

## TUMOUR CELLS IN THE CEREBROSPINAL FLUID

BY

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The study of the cellular content of the cerebrospinal fluid (C.S.F.) from patients with diseases of the central nervous system, especially cerebral tumours, has required the use of a technique in which cell cytology is well preserved.

A newly developed method for preparing smears of the concentrated cells suspended in bovine albumin fulfils this requirement and has been used for the routine examination of these cells in conjunction with Leishman's stain.

During the course of studying preparations made from normal cerebrospinal fluid and from fluids obtained from patients with known lesions of the central nervous system we recognized three cell types, suggesting they be called M, G, and lymphocyte cells (Marks and Marrack, 1960).

In some of the pathological fluids additional cell types, which were readily recognizable, such as polymorphs, eosinophils, and plasma cells, appeared. In a few preparations, cells which fulfilled the criteria reviewed by Spriggs (1954) for neoplastic cells in the cerebrospinal fluid were seen and they had features very similar to those described for neoplastic cells in bone marrow (Undritz, 1952), peripheral blood (Pruitt, Hilberg, and Kaiser, 1958), and serous exudates (Spriggs, 1957).

When it is considered justifiable to do a lumbar puncture, the routine search for tumour cells in the fluid obtained is rewarding since their recognition, although implying a hopeless long-term prognosis, may save the patient the rigours of further investigations. In a few cases it may lead to the institution of therapy, which although only palliative, may restore to the patient a useful life of up to several years (Heathfield and Williams, 1956). Infrequent sporadic reports of cases in which neoplastic cells were recognized in the cerebrospinal fluid have appeared in the literature since Dufour (1904) recorded their first recognition. A large proportion of these earlier cases were recognized by the finding of clumps of cells in the counting chamber while making a routine cell count or by the wet film technique. This infrequency would seem not to

be due to the rarity with which tumour cells are exfoliated into the cerebrospinal fluid, but to the difficulty in making preparations suitable for their identification.

This paper records our experiences in 21 cases in which abnormal cells, considered to be neoplastic, were identified in the cerebrospinal fluid on one or more occasions.

### Methods and Material

Smears were made from the spun deposit obtained from all fresh specimens of cerebrospinal fluid sent to the laboratory for routine examination which contained more than 5 cells/mm.<sup>3</sup> during a period of 14 months by the following method.

The fluid remaining after a cell count has been made is placed in a conical centrifuge tube and spun at 3,000 r.p.m. for at least 10 minutes. The supernatant is tipped off by inverting the tube rapidly, and is used for determining protein, glucose, Wassermann reaction, etc. The inverted tube is placed mouth downwards on a piece of filter paper for 10 to 30 minutes so that all excess fluid is removed.

With a fine-bore Pasteur pipette (internal diameter about 0.5 mm.) 3-4  $\mu$ l. bovine albumin (Armour 30%)<sup>\*</sup> is introduced and thoroughly mixed with the deposit by gently tapping the bottom of the tube. (Recently we have obtained improved results by adding E.D.T.A.<sup>†</sup> (0.1%) to the bovine albumin.) This fluid containing the suspended deposit is taken up in the same pipette and placed on one or two glass slides previously washed in alcohol and dried. Smears are then made in exactly the same manner as employed for blood, using the edge of a slide as a spreader.

The films are dried as quickly as possible in air, fixed and stained with Leishman. Care must be taken not to blot or wipe the films once they have been stained. They may be kept indefinitely if mounted immediately in Gurr's neutral mounting medium<sup>‡</sup> which does not cause fading or alteration of the colour of the stained cells.

An alternative method for use when there is a very heavy deposit, as for instance in cases of purulent

<sup>\*</sup> Armour Laboratories, Hampden Park, Eastbourne, England.

<sup>†</sup> E.D.T.A. (disodium ethylene diamine tetra acetic acid), L. Light & Co. Ltd., Colnbrook, Bucks, England.

<sup>‡</sup> G. T. Gurr, Ltd., 136 New Kings Road, London, S.W.6, England.

meningitis, is to suspend the initial deposit in about 0.5 ml. of 10% bovine albumin and recentrifuge. Excess albumin is poured off and the tube left to drain for a few minutes only. The deposit is then taken up and smeared as before. This modification is necessary because it has been found that the natural stickiness of the white cells plus concentrated albumin makes the preparation of satisfactory slides impossible by the former method (Marks and Marrack, 1960).

Cells were counted and the protein concentration estimated in these fluids by the methods described by Greenfield and Carmichael (1925) and the glucose by a glucose-oxidase method (Marks, 1959).

### Results

The findings in cerebrospinal fluid in 17 cases are summarized in Table I. Four patients (Nos. 3, 9, 12, and 16) were known to have had primary malignant tumours outside the central nervous system previously treated surgically; in one patient (No. 13) the diagnosis was made by biopsy at the time that the cerebrospinal fluid was taken for examination. In a further seven patients (Nos. 2, 5, 6, 8, 10, 11, and 14) the diagnosis of neoplasia was made or

strongly suspected on cerebrospinal fluid cytology before confirmation by biopsy or necropsy was obtained; and in four (Nos. 1, 4, 15, and 17) the diagnosis has not been confirmed histologically, although in two of these patients air studies indicated a large suprasellar mass.

**Features of Cells Normally Found in Cerebrospinal Fluid.**—Fluids containing less than 5 cells per c.mm. have been considered normal, and their cells the normal constituents of cerebrospinal fluid, and we have been able to distinguish three types of cell (Fig. 1).

(1) *Lymphocytes.*—These are small, round cells, about  $10\mu$  in diameter, in which the nucleus/cytoplasm ratio is very high. The nucleus stains densely with blocks of intense chromatin. No nucleoli are seen. The cytoplasm stains very faintly and may contain azure granules.

These cells are so similar to lymphocytes in the blood that we propose to use this term to describe them. They constitute about 10 to 30% of the cells present.

TABLE I  
FINDINGS IN CEREBROSPINAL FLUID FROM 17 CASES CONTAINING NEOPLASTIC CELLS

	No.	Date	Cells/mm. <sup>3</sup>	Protein/100 ml.	Glucose/100 ml.	Lange Curve	Histology and Remarks
Lumbar Fluids	1	8.5.58	112	90	60	N/C	No biopsy, ?medulloblastoma
		9.5.58 (V)	31	30	—		
		12.5.58	27	50	58		
		30.7.58	1	40	55	N/C	
		(after DxR)					
	2	13.8.58	153	200	52	MZ	Astrocytoma Grade 3
		15.8.58	450	300	47		
		18.8.58	140	280	56		
		20.8.58	69	250	56		
		25.8.58	86	280	51		
		3.9.58	190	360	62		
	3	1.6.58	1	35	—	N/C	Secondary cancer from breast
		25.8.58	112	130	28	N/C	
	4	5.9.58	183	150	—	FZ	None
	*5	2.10.58	54	400	21	MZ	Secondary cancer from bronchus
		11.10.58	18	450	—		
	*6	16.9.57	1	30	—	N/C	Secondary cancer from parotid
	16.10.58	18	80	—	MZ		
	31.10.58	24	70	54	MZ		
*7	21.11.58	46	240	17	N/C	No neoplasm found at necropsy	
	3.12.58	85	280	20	MZ	See case history	
8	28.2.59	21	80	14		Medulloblastoma	
	28.2.59	24	90	13			
9	18.7.59	4	40	—	N/C	Secondary cancer from lung	
	28.7.59	B1	—	9			
	28.7.59 (V)	1	30	48	N/C		
Ventricular Fluids	*10	15.8.58	39	35	49	N/C	Melanoma
		R.	26	40	36		
		L.	200	450	68		Astrocytoma
	11	30.8.58	74	25	62	N/C	Secondary cancer from stomach
	12	25.9.58	10	190	—	MZ	Secondary cancer from bronchus
	13	6.9.58 (LP)	12	200	85	MZ	Astrocytoma
	14	16.10.58	29	30	—	MZ	No biopsy, suprasellar mass on A.E.G.
	15	4.12.58	40	35	—	MZ	Melanoma
	16	23.1.59	0	35	—	FZ	Melanoma
		R.	50	30	—		
17	31.7.59	11	15	—	MZ	No biopsy, suprasellar mass on A.E.G.	

N/C = No change.

FZ = First-zone curve (paretic).

B1 = Heavily bloodstained.

MZ = Mid-zone curve (meningitic).

V = Ventricular fluid.

\*Repeated in Appendix.

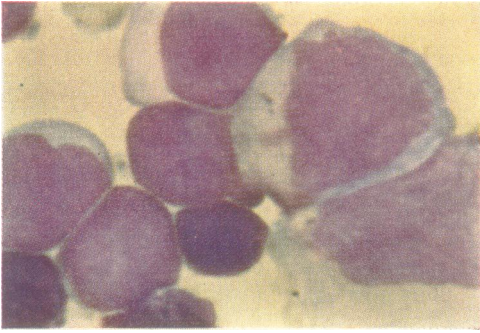


FIG. 1

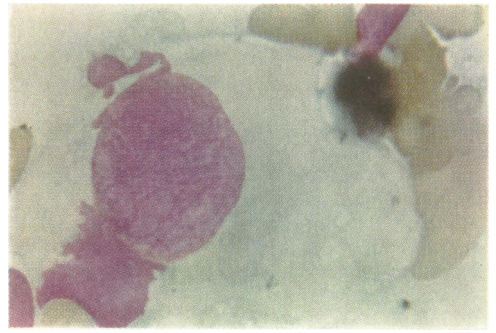


FIG. 2

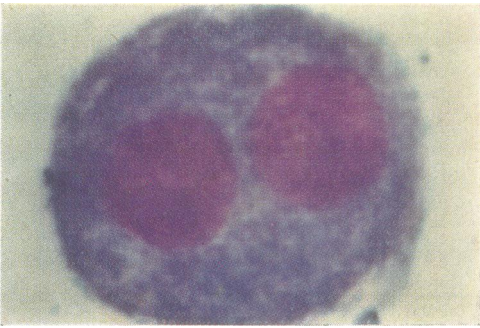


FIG. 3

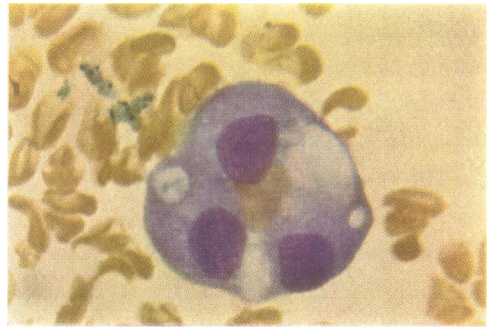


FIG. 4

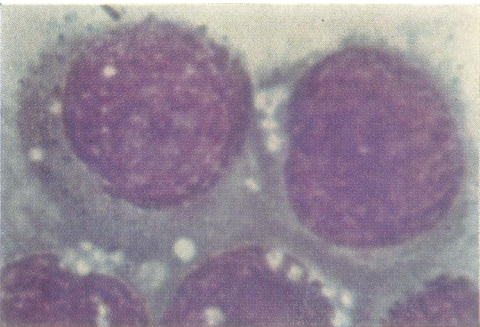


FIG. 5

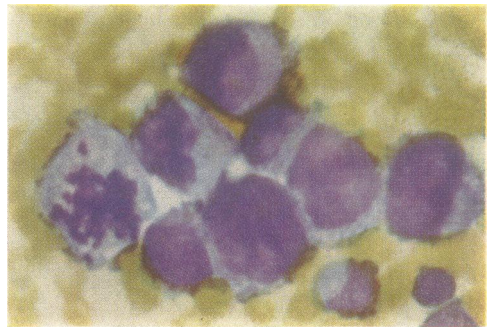


FIG. 6

FIG. 1.—The cell types that occur in normal cerebrospinal fluid. The two large cells on the right are typical G cells, the small centre cell a lymphocyte, the four remaining cells being M cells. Leishman  $\times 800$ .

FIG. 2.—A very large neoplastic cell with nucleoli found in the cerebrospinal fluid from a case of primary carcinoma of parotid (Case 6) with adjacent red cells. Leishman  $\times 650$ .

FIG. 3.—A very large cell with two nuclei from the lumbar cerebrospinal fluid of Case 3 with carcinoma of the breast. Leishman  $\times 1,120$ .

FIG. 4.—A syncytial cell from the ventricular fluid of Case 16 with primary melanoma of the eye. Leishman  $\times 500$ .

FIG. 5.—Neoplastic cells from the ventricular fluid of a patient (Case 10) with primary melanosis of the leptomeninges showing a high nuclear/cytoplasmic ratio and nucleoli. Leishman  $\times 960$ .

FIG. 6.—Neoplastic cells from the ventricular fluid of a patient (Case 12) with carcinoma of the stomach showing one cell in metaphase. Leishman  $\times 340$ .

(2) *M Cells*.—These mononuclear (M) cells superficially resemble lymphocytes but are larger, 10-20 $\mu$ , and the nucleus stains evenly and much less heavily than in the former. The nucleus, which is often indented, may contain one or rarely two, nucleoli. The cytoplasm is basophilic and never contains granules. These cells are the most frequently found in normal cerebrospinal fluid and constitute about 70% of all cells present.

(3) *G Cells*.—These are large mononuclear (G) cells superficially resembling the monocytes of the blood. However, they have less densely staining nuclei which are often deeply subdivided to almost as great a degree as in polymorphonuclear leucocytes. Unlike the latter there are never any intracytoplasmic granules present. These cells do not as a rule contain nucleoli but may do so occasionally.

It is important to recognize these cells as normal constituents of cerebrospinal fluid as their large size (15-30 $\mu$ ) may lead to the unwarranted suspicion of neoplasia.

We have not found any of the granular cells of the blood, *i.e.*, polymorphonuclear, eosinophilic, and basophilic leucocytes, in specimens of presumably normal cerebrospinal fluid (Marks and Marrack, 1960).

**Features of Neoplastic Cells in Cerebrospinal Fluid.**—No unequivocal criteria for the identification of neoplastic cells can be given, but in our experience they manifest some characteristic features which are present to a greater or lesser extent in each individual case.

(1) (*a*) They are cells of types not found in the normal cerebrospinal fluid and (*b*) do not have the characteristics of well-recognized cell types found in some pathological fluids, *e.g.*, polymorphs and plasma cells.

(2) They are usually exceptionally large, being greater than 20 $\mu$ , and frequently contain two or more nuclei; they occasionally may be represented by syncytia (Figs. 2, 3, 4).

(3) The ratio of the area of the nucleus to the cytoplasm is often high, and the nuclei frequently contain two or more large nucleoli (Fig. 5).

(4) Active mitosis may be observed in a moderate number of the neoplastic cells (Figs. 6, and 7).

While no single one of the features mentioned above is pathognomonic of neoplasia, preparations with cells exhibiting all of them can safely be considered diagnostic (Figs. 6 and 7).

More often cells displaying one or even two of these characteristics are found, and it is impossible to do more than consider the possibility of their having a neoplastic origin. We therefore recommend repeating the examination, preferably with the

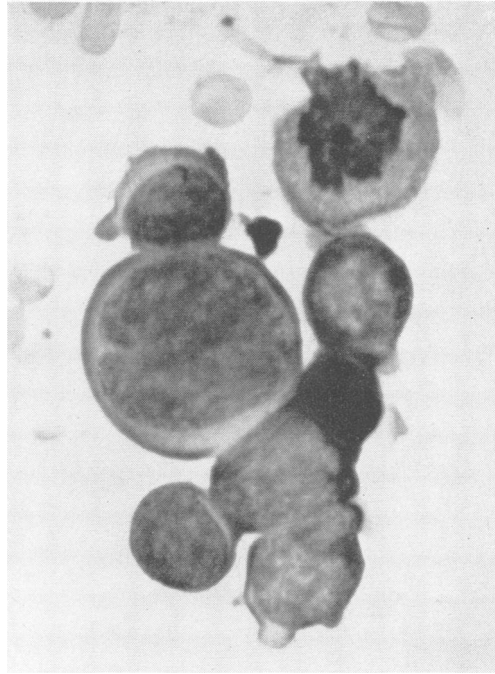


FIG. 7.—A group of cells from the ventricular fluid of Case 13 with carcinoma of the bronchus, showing a large atypical cell and a cell in mitosis. Leishman  $\times 1,184$ .

injection of air into the theca before withdrawing the fluid (Marrack and Marks, unpublished observations).

Attempts at the diagnosis of neoplasia in the absence of at least three of the above criteria are unjustified, and may have unfortunate consequences in wrong treatment and prognosis.

**Nature of Primary Lesion.**—It has not been found possible, by this method, to distinguish with any degree of certainty between primary and secondary tumours of the nervous system, but large cell size, basophilic cytoplasm, and intensely basophilic nucleus favour a secondary carcinomatous origin (Fig. 3). The same difficulty was experienced by Cairns and Russell (1931) and by McMenemey and Cumings (1959).

**False Negative Results.**—We have made no attempt to determine the relative frequency of positive findings in cases of primary and secondary neoplastic disease of the central nervous system. Undoubtedly, there are many cases in which no tumour cells are exfoliated into the cerebrospinal fluid, since tumours do not always impinge on the subarachnoid space and even in those cases where they do, and exfoliate their cells into the cerebro-

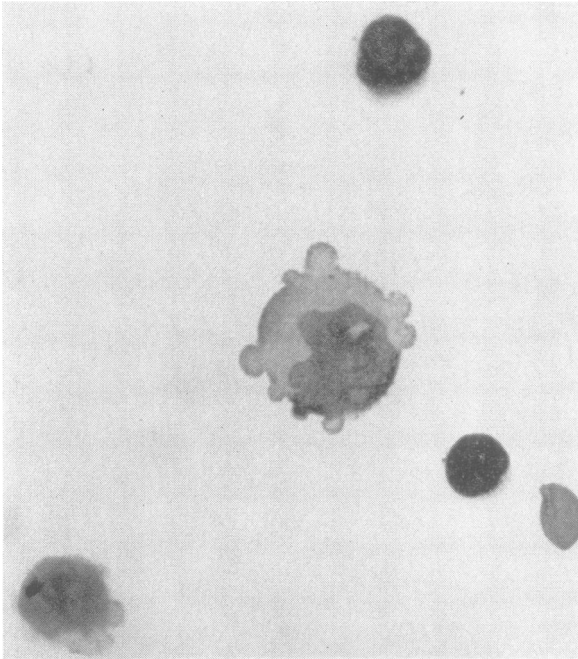


FIG. 8

FIG. 8.—Large atypical cell with nucleoli from Case 7. Leishman  $\times 1,040$ .

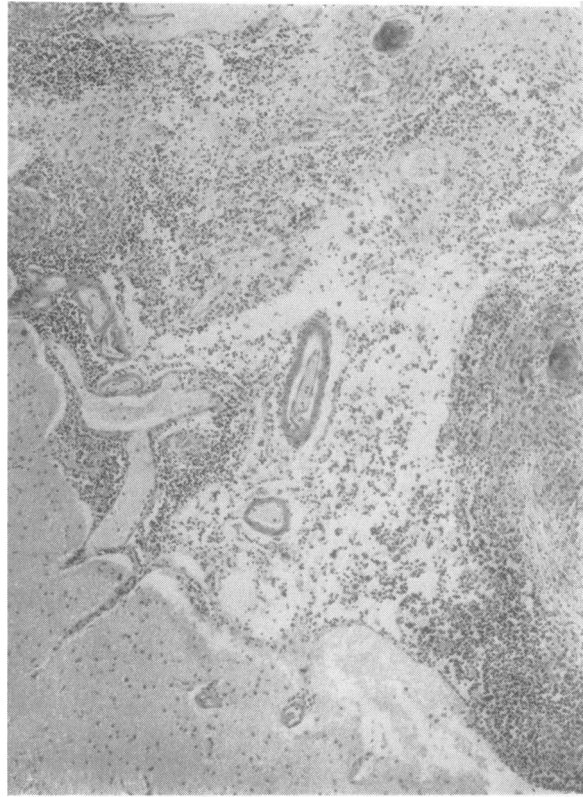


FIG. 9

FIG. 9.—Section of cortex and meninges (Case 7) showing non-specific granulomatous infiltration with giant cells (*cf.* Fig. 8). Haematoxylin and eosin  $\times 55$ .

spinal fluid, it is impossible, as yet, always to recognize the smeared cells as neoplastic by the methods currently employed.

In one patient, in whom the diagnosis of carcinomatous meningeopathy was strongly suspected clinically during life and confirmed at necropsy, cytological confirmation was not obtained despite extensive and repeated searching of preparations from the cerebrospinal fluid. The technique described by Larson, Robson, and Reberger (1953), in which tumour cells are swept off the meninges by agitation of the cerebrospinal fluid by repeated withdrawal and reinjection, has not been regularly used, although it would probably reduce the frequency of false negative results.

**False Positive Results.**—Much more serious is the identification of cells as being neoplastic when they are not, since the diagnosis of malignancy may lead to the withholding of therapy in potentially curable conditions. During the 14 months in which this technique has been in routine use, cells suspected of being neoplastic were found in the cerebrospinal fluid of four patients, other than Case 7 reported

here, and were subsequently considered to have other lesions. One had tertiary syphilis, another had sarcoidosis, and two were ultimately diagnosed as suffering from "encephalitis". In none were more than two of the features described above for neoplastic cells observed. Case 7 (see appendix) is a good example of the difficulties encountered in being certain that grossly abnormal cells are neoplastic (Figs. 8 and 9).

### Discussion

General awareness of the condition in which the meninges become infiltrated by metastatic carcinoma (carcinomatous meningeopathy) has led to fresh attempts to identify neoplastic cells in the cerebrospinal fluid. These have largely been unsuccessful due to the fragility of cells when suspended in non-proteinacious solutions. Spriggs (1954) was able to make suitable dry preparations and McCormack, Hazard, Belovich, and Gardner ((1957) have recorded their experience in 27 cases using a wet-film method. The methods of Spriggs (1954) and McMenemey and Cumings (1959) may

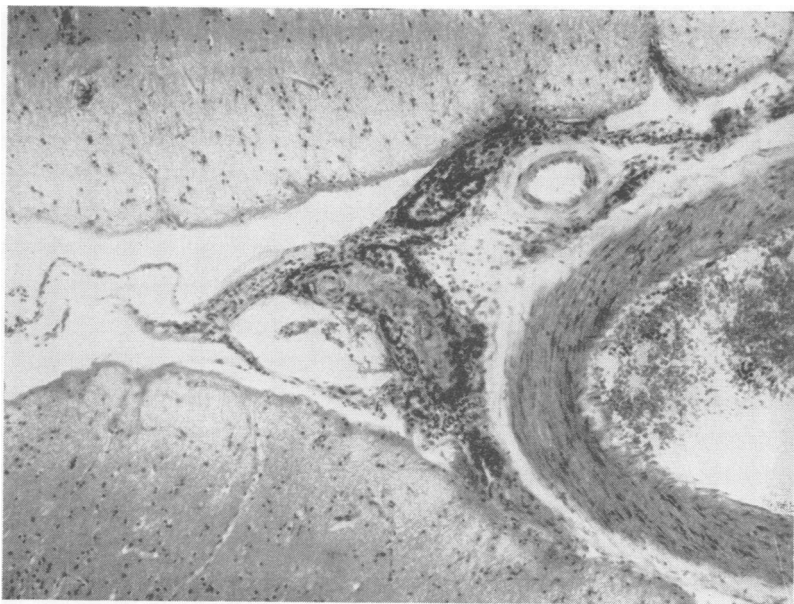


FIG. 10.—Section of cortex and meninges (Case 5) with carcinoma of bronchus, showing localized neoplastic infiltration of the meninges in a sulcus and unaffected cortex. Haematoxylin and eosin  $\times 85$ .

be improved by the addition of a small amount of albumin to the suspending fluid as this facilitates spreading of cells on slides. Such preparations also have the advantage over the wet-film technique of permanence and greater ease of identification.

Localized intracranial tumours, including those which may exfoliate cells into the ventricles, are usually demonstrated by air studies followed by surgical biopsy. Occasionally, however, air studies are negative in the presence of such an intracranial mass and as a consequence no surgical biopsy is made, *e.g.*, Case 6 (Appendix), yet neoplastic cells may be found in the cerebrospinal fluid (Fig. 2), and it is impossible to know in what proportion of the cases meningeal infiltration occurs in addition. However, it is in the diagnosis of diffuse carcinomatous infiltrations of the meninges, in the absence of focal central nervous system signs, and frequently with no evidence of a primary lesion elsewhere (Appendix, Case 10) that examination for malignant cells in the cerebrospinal fluid is most valuable. Several excellent reviews of the clinical manifestations of the condition have appeared recently (Jacobs and Richland, 1951; Fischer-Williams, Bosanquet, and Daniel, 1955; Heathfield and Williams, 1956) and this aspect will not be discussed here.

Case 5 illustrates the possibility of overlooking neoplastic infiltration of the meninges and cortex and stresses the need for a thorough histological search of the whole cerebrospinal axis before the diagnosis of carcinomatous encephalopathy not due

to metastatic involvement can be established (Fig. 10 and Case 5 Appendix).

Certain other findings during examination of the cerebrospinal fluid may be helpful in the diagnosis of diffuse neoplastic infiltration of the meninges. The protein level in this series was often high—above 200 mg./100 ml.—and the glucose level pathologically low. Of the lumbar fluids in which the glucose was estimated, four were below the normal limit of 40 mg./100 ml. (Marks, 1960). The low sugar level in this type of case (Berg, 1953; Bayne and Darby, 1956; McElligott and Smith, 1958) can lead to the mistaken diagnosis of tuberculous or fungal meningitis unless the possibility of neoplastic infiltration is borne in mind (Murphy, 1955). This alteration is not invariable in cerebral neoplastic disease and has, in our experience, borne no direct relationship either to the number of cells in the fluid or to the nature of the tumour, being found in gliomatous as well as in secondary carcinomatous disease. The cellular elements, with the exception of the neoplastic cells, are usually, in our experience, of the M variety; polymorphs were present in only three of the 17 patients.

The diagnosis of neoplastic meningeopathy is based in the first instance on the identification of neoplastic cells in the cerebrospinal fluid. This may be very simple when suspicion is high and numerous tumour cells are present, such as in Case 3, or very difficult when extremely few identifiable cells are present, as in Case 6. A thorough search of the film, such as is made for tubercle bacilli in suspected

tuberculous meningitis, may be necessary before the diagnosis can be made. However, it is often impossible to do more than report the presence of atypical cells and suggest that they may be neoplastic. Platt (1951) reports the results of his examination of the cerebrospinal fluid for tumour cells in five grades ranging from negative (Grade 1) to pathognomonic of neoplasia (Grade 5). Very few cases fall into the latter category, in our experience.

### Summary

The cells of the cerebrospinal fluid have been examined routinely, using a new technique for preparing smears, before staining them with Leishman's reagent. Cells reported to be tumour cells were seen in preparations from 17 patients. Confirmation of the diagnosis was obtained in 12, with one false positive. The cytological features of the cells have been discussed and reference is made to the observation of false positive results in four cases outside this series. The technique has proved suitable for routine use and of clinical value. Low glucose levels were an associated feature in some cases.

We should like to thank the physicians and surgeons

of the National Hospital, Queen Square, London, for the opportunity to study patients under their care and Professor Cumings for his advice.

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### REFERENCES

- Bayne, J. R. D., and Darby, P. W. (1956). *Ann. intern. Med.*, **45**, 285.  
 Berg, L. (1953). *Neurology*, **3**, 811.  
 Cairns, H., and Russell, D. S. (1931). *Brain*, **54**, 377.  
 Dufour, H. (1904). *Rev. neurol.*, **12**, 104.  
 Fischer-Williams, M., Bosanquet, F. D., and Daniel, P. M. (1955). *Brain*, **78**, 42.  
 Greenfield, J. G., and Carmichael, E. A. (1925). *The Cerebro-Spinal Fluid in Clinical Diagnosis*. Macmillan, London.  
 Heathfield, K. W. G., and Williams, J. R. B. (1956). *Brit. med. J.* **1**, 328.  
 Jacobs, L. L., and Richland, K. J. (1951). *Bull. Los Angeles neurol. Soc.*, **16**, 335.  
 Larson, C. P., Robson, J. I., and Reberger, C. C. (1953). *J. Neurosurg.*, **10**, 337.  
 McCormack, L. J., Hazard, J. B., Belovich, D., and Gardner, W. J. (1957). *Cancer*, **10**, 1293.  
 McElligott, M., and Smith, B. J. (1958). *Brit. med. J.*, **1**, 875.  
 McMenemeny, W. H., and Cumings, J. N. (1959). *J. clin. Path.*, **12**, 400.  
 Marks, V. (1959). *Clin. chim. Acta*, **4**, 395.  
 — (1960). *J. clin. Path.*, **13**, 82.  
 — and Marrack, D. (1960). To be published.  
 Murphy, E. F. (1955). *Lancet*, **1**, 231.  
 Platt, W. R. (1951). *A.M.A. Arch. Neurol. Psychiat.*, **66**, 119.  
 Pruitt, J. C., Hilberg, A. W., and Kaiser, R. F. (1958). *New Engl. J. Med.*, **259**, 1161.  
 Spriggs, A. I. (1954). *J. clin. Path.*, **7**, 122.  
 — (1957). *The Cytology of Effusions in the Pleural, Pericardial and Peritoneal Cavities*. Heinemann, London.  
 Undritz, E. (1952). *Sandoz Atlas of Haematology*. Sandoz, Basle.

## APPENDIX

### Case Reports

**Case 6 (No. 74533).**—This 52-year-old man was first admitted to the care of Dr. Macdonald Critchley on September 9, 1957, with a history of pain in the left side of the face for one year. Both temporomandibular joints had been operated upon for trismus, due to ankylosis, at another hospital. Temporary improvement followed but some months later the pain recurred and he was admitted to this hospital. At the time he was a thin, but otherwise fit man. There was an area of hypaesthesia in the distribution of the left fifth nerve, and some diminution in the power of the left arm with clumsiness of movement. The nasopharynx was normal. The cerebrospinal fluid was normal, protein 30 mg./100 ml. and 1 lymphocyte/mm.<sup>3</sup> Following alcohol injection of the left trigeminal ganglion there was marked symptomatic improvement and his pain disappeared.

He was readmitted one year later on September 20, 1958, with recurrence of facial pain and difficulty in swallowing. On this occasion he was an obviously sick man with multiple cranial nerve palsies. A smooth mass was palpable in the nasopharynx; biopsy only showed chronic inflammatory tissue (Dr. W. P. G. Mair). The cerebrospinal fluid was colourless and contained protein, 80 mg./100 ml., and 18 white cells/mm.<sup>3</sup>. A second

specimen two weeks later contained 24 white cells. Leishman smears showed a small number of huge, atypical cells with enormous nuclei containing 2 to 4 nucleoli (Fig. 2). Air encephalography was normal.

His illness terminated fatally four weeks later. Post-mortem examination (Dr. W. P. G. Mair) revealed a carcinoma, arising in the left parotid gland, entirely unsuspected during life, which had spread to involve the seventh and eighth cranial nerves and was infiltrating the meninges. There were no other secondary deposits.

**Case 10 (No. 80545).**—A 49-year-old man was transferred from St. Richard's Hospital, Chichester, under the care of Dr. William Goody on August 11, 1958, with the presumptive diagnosis of posterior fossa tumour.

He had been well until four months previously, when he began to suffer from headaches lasting about 10 minutes, made worse by lying down. There was bilateral papilloedema and slight, fine lateral nystagmus. The left plantar response was extensor.

Ventriculography showed a somewhat enlarged left lateral ventricle but no localizing signs. The ventricular fluid obtained at this time contained protein, 35 mg./100 ml., and 39 white cells/mm.<sup>3</sup> These were seen in the Leishman stained smear to be moderately large cells, atypical for the cerebrospinal fluid, with abnormal nuclei and conspicuous nucleoli (Fig. 5). The

diagnosis was considered to be one of secondary carcinoma and a course of radiotherapy to the whole cerebrospinal axis was given. There was some temporary improvement but he died six months later at St. Richard's Hospital, Chichester.

Permission for necropsy was limited to the head only.

Report by Dr. C. H. R. Knowles (February 4, 1959):

"There was widespread dark brown pigmentation of the leptomeninges, symmetrical in distribution. Over most of the cerebellum and temporal lobes, the interpeduncular fossa and the inferior surfaces of the frontal and occipital lobes, and in the main fissures and sulci, the areas of pigmentation were virtually confluent. Over the lateral and superior surfaces of the brain the pigmentation appeared mainly in the form of small discrete flecks, 1-2 mm. in diameter. There was no obvious thickening of the meninges, and nothing resembling tumour nodules was found. . . . In the most severely affected parts, for example, the inferior surface of the temporal lobes, the subarachnoid space appears to be completely obliterated by a diffuse sheet of cells about 300 $\mu$  thick. Nearly all the cells are rounded and between 5 and 14 $\mu$  in diameter. . . . The pigment fails to give the reaction for free iron but has the typical appearance of melanin in a section stained by Masson's method. In a few places collections of the abnormal cells extend for a short distance into the brain in the perivascular spaces, but no infiltration of nervous tissue has been seen in any of the sections. . . ."

In Dr. Knowle's opinion this was a case of primary diffuse melanomatosis of the leptomeninges.

**Case 7 (No. 82665).**—A woman aged 62 years was admitted under the care of Dr. J. St. C. Elkington on November 21, 1958. She had been well until July, 1958, when she was found to have diabetes mellitus. In the following months she developed leg weakness, became demented, and complained of failing vision. Elsewhere she was found to have a persistently low cerebrospinal fluid glucose level. On examination at this hospital, she showed moderate dementia, the deep reflexes were brisk and the plantar responses extensor.

Lumbar puncture produced a clear, colourless fluid,

protein 240 mg./100 ml., glucose 17 mg./100 ml., cells 46/mm.<sup>3</sup> The Leishman smear revealed a small proportion (0.5%) of big atypical cells containing large nucleoli (Fig. 8). No mitotic figures were seen. In conjunction with the clinical picture the diagnosis of carcinomatous meningeopathy was made. No primary neoplasm was found and an A.E.G. revealed only moderately dilated lateral ventricles (Dr. H. Davies).

When heard of in August, 1959 (Dr. N. S. Alcock), she was gradually and progressively deteriorating. A necropsy was done by Dr. G. Stewart-Smith at Exeter on September 7, 1959. The gross appearance of the brain was not inconsistent with the firmly held clinical diagnosis of malignant neoplasia and the spinal cord was not examined. However, the histology of material taken from several areas of granular meningitis around the base of the brain showed chronic granulomatous inflammation. No caseation was seen though there were many foreign body giant cells (Fig. 9). The Ziehl-Neelsen-stained sections did not show any acid-fast rods. The histological picture was consistent, in the slides examined by Professor W. Blackwood, with the diagnosis of non-specific leptomeningitis. Dr. Stewart-Smith reported that there was no evidence of a primary neoplasm, tuberculosis, or other relevant pathology in the other organs in the body. In the face of this evidence our cytological diagnosis of neoplastic cells is presumed to be wrong. This is the second patient with a condition indistinguishable from Boeck's sarcoidosis of the central nervous system whose cerebrospinal fluid has contained cells which were considered by us to have three of the four characteristics associated with neoplastic cells. (No mitoses were seen.)

**Case 5.**—This necropsy revealed a primary carcinoma of the lung with no macroscopic secondaries. The only macroscopic lesion in the central nervous system was a tiny, slit-like cavity in the head of the caudate nucleus. The meninges appeared normal or, at the most, showed a slightly increased opacity in the mid-thoracic region. Histologically, they were shown to be extensively infiltrated (Fig. 10) with carcinoma cells (Dr. M. R. Crompton).