

THE VALUE OF THE EXAMINATION OF THE CEREBROSPINAL FLUID IN THE DIAGNOSIS OF INTRACRANIAL TUMOURS

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Examination of the lumbar cerebrospinal fluid in the diagnosis of cerebral tumour is less often resorted to than formerly, partly because in some instances there may be a risk of coning after lumbar puncture, but more especially because arteriography and ventriculography are now more frequently used for locating the tumour and examination of the ventricular fluid is often found to be more convenient. Nevertheless, if adequate precautions are taken, the examination of the lumbar cerebrospinal fluid is also not without its use in differential diagnosis.

In 1954 the authors read a paper at the 2nd International Congress of Clinical Pathology at Washington on some findings, including the presence of tumour cells, in the cerebrospinal fluid obtained from patients with cerebral tumours. Since then Locoge and Cumings (1958) have reviewed their results in over 12,000 fluids examined, and of these 835 were from patients with various types of intracranial tumour. The present paper records the findings in a total of 916 patients with histologically verified intracranial tumours of certain types seen at the National Hospital, Queen Square, between 1936 and 1957, and at Maida Vale between 1950 and 1957. Attention has been directed to the cell count and to the total protein content, with special reference to the finding of tumour cells and to the sugar content of the fluid.

Method and Material

Cerebrospinal fluid was obtained before operation and the cells counted in a Fuchs-Rosenthal chamber. The method of Mestrezat as given by Greenfield and Carmichael (1925) was used for the protein estimation. The sugar content was estimated by the method of Folin and Wu (Harrison, 1930).

During the past few years films have been prepared from a centrifuged deposit of cerebrospinal fluid in all likely cases of tumour, and these, after rapidly drying and fixing in methyl alcohol, have been stained by Leishman's method, which in our hands

has yielded better results than Papanicolaou's method. The principal groups of tumours investigated are set out in Table I to some extent anatomically; thus the gliomata from the cerebral hemispheres come first, followed by the tumours of the cerebellum, acoustic neuromas, meningiomas, tumours of and around the pituitary, and finally metastatic carcinoma.

Results

Table I records the results of the cell count and the protein content in the fluids from patients with various tumours listed according to their site and nature.

It has been found in this series, as in that of Locoge and Cumings (1958), that pleocytosis is most commonly seen in gliomas.

On a percentage basis, however, there was little difference between the cell count in a malignant glioma (astrocytic glioma, Kernohan grading III and IV) and in metastatic carcinoma of the brain, for in both series the count was raised in 20% and exceeded 10 in just over 15% of cases. But the less rapidly growing astrocytic gliomas of the cerebrum (Kernohan grades I and II) showed appreciably lower figures, not substantially different from those found in a small series of cases of oligodendroglioma. Rapidly spreading tumours involving the corpus callosum or the optic chiasm were especially associated with high cell counts.

A raised count appears to be of serious import and suggests that the tumour is in contact with the ventricles; if, in addition, the fluid is tinged yellow, necrosis or haemorrhage should be suspected and this is usually indicative of malignancy.

As to the nature of the cells as seen in the counting chamber and in films stained by Leishman's method after fixation in methyl alcohol, they are usually neutrophils, lymphocytes, and histiocytes, including compound granular corpuscles. The presence of the latter two types

TABLE I
CELL COUNT AND PROTEIN CONTENT IN VARIOUS TUMOURS

Percentage of Cases with			Number of Cases	Variety of Tumour	Percentage of Cases with		
5 Cells or Over per c.mm.	10 Cells or Over per c.mm.	20 Cells or Over per c.mm.			50 mg. Protein/100 ml. or Over	100 mg. Protein/100 ml. or Over	200 mg. Protein/100 ml. or Over
6.7	6.7	6.7	15	<i>Tumours sited in cerebrum :</i>			
8.9	5.1	3.8	79	Oligodendroglioma	40.0	26.7	Nil
				Astrocytoma (Kernohan's grade I and II)	51.9	24.1	8.9
20.4	15.7	10.5	172	Glioblastoma (Kernohan's grade III and IV)	67.4	31.4	14.5
13.3	6.7	6.7	30	<i>Glioma pontis</i>	63.3	30.0	6.7
				<i>Tumours sited in cerebellum :</i>			
12.5	6.2	6.2	16	Astrocytoma	68.6	31.3	18.8
9.1	4.5	4.5	22	Haemangioblastoma	54.5	27.3	13.6
13.3	6.7	Nil	15	Medulloblastoma	46.6	6.7	6.7
4.0	Nil	"	50	<i>Acoustic neuroma</i>	98.0	84.0	58.0
4.8	0.8	"	126	<i>Meningioma</i>	73.8	33.3	7.9
				<i>Tumours involving sella turcica :</i>			
12.8	8.5	4.3	47	Chromophobe adenoma	74.5	38.3	6.4
Nil	Nil	Nil	10	Eosinophil adenoma	80.0	40.0	Nil
11.5	3.8	3.8	26	Craniopharyngioma	61.5	30.4	15.4
20.4	15.3	8.5	59	<i>Secondary carcinoma</i>	74.5	33.9	10.4

betokens probable necrosis in the tumour and the adjacent brain tissue, while a lymphocytic pleocytosis indicates a reaction on the part of the adjacent ependyma or pia arachnoid.

Tumour cells have been identified in 17 fluids, but only in the last six years or so has a serious search been made for such cells. An account of 13 of these cases will be given.

Astrocytes or glioblasts were only once identified in the spinal fluid and the tumour was subsequently proved to be an astrocytic glioma (Kernohan grade IV).

Case 1 (N.H. 62675).—A married woman of 40 years, under the care of Mr. Wylie McKissock, gave a two-month history of headache and vomiting associated with mental deterioration and followed by confusion and weakness of the legs for three weeks and one attack of unconsciousness 11 days before admission. On examination, long-standing papilloedema, but no other cranial nerve defects, was found. Some weakness and slight incoordination in the arm and face and a trace of aphasia were noted. Ventriculography showed a filling defect in the left anterior horn extending to an area of calcification in the left mid-frontal region. At operation a large astrocytoma grade IV (Professor W. Blackwood) was found and partly removed from the left frontal region. Necropsy confirmed the clinical findings. The left ventricular fluid contained 1,500 tumour cells per c.mm. (Fig. 1) and 240 leucocytes per c.mm. The protein was 170 mg. per 100 ml.

We have not identified tumour cells in the lumbar cerebrospinal fluid in cases of hemisphere ependymoma or oligodendroglioma, but in one instance of the latter where the tumour was located in the right frontal lobe, tumour cells

resembling epithelial cells were found in the ventricular fluid.

Case 2 (M.V. 36241).—A woman aged 42 was admitted under the care of Dr. P. Sandifer with a history of lack of concentration, failing memory, confusion over a period of two months, and headache.

On admission she was found to be severely demented and resistive with a left hemiparesis maximum in the arm, early papilloedema, and probably left hemianopia. An accurate assessment of sensory changes was not possible. The E.E.G. indicated a deep-seated lesion in the right frontal lobe near the midline. The right ventricular fluid was blood-stained, with a faintly yellow supernatant fluid and 90 cells per c.mm., most of them being mononuclears with centrally placed nuclei and swollen cytoplasm. In the counting chamber both the nuclei and the cytoplasm of the cells were unusually refractile and prominent, and small clusters were occasionally seen. They gave the appearance of being epithelial cells. The erythrocyte count was 980 per c.mm. and the protein value 225 mg. per 100 ml. The left ventricular fluid showed cells of similar appearance which numbered 70 per c.mm. There were very few erythrocytes. The protein content was 70 mg. per 100 ml., but the supernatant fluid was faintly yellow.

At operation (Mr. Valentine Logue) an oligodendroglioma was found in the head of the right caudate nucleus extending out into the frontal lobe and also backwards.

There were no significant differences in the cell counts as between cerebellar astrocytomas, medulloblastomas, or glioma pontis, and in no instance of tumour in these situations were malignant cells identified in the fluid. The medulloblastoma, however, by reason of its situation and undifferentiated character could be

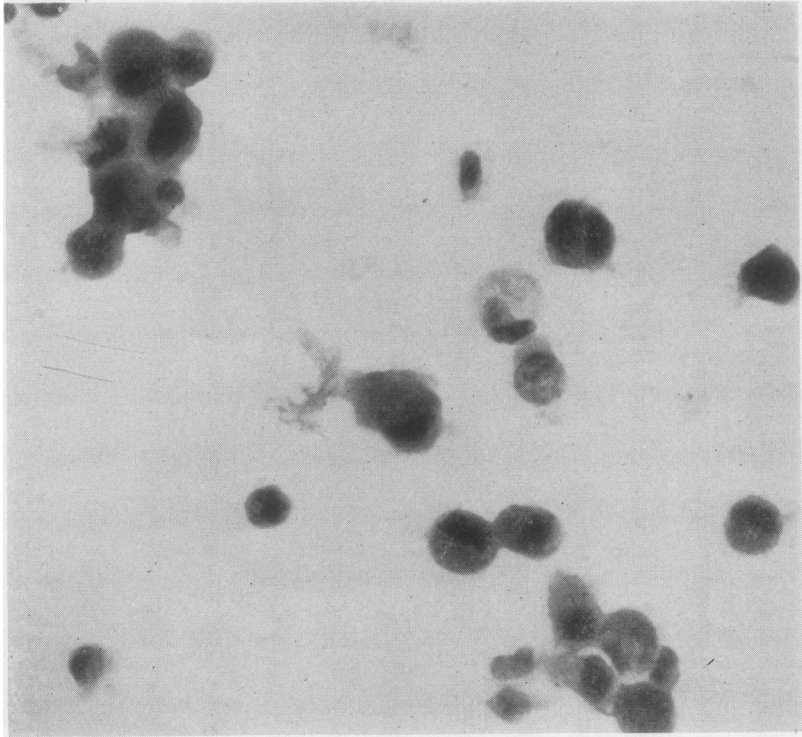


FIG. 1.—Case 1: Cells of astrocytic glioma (Kernohan grade IV), $\times 720$.

expected frequently to shed tumour cells into the subarachnoid space, for in the absence of prophylactic radiation seeding frequently occurs along the cerebrospinal axis. The number of cases in the series, however, was but 15 and only in one did the count exceed 5 cells per c.mm. The cell count was raised in cerebellar haemangioblastoma less frequently than in astrocytoma or medulloblastoma.

In lumbar fluids from cases of chromophobe adenoma the cells have appeared to be mostly lymphocytes although some neutrophils have also been seen. In one instance, however, where the count was only 14 per c.mm., tumour cells were identified in the deposit and in their disposition were thought to bear some resemblance to the structure of a chromophobe adenoma.

Case 3 (M.V. 40801).—A man aged 27 was admitted under the care of Dr. S. Nevin with a two-year history of increasing irritability, loss of memory, obesity, and frontal headaches. More recent symptoms included drowsiness and deterioration in

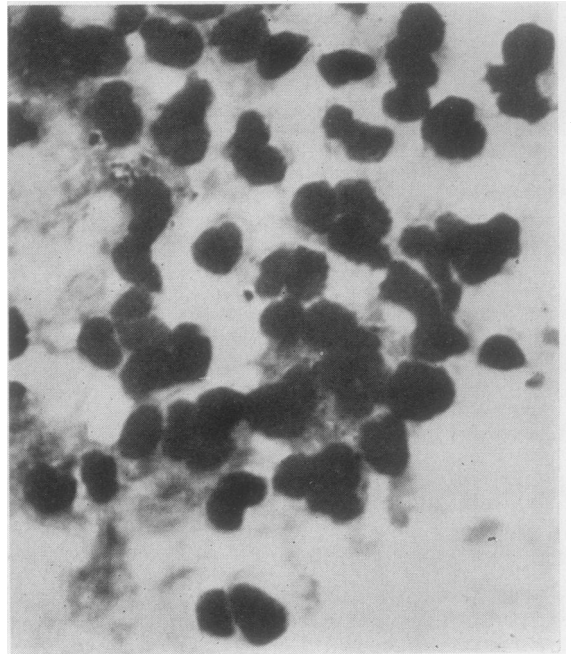


FIG. 2.—Case 3: Cells from chromophobe adenoma of the pituitary, $\times 850$.

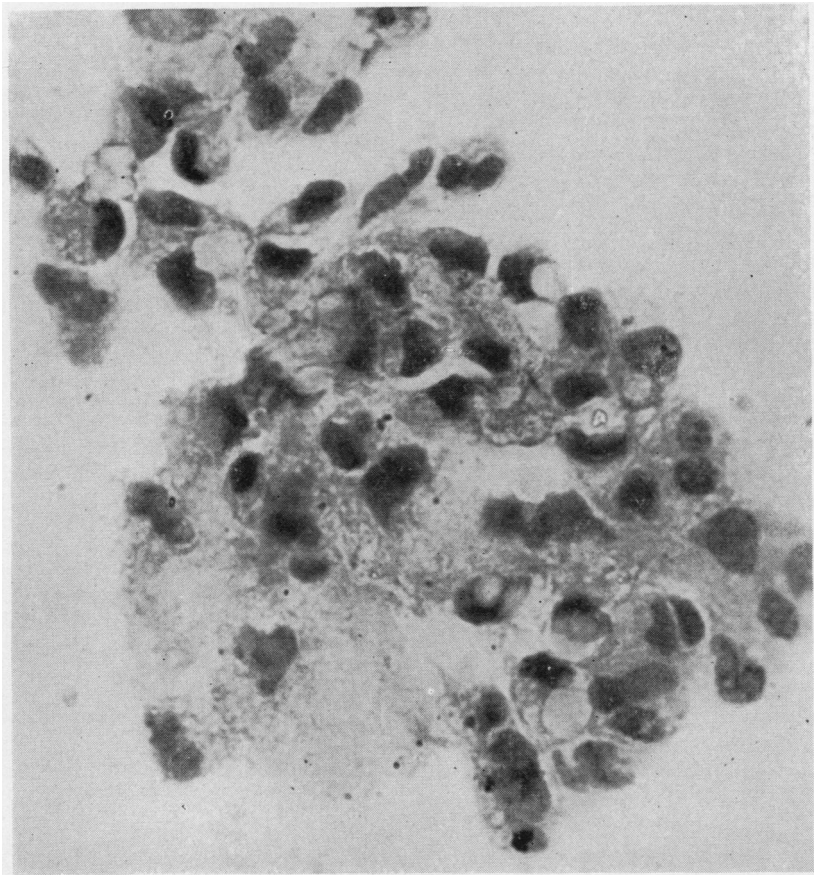


FIG. 3.—Case 4: A plaque of cells from a meningioma, $\times 750$.

visual acuity. Positive signs consisted of a right lower temporal quadrantic defect, right hemiparesis, left-sided anosmia, and a right pupil which was larger than the left, with a poor convergence reflex.

Radiographs showed considerable enlargement of the pituitary fossa with undercutting of the anterior clinoids (Dr. D. Sutton). Lumbar puncture revealed a pale yellow fluid with 14 cells per c.mm., tumour cells being found in clusters (Fig. 2). The protein was 183 mg. per 100 ml. An air encephalogram confirmed the presence of a pituitary tumour. At operation Mr. V. Logue found a large purplish tumour lying mesially below the right optic nerve, which was running an almost vertical course, and also laterally. Histologically it was a chromophobe adenoma.

The cell count in suprasellar tumours was found to be similar to that of the chromophobe adenoma, being raised in 11.5% of instances of the former and in 12.8% of the latter. In a small series of 10 cases of eosinophilic adenoma the cell count was normal in all.

In acoustic neuromas and in meningiomas the cell count was rarely raised, but, in one instance of the latter, masses of cells were found and identified as tumour cells.

Case 4 (N.H. 2454).—A man of 54, under Sir Charles Symonds, had suffered for seven years from attacks of feeling as though he were losing consciousness associated with an inability to speak. When first examined in 1947 there was a slight facial weakness with increased arm jerks. Uncinate fits were considered a likely diagnosis. In 1954 he had intense pain on the left side of the head, tinnitus, dysphasia, dysgraphia, and some degree of impairment of comprehension. Motor power was good but tendon jerks were increased. There was slight papilloedema. The lumbar cerebrospinal fluid contained 1 cell per c.mm. and the protein was 140 mg. per 100 ml. (Fig. 3).

At operation (Mr. Wylie McKissock) a meningioma on the outer wing of the left sphenoid was found and removed. The patient remains well.

Carcinoma cells were probably present in most of the 20% of cases of secondary carcinoma of the brain in which the cell count was 5 per c.mm. or over, but only in a small proportion have we recognized them as such. Not all of the cells found in the cerebrospinal fluid in cases of carcinoma of the central nervous system were neoplastic; neither may the cell count be always raised. Secondary depositions of tumour around the subarachnoid space and ventricular space were particularly apt to cause a raised cell count and sometimes tumour cell desquamation. Tumour cells seem to be specially prolific when the cauda equina is secondarily involved by dissemination from higher up in the cerebrospinal axis.

The carcinoma cell is recognizable by reason of its bizarre character, its irregular and often massive nucleus, and its hyperchromatism. Cytoplasmic vacuolation is not infrequent, while mitosis is often observed. Vacuolation of the nucleus is less commonly found. Clusters of cells in which the irregularity in size of the individual cells can often be noted and multinucleate forms are common findings. A mucoid degeneration of the cytoplasm may occur with peripheral displacement of the nucleus, giving rise to "signet ring" forms. When such a change takes place in a multinucleated cell, the nuclei become scattered and displaced to the periphery in a mammillated fashion (Fig. 7).

In neurological hospitals a bronchial origin seems to be by far the most frequent cause of cerebral carcinomatosis.

It does not seem possible to identify the histological type of carcinoma from the appearance of the cells in the cerebrospinal fluid; nor is it always feasible to distinguish as between carcinoma and glioma cells.

The presence of mitosis must not in itself be accepted as evidence of malignancy, for just as endothelial cells may be encountered in pleural or peritoneal fluids in a stage of mitosis or in the form of a binucleated dividing cell so may they be found in cases of recovering meningitis. Carcinomatosis of the meninges bears a further resemblance to carcinomatosis of the pleural and peritoneal cavities because malignant cells, on account of their invasive propensity, may induce bleeding with subsequent discoloration of the fluid.

A few examples of the findings in cases of secondary carcinoma may be cited.

Case 5 (N.H. 64329).—A man of 44, under the care of Dr. M. Critchley, suffered from

headache for eight weeks, vomiting for four weeks, and double vision for two weeks. He appeared to have lost weight. The pupils were unequal, the left being larger, and both reacted to light slowly. There was a left-sided ptosis and some loss of eye movements on that side. There was a slight loss of sensation on the right side of the face. No other physical signs were present apart from slight clubbing of the fingers and toes. Death occurred four weeks later without further signs or evidence of any primary tumour. No necropsy was permitted. The cerebrospinal fluid contained 790 cells per c.mm., of which 60% were carcinoma cells (Fig. 4); the protein was 900 mg. and the sugar 16 mg. per 100 ml.

Case 6 (M.V. 33241).—A housewife, aged 53, was admitted to hospital under the care of Dr. R. A. Henson with a six months' history of general irritability with buzzing noises in the ears and later giddiness. A month later she developed a frontal headache, a sense of pressure over the eyes, photophobia, and frequent vomiting. For the previous few weeks she had complained of increasing unsteadiness on her legs. There was no history of mental deterioration, but her speech was said to be slurred, especially at night. During the week before admission she had been noted to be disorientated and confused and had complained that "things did not make sense."

The physical signs indicated a midline posterior fossa tumour, but the history of dysphasia suggested the possibility of there being other tumours too, but no likely primary source for them could be found.

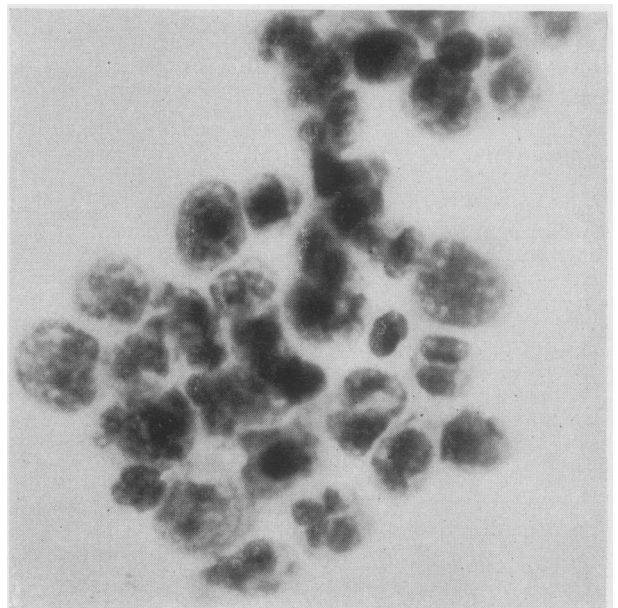


FIG. 4.—Case 5: A collection of carcinoma cells, $\times 950$.

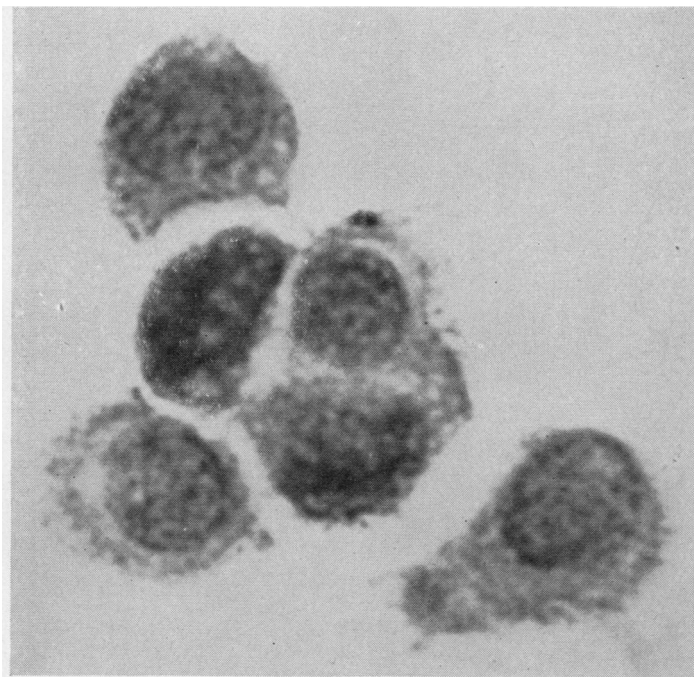


FIG. 5.—Case 6: Carcinoma cells (primary in lung), $\times 1,500$.

Cerebrospinal fluid (2.5 ml.) removed by lumbar puncture was blood-stained, the supernatant layer after centrifugation being pale yellow. There were 21 cells (Fig. 5) per c.mm. (neutrophils 60%, lymphocytes 25%, and tumour cells 15%), chlorides 705 mg., and glucose 55 mg. per 100 ml. The Wassermann reaction was negative. The pressure was 210 mm. The fluid from the left ventricle was clear and colourless, but 45% of 22 cells were deemed to be neoplastic. The protein was 20 mg. per 100 ml. Ventriculography revealed no evidence of a space-occupying lesion.

In a subsequent lumbar fluid sample with a cell count of 93 per c.mm., of which one third were tumour cells, the glucose level was only 30 mg. per 100 ml. At no time was papilloedema observed and a repeat ventriculogram failed to show more than a slight degree of dilatation of the lateral ventricles. The haemoglobin, blood count, and E.S.R. were normal, but a search of a blood film revealed a promyelocyte and two erythroblasts. There was no radiological evidence of bony metastases and no primary tumour was located. Death occurred one month later.

At necropsy a small softened (squamous) carcinoma was identified towards the periphery of the lower lobe of the right lung, with carcinomatosis of the leptomeninges. No other metastases were identified. Other pathological findings were healed rheumatic carditis, healed tuberculous adenitis of the mesentery, cholelithiasis, and early biliary cirrhosis.

Case 7 (M.V. 26360).—A cigarette smoker, aged 42, was admitted under the care of Dr. S. Nevin with a six weeks' history of a steadily progressing weakness of the right leg and tingling in the right calf. Within a week the symptoms had spread to the opposite side. Three weeks before admission he complained of aching in the back of the neck followed by pain behind the left eye and transient diplopia.

On examination, he was found to have signs consistent with a cauda equina lesion and, in addition, left-sided ptosis, diplopia on looking down, and left dysphasia. The blood count and the E.S.R. were both normal. Four cerebrospinal fluids were examined, with results seen in Table II.

Although this patient had a left hilar shadow at the time of the first lumbar puncture, tumour cells were not identified until the third fluid was examined.

Necropsy confirmed the presence of a bronchial oat-cell carcinoma in the left upper lobe with extensive deposits in the cauda equina which were thought to have spread from a metastasis involving the left caudate nucleus and choroid plexus. There were several other small metastases in the brain and

also in the liver, thyroid, pancreas, kidneys, adrenals, left hilar, left subclavicular and bilateral cervical lymphatic nodes, and in the diaphragm.

TABLE II
RESULTS IN CASE 7

Date of specimen ..	6/2/52	21/2/52	24/3/52	17/4/52
Appearance ..	Colourless	Faintly yellow	Faintly yellow	Yellow
Cells per c.mm. ..	22	90	93	43
R.B.C.s per c.mm.	10	42	< 10	2,794
Protein (mg. per 100 ml.)	200	360	200	360

Case 8 (M.V. 40245).—A man aged 34, with a variety of recent occupations, a liking for dog racing and an "intermittent" smoker, was admitted under the care of Dr. Helen Dimsdale with a six weeks' history of headaches, stiffness of the neck, and deterioration of vision. For the past two weeks he had had episodes of vomiting.

On examination, he was drowsy and confused, with a slurring dysarthria. There was gross papilloedema, nystagmus both to right and left, a complete left and partial right abducens paralysis, bilateral depression of the corneal reflex more on the left than on the right, left facial weakness, deafness on the left, and bilateral extensor responses but with limb hypotonia. There was bilateral ataxia.

In view of the possibility of an acoustic neuroma, he was transferred to the care of Mr. Valentine Logue. A right frontal burr hole yielded at a depth of 4 cm. clear and colourless fluid under a pressure of 100 mm. which revealed 7 cells and 393 erythrocytes per c.mm., a protein level of 18 mg. per 100 ml. and a glucose level of 70 mg. per 100 ml. On centrifuging, this slightly hazy fluid became clear and was colourless. The cells, apart from a very occasional neutrophil, included lymphocytes and what were thought at first to be arachnoidal cells. These cells had a clear cytoplasm and a rather pyknotic nucleus usually displaced to the periphery. The Lange and Wassermann reactions were negative. A ventriculogram suggested a communicating hydrocephalus, but no clear evidence was obtained of an expanding lesion.

The lumbar fluid three days after ventriculography contained 42 cells and 560 erythrocytes per c.mm., the supernatant layer being pale yellow. The cells consisted of 5% neutrophils, 35% lymphocytes, and 60% "arachnoidal" cells, some of which were actively dividing. The protein was 55 mg. and the glucose 55 mg. per 100 ml. Three days later the cell count was 48 per c.mm. and the cytology substantially the same, but the protein was now 310 mg. per 100 ml. and the glucose only 21 mg. per 100 ml. Several of

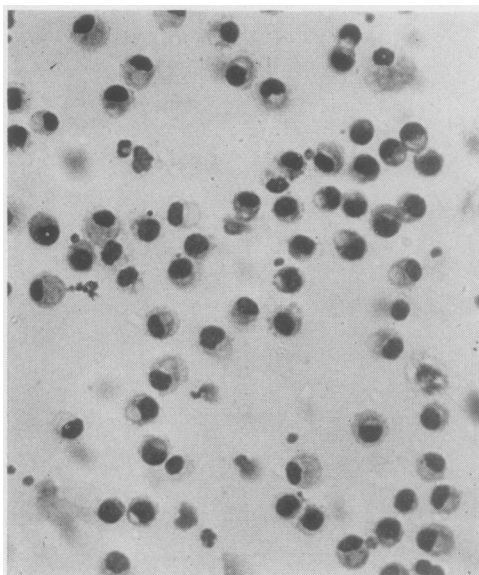


FIG. 6.—Case 8: Large numbers of carcinoma cells with signet ring forms, $\times 550$.

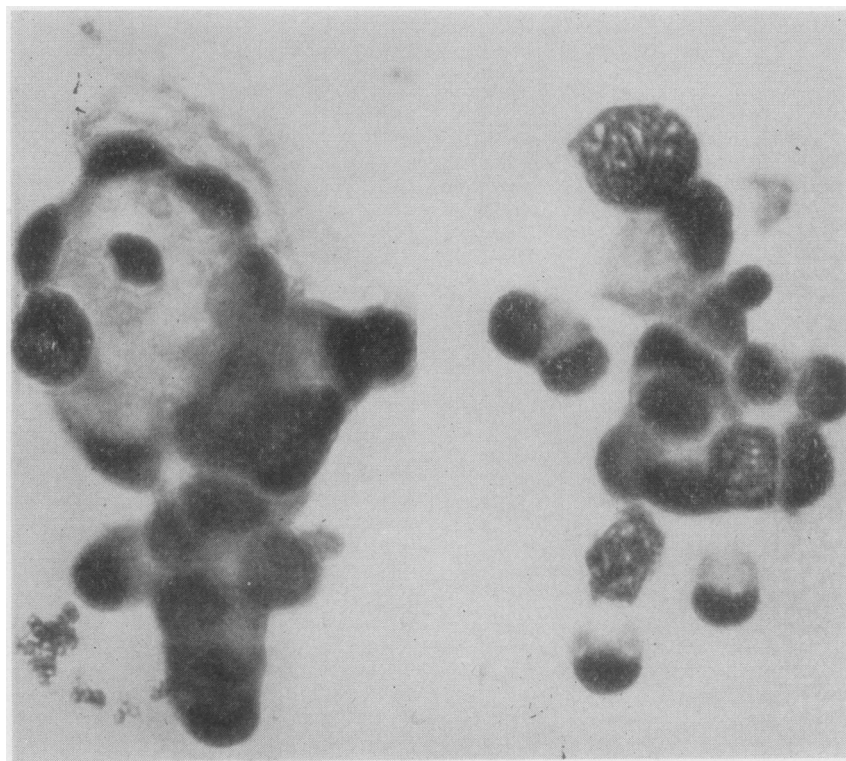


FIG. 7.—Case 8: A small clump of cells from the same case as Fig. 6, $\times 750$.

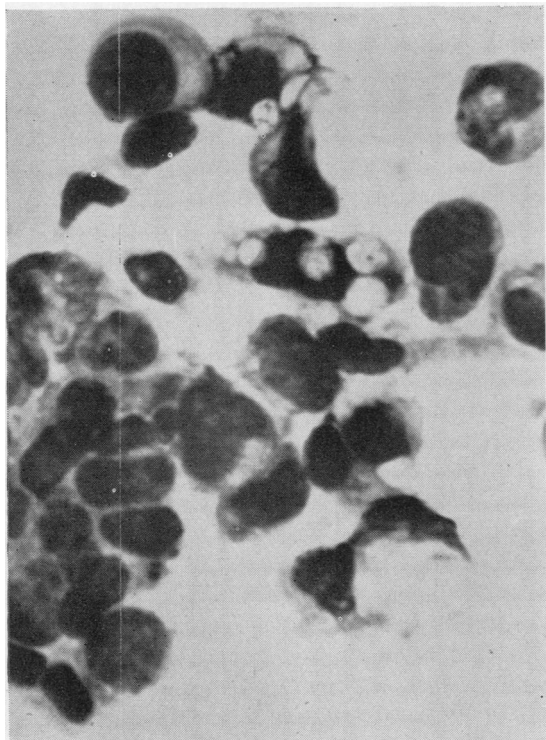


FIG. 8.—Case 9: A group of carcinoma cells, $\times 1,150$ (primary in bronchus).

the cells were showing cytoplasmic vacuolation and some of the nuclei were larger than others and pyknotic. Carcinomatosis was by now regarded as the only probable diagnosis. As subsequent specimens were examined the cells become more certainly malignant and true signet ring forms were common (Figs. 6 and 7). Cells also appeared in clusters and there were many dividing forms. Two weeks after admission the cell count was 35 per c.mm. and the protein level 125 mg. per 100 ml.

Fluid in the right ventricle was by now faintly smoky with 23 cells per c.mm., mostly neoplastic, and 650 erythrocytes. The glucose level was 70 mg. per 100 ml., but varied from time to time, falling to 17 mg., and bore little reference to the tumour cell count. Death occurred one week later. At necropsy the brain showed an extensive meningeal carcinomatosis, but the primary source of the tumour was not identified. The carcinoma cells were at times arranged in imperfect alveoli and the cytoplasm was both plentiful and clear. At other times the cells resembled signet rings or they sometimes conformed to tall columnar epithelium.

Case 9 (M.V. 40915).—A widow, aged 58, was admitted under the care of Mr. Valentine Logue with a history of cough, pain, and dyspnoea extending over a period of 17 months. In another hospital bronchoscopy had revealed a probable carcinoma of the left

lower lobe bronchus, but the histological findings were inconclusive. There was an associated basal pleural effusion. Further biopsies were again inconclusive, but pleural aspiration revealed cells suggestive of neoplasia.

Progressive drowsiness and loss of weight had developed during the two months before the present admission and a previous lumbar puncture had yielded a fluid with 60 cells ("lymphocytes") per c.mm. and 200 mg. protein per 100 ml. She was found to have, in addition to the marked drowsiness, left hemianopia, neck stiffness, increased left upper limb reflexes, and a right-sided grasp reflex.

Lumbar puncture revealed a slightly yellow fluid with 43 cells and 56 erythrocytes. The cells consisted of lymphocytes and tumour cells in about equal numbers (Fig. 8). The protein was 170 mg. and the glucose level 45 mg. per 100 ml. Two days later the cells were 55 per c.mm. and the glucose level 23 mg. per 100 ml. Equivocal pathology, similar to that found in the thoracic biopsies, was revealed in the piece of brain obtained from the ventricular needle.

At necropsy a massive sclerosing carcinoma was found in the mediastinum encircling the left lower bronchus. The brain showed a generalized opacity of the meninges due to the presence of atypical carcinoma cells, together with a metastasis in the right fornix invading the corpus callosum and involving the choroid plexus. There was, in addition, a widespread infiltration of the brain-stem by malignant cells. This case will be reported in greater detail.

Case 10 (M.V. 29621).—A machine operator, aged 44, was admitted under the care of Dr. P. Sandifer, with a six weeks' history of occipital pain associated with some stiffness of the neck. In the course of a few days the pain had spread over the left shoulder and down the arm and into the palm and all the fingers. Later, there had been a progressive weakness of the legs and a heavy numbness "like lead" associated with dysuria. Eventually a weakness of the right arm had developed.

On examination, he was noted to be a wasted man with early clubbing of the fingers. There was evidence of involvement of the roots of C5, C6, and C7 on both sides and of the cauda equina.

Cisternal puncture found a fluid faintly smoky and yellow. There were 31 cells per c.mm., 10% of which were malignant, and 853 erythrocytes. The protein was 130 mg. per 100 ml. The lumbar fluid was heavily blood-stained, the supernatant fluid being faintly yellow. There were only 48 cells counted against 10,240 erythrocytes, but they included a large proportion of malignant cells. The protein was 480 mg. per 100 ml. Radiographs revealed a rounded opacity at the left hilum suggestive of a carcinoma, while a myelogram showed multiple lateral indentations and filling defects in the region of C6-C7 on the right and C4-C5 on the left. He was referred for deep x-ray treatment and died in another hospital, no necropsy being sanctioned.

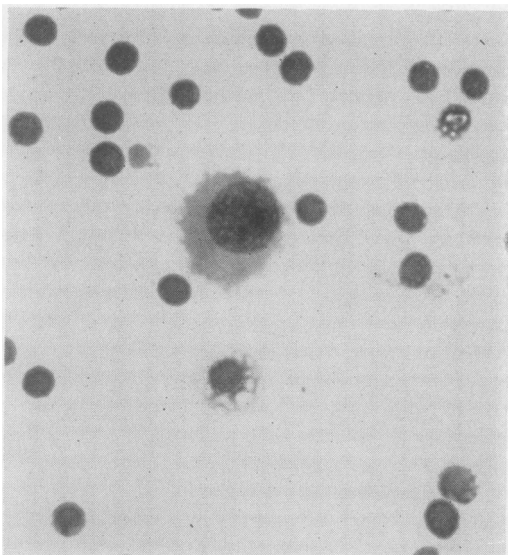


FIG. 9.—Case 11: A single melanoma cell (secondary melanotic metastasis), $\times 750$.

Case 11 (N.H. 53106).—A married woman of 28, under the care of Mr. Wylie McKissock, had had a malignant melanoma removed from the left calf nine months earlier. A block dissection of glands had also been carried out. Five months before admission she had a normal child, but during the past four weeks had had lassitude and headache for five days. Later, vomiting and meningismus were prominent features. On examination, she was drowsy with neck stiffness, bilateral ptosis, and slight weakness in the arms and legs. Plantar responses were extensor and some hyperalgesia and hyperaesthesia of the legs were found. Ventriculography suggested a space-occupying lesion in the left frontal region. The right ventricular fluid showed 320 cells per c.mm., mostly tumour cells, suggestive of an origin from a melanoma and with a protein of 65 mg. per 100 ml. (Fig. 9).

The findings in two other patients will be mentioned, for tumour cells were found in the cerebrospinal fluid of both, although neither had a brain tumour.

Case 12 (M.V. 36211).—A warehouse worker, aged 64, under the care of Sir Russell Brain, had had several previous admissions to hospital on account of right temporal headache and symptoms and signs over a period

of about four years, pointing to an expanding lesion compressing the anterior surface of the medulla and pons. The cerebrospinal fluid initially was under normal pressure with 4 cells per c.mm. and a protein content of 68 mg. per 100 ml. At the penultimate admission, however, the lumbar fluid had shown 11 cells ("small lymphocytes with occasional large mononuclears") and a protein content of 92 mg. per 100 ml. During his last admission the burr holes already present were re-entered and the fluid on both sides was found to be under considerable tension. That on the right was examined; the cells numbered fewer than 1 per c.mm. and the protein was 10 mg. per 100 ml. A catheter was inserted on this side. Before operation Mr. V. Logue tapped the left ventricle and the fluid was found to be faintly yellow with 22 cells per c.mm., a glucose level of 90 mg. per 100 ml., and a protein of 36 mg. per 100 ml. The cells were found to be neoplastic (Fig. 10), the most striking feature being a remarkable degree of cytoplasmic vacuolation in some of them. In addition there were occasional but noteworthy instances of intranuclear vacuolation (Dr. Helen C. Grant). Exploration revealed a large, whitish mucoid tumour seemingly arising from the basi-sphenoid and displacing the pons, medulla, and cord upwards and backwards. Histologically, it was a typical chordoma exhibiting the characteristic vacuolation both of the cytoplasm and of the nuclei.

The retrograde spread of the tumour cells had presumably been rendered possible on account of the high infratentorial pressure and the supratentorial drainage.

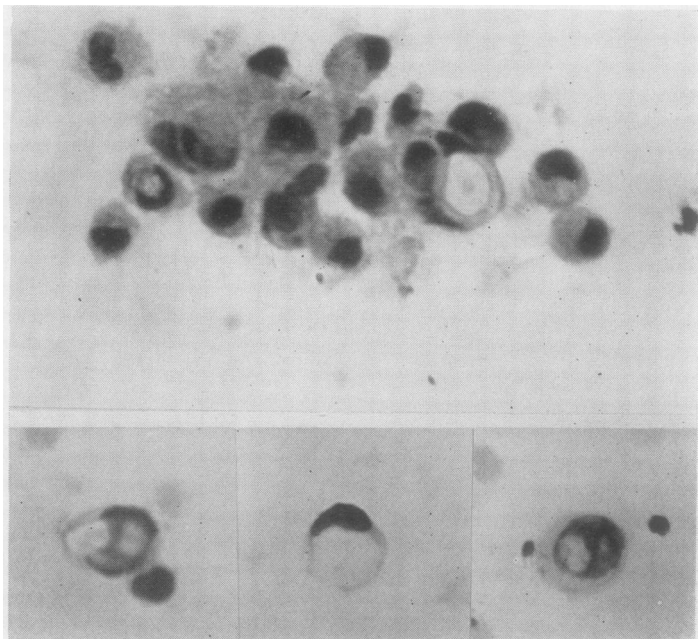


FIG. 10.—Case 12: Tumour cells from an intracranial chordoma, $\times 700$.



FIG. 11.—Case 13: Typical plasma cells (spinal myeloma), $\times 750$.

Case 13 (N.H. 53471).—A man of 43, under Mr. Harvey Jackson, had suffered from paraplegia for three months. He had signs suggesting a lesion in the region of the fourth thoracic vertebra with pressure on the spinal cord. The report of the radiograph (Dr. J. W. D. Bull) showed partial destruction of the left pedicle of D5. At operation portions of an extradural tumour and of the surrounding muscle were removed and shown to be infiltrated by a plasma cell myeloma (Professor W. Blackwood). A very small amount of cerebrospinal fluid was obtained and contained 16 cells per c.mm. including numerous plasma cells (Fig. 11).

So far as the protein values are concerned, the most striking feature is the constancy with which a raised value is obtained in cases of acoustic neuroma. In only one out of the 50 cases was the protein level below 50 mg. per 100 ml., while a figure of 200 mg. per 100 ml. was exceeded in 58%. The tumour which next most frequently yielded a fluid with a protein level in excess of 200 mg. per 100 ml. was a cerebellar astrocytoma, this value being exceeded in 18.8% of cases. However, the tumour which in its ability to give rise to a protein content of over 50 mg. per 100 ml.

came next to the acoustic neuroma was the eosinophil adenoma of the pituitary at 80%, followed by the chromophobe adenoma and metastatic carcinoma both at 74.5%.

Discussion

In so far as the alterations in cell count and protein content in the cerebrospinal fluid are concerned, the findings in this group correspond closely with the results found by Locoge and Cumings.

Most interest, however, centres around the finding of neoplastic cells in the cerebrospinal fluid. Spriggs (1954) found malignant cells in the fluids of seven patients, and he collected from the literature 66 instances of malignant cells being recorded as present in the C.S.F., and, of these, 47 were in patients who were subsequently found to have secondary carcinomatosis.

The rarity with which tumour cells have been identified in the cerebrospinal fluid in cases of primary intracranial tumours is in contrast to the increasing frequency with which they have been recognized in meningeal carcinomatosis. We propose, therefore, to consider these groups separately.

Primary Intracranial Tumours.—The 21 reported instances in which malignant cells have been identified in the cerebrospinal fluid are recorded in Table III, and except where stated the fluids were obtained by lumbar puncture.

The cytological diagnosis of intracranial tumours other than carcinoma is a matter of some difficulty, because exfoliation seems to be much less frequent in the primary tumours, in spite of the fact that the cell count may often be raised, especially in malignant gliomas. The most important source of confusion is the macrophage, for abnormal degrees of swelling may be seen in this cell, especially in fluids which have been standing for any length of time. The advice of Cairns and Russell (1931) in this connexion should be heeded. The presence of mononuclear cells, they say, other than lymphocytes, should always arouse suspicion. But as with the carcinoma cell the criteria of recognition are the varying sizes of the cell, and in particular its nucleus, the presence of cytoplasmic vacuoles, and the degree of hyperchromatism. The presence of clumps of such cells is even more in favour of malignancy. A helpful point at times is an increased refractility. This was noted by Walt (1939) in his case of medulloblastoma and was useful in distinguishing these cells from lymphocytes. It was a feature noted in our case

TABLE III
REPORTED CASES OF MALIGNANT CELLS IDENTIFIED
IN C.S.F.

Author	Date	Site and Nature of Tumour
Rindfleisch	1904	Tumour of third ventricle
Loeper and Crouzon	1906	"Sarcoma of occipital lobe"
Sicard and Gy	1908	"Sarcoma of dura"
Guillain and Verdun	1911	Juxtaventricular glioma
Fischer	1922	Part 2, case 1, multiple tumour Case 3, glioma
Cairns and Russell . .	1931	Pituitary adenoma
Ostertag	{ 1932 1933 }	Spongioblastoma of cerebellum
Ford	1937	Medulloblastoma
Walt	1939	
Schroeder <i>et al.</i> . . .	1945	Glioma of cerebellum (ventricular fluid)
Platt	1951	Case 5, glioblastoma multi-forme (ventricular fluid) Case 6, perithelial sarcoma of cerebellum (cisternal fluid) or medulloblastoma
Larson <i>et al.</i>	1953	Case 4, astroblastoma III at R. hemisphere Case 5, astrocytoma II at posterior parietal
Spriggs	1954	Case 5, medulloblastoma Case 6, glioblastoma multi-forme involving pineal region and thalamus
McCormack <i>et al.</i> . . .	1957	Case 20, medulloblastoma Case 21, pinealoma Case 22, glioblastoma multi-forme
Adams	1958	Case 2, glioblastoma multi-forme

of an oligodendroglioma (Case 2). In general, it is safer to admit that glioma cells cannot with confidence be distinguished from carcinoma cells: the only definite exceptions are the myeloma cell and the signet ring cell, which latter suggests a carcinoma with a primary site in the bronchus or the gastro-intestinal tract.

In some instances, in a hemisphere ependymoma, for instance, tumour cells could be expected with greater frequency in the ventricular than in the lumbar fluid, but the reverse would normally obtain in an ependymoma in the fourth ventricle or in a medulloblastoma. Astrocytic glioma as well as other forms of cerebral tumour not infrequently involve the ependymal walls of the lateral ventricles so that cytological examination of the ventricular fluid may often prove to be more rewarding than the lumbar fluid.

On two occasions cells have been found in the cerebrospinal fluid which appeared to resemble astrocytes, and in one instance in which the cell count was raised a diagnosis of astrocytoma was suggested, but at necropsy the disease proved to be multiple metastatic carcinoma.

Secondary Intracranial Tumours.—Carcinoma cells were first identified in the cerebrospinal fluid by Dufour (1904). Since the review of the literature by Spriggs (1954) a few other workers have recorded finding these cells. McCormack,

Hazard, Belovich, and Gardner in 1957 found tumour cells in 17 cases, while Ravina, Pestel, and Thielen (1955) reported one case with tumour cells present but with no increase in total cell count. In the four cases described by Dodge, Sayre, and Svien (1952) the "large mononuclear cells" were not stated to be carcinoma cells as such, but in each instance the glucose content of the fluid was low. Others who have found carcinoma cells in the cerebrospinal fluid include Dattner (1952), Fischer-Williams, Bosanquet, and Daniel (1955), Reiseger (1956), and Heathfield and Williams (1956). As carcinoma cells have been found in fluids with no significant pleocytosis, a careful search of the centrifuged deposit will in such cases sometimes aid diagnosis. On the other hand, a carcinomatous involvement of the leptomeninges may excite a lymphocytic pleocytosis without any carcinoma cells appearing in the fluid. Strange (1952) found the cell count to be raised above 7 per c.mm. in 21 out of 30 fluids from 14 cases of meningeal carcinomatosis, but she makes no reference to the presence of malignant cells.

A low sugar content of the fluid was found by us on a number of occasions and this has also been observed in fluids when tumour cells had not been found during life, although necropsy later showed a carcinomatous meningitis. Other observers have commented on the low glucose content in cases of neoplastic disease of the meninges ever since Guillain and Verdun (1911) found sugar not detectable in the cerebrospinal fluid in one such case. This subject was discussed by Dodge *et al.* (1952), and they concluded that the fall was due in part to an acceleration of the metabolism of the tumour cells, and to a mechanical blocking of the blood-brain barrier so that crystalloids were not able to pass. Strange (1952) believed that carcinoma cells utilized glucose, but that stasis was also present. It seems to be generally agreed that when the glucose content is low the meningeal involvement is extensive. There is, however, no particular correlation between the number of tumour cells and the level of the glucose content in the fluid. Nevertheless, McCormack *et al.* (1957) advised an intensification of the search for malignant cells if the glucose content is found to be low, and our findings support this opinion. McCormack, Hazard, Gardner, and Klotz (1953) have reported figures as low as 11 and 13 mg. per 100 ml., McElligott and Smith (1958) record a value of 11 mg. per 100 ml., while Dodge *et al.* (1952) have noted a figure as low as 2.5 mg. per 100 ml., and both these last authors and Eaton (1952) report

cases in which no sugar was detectable. In 17 out of 18 cases of meningeal carcinomatosis studied by Berg (1953) the glucose content was below 50, while Strange in 18 recordings from seven cases found no value over 47 and one was as low as 9 mg. per 100 ml.

Other workers who have obtained figures for cerebrospinal fluid sugar of below 40 mg. per 100 ml. include Meissner (1953) in two cases, Murphy (1955) in one case, Jacobs and Richland (1951) in two cases, while Fischer-Williams *et al.* (1955) record a level of 50 mg. per 100 ml. and Reiseger (1956) a case with a level of 44 mg. per 100 ml.

Summary

The cerebrospinal fluid findings are reviewed in 916 patients with histologically verified intracranial tumours, the cell count and protein values being analysed according to the different categories of tumour, and their significance discussed.

Pleocytosis is most commonly found in glioma, but on a percentage basis it is as common in carcinomatosis of the brain. Tumour cells, however, are rarely found in gliomas but frequently in carcinoma.

Thirteen cases are reported in which tumour cells have been identified in the cerebrospinal fluid. They include instances of pituitary adenoma (only once previously described) and, for the first time, of oligodendroglioma, chordoma, and meningioma.

A falling glucose level is highly suggestive of carcinomatous meningitis and the search for tumour cells should be intensified. A cell count within the limits of normal does not exclude this diagnosis.

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