorized the following "approved names" of drugs, selected by the British Pharmacopoeia Commission. The last supplementary list was published in the *Journal* of December 12, 1953 (p. 1321).

Approved Name	Other Names
Aminopterin sodium	Sodium 4-aminopteroylglutamate.
Bacitracin	An antibiotic produced by a strain of <i>Bacillus subtilis</i> .
Benzathine penicillin	<i>NN'</i> -dibenzylethylenediamine di-benzylpenicillin. "Dibencil," "Neolin," "Penidural," "Permapen."
Benzethonium chloride	Benzylidimethyl- <i>p</i> -(1:1:3:3 - tetramethylbutyl)phenoxyethoxyethylammonium chloride. "Phemeride," "Phemerol chloride."
Dehydrocholic acid	3:7:12-Trioxocholanic acid. "Decholin," "Dehydrocholin."
Dichloroxylenol	2:4-Dichloro-3:5-xyleneol.
Dihydrotachysterol	"A.T. 10."
Dyfos	Diisopropyl fluorophosphonate. "DFP."
Erythromycin	An antibiotic produced by a strain of <i>Streptomyces erythreus</i> . "Erythrocin," "Ilotycin."
Fumagillin	An antibiotic produced by certain strains of <i>Aspergillus fumigatus</i> .
Nicotinyl alcohol	3-Pyridylmethanol. "Ronicol" is the tartrate.
Pentolinium tartrate	Pentamethylene-1:5-bis-(1-methylpyrrolidinium tartrate). "Ansolysen."
Primaquine	8-(4-Amino-1-methylbutylamino) - 6-methoxyquinoline.
Reserpine	An alkaloid obtained from <i>Rauwolfia serpentina</i> Benth. "Serpasil."
Sodium acetizoate	Sodium 3 - acetamido-2:4:6-triiodobenzoate. "Diaginol."
Tetracycline	4-Dimethylamino-1:4:4a:5:5a:6:11:12a-octahydro-3:6:10:12:12a-pentahydroxy-6-methyl-1:11-dioxonaphthacene - 2 - carboxamide. "Achromycin."
Tretamine	2:4:6-Tri(ethyleimine)- <i>s</i> - triazine. "Triethanamelamine," "Triethylene melamine," "TEM."