Section of Oncology

President P E Thompson-Hancock FRCP

Meeting 12 March 1975

Tumours of the Central Nervous System

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Comparative Aspects of Tumours of the Central Nervous System in the Dog

Neoplasia of the central nervous system in the domestic species is most common in the dog, usually in animals over 3 years of age. In a survey of 21 affected animals (Palmer *et al.* 1974) 10 of the tumours were found in the Boxer breed and all of these occurred in the forebrain, mostly in the region of the diencephalon. A study of the correlation of clinical manifestations with the position of the underlying tumour is also profitable in the dog, because this is one of the domestic species on which a meaningful neurological examination can be undertaken. Originally it was considered that such a correlation might be a simple reflection of those parts of the brain ablated by the tumour, but later other factors were found to influence the genesis of clinical signs. It is the purpose of this paper to review these factors, to consider the more common clinical signs, the types of tumour and to indicate a possible role of such studies in broader aspects of comparative medicine. The work is based on a study of 32 animals affected by naturally-occurring tumours (Palmer 1960, 1961, Palmer *et al.* 1974).

Apart from brain tissue actually infiltrated by a tumour, the presence of a space-occupying lesion within the non-expansible cranial cavity leads to local necrosis, subtentorial herniation, compression of the hypothalamus and coning of the cerebellum. In this context it must be recalled that the cranial cavity of the dog is relatively small compared to that of man and there is little space to accommodate an expanding foreign object without it impinging on a vital structure. Subtentorial herniation usually involves the cingulate gyrus; compression of the hypothalamus, often seen in the dog, can be likened to temporal herniation of man, inasmuch as in the dog the hippocampus expands medially but fails to luxate into the posterior fossa. Herniation together with obliteration of the ventricular system, especially at the level of the aqueduct, leads to hydrocephalus and raised intracranial tension. In severe instances this is accompanied by ischæmic type necrosis of the pyriform cortex, the cingulate gyrus and small areas of focal necrosis in the brain stem. Regions of brain, other than those directly compromised by tumour, may also be affected by secondary metastases. Many gliomas in the dog occur in the region of the subependymal plate, indeed several authors have suggested that the tumour may arise from this region of permanent cell division (Fischer 1966, Stavrou *et al.* 1970, Blakemore & Jolly 1972). From this region tumour cells can easily gain entry into the ventricular system, where they can be transported in the CSF to a distant site where they may be responsible for another tumour. All these secondary effects may result in neurological signs not directly linked to ablation of nervous tissue by the original tumour, and a diagnostic problem more complicated than that posed by the primary tumour.

Another consequence of gliomas arising from the subependymal plate is that the neuroanatomical localization of their origin tends to dictate the pattern of clinical signs. It must be recalled that the subependymal plate is localized to an area dorsal to the head of the caudate nucleus. For this reason many tumours arise rostrally in a cerebral hemisphere, later involving the thalamus, internal capsule, visual pathways, hypothalamus and eventually the opposite hemisphere. For this

Table 1

Predominant clinical signs in 21 dogs affected by intracranial neoplasms

Clinical sign	*No. of total cases*
Change of temperament	17
Locomotor deficiency	17
Visual defect (including pupils)	15
Papillœdema	10
Circling	10
Hemiplegia	8
Fits	8
Hemianopia	7
Head turn and/or tilt	7
Bulbar including eye deviation and cranial nerve paralysis	7
Nystagmus	6
Sensory deficit	4
Pituitary	3

reason signs of cerebral derangement are more common than those due to brain-stem involvement and can often be attributed to damage of these designated structures.

A survey of neurological signs in 21 cases of brain tumour in the dog is presented in Table 1 (*see* Palmer *et al.* 1974). Change of temperament and evidence of locomotor abnormality are usually the presenting signs. An owner will report that for some time before profound behavioural manifestations were noticed, the animal became dull and may have lost acquired habits. It may have soiled the house and failed to react to command; sometimes the animal becomes vicious. Locomoter deficiency may take the form of walking in circles, indicating involvement of a cerebral hemisphere (the adversion syndrome, White & MacCarty 1959) or of the vestibular apparatus. Such circling is often accompanied by tilting of the head towards the side of the lesion. Hemiplegia follows tumour invasion of the internal capsule, when it is often accompanied by signs of hemianopia and loss of sensation from the hemiplegic side of the body. Spasticity may be evident in the hind-legs, and this is usually present bilaterally, even when a tumour is confined to one cerebral hemisphere. In other cases an animal may show generalized limb weakness and become totally quadriplegic.

Fifteen of the 21 dogs in our series showed signs of visual disturbance which ranged from total blindness to field defects. The former is not difficult to diagnose because the animal will collide with obstacles when introduced to strange surroundings and tend to walk with a high-stepping gait. If the tumour has affected the optic nerve or optic chiasma, blindness is likely to be accompanied by a degree of pupillo-dilatation and decreased light reflexes. Slight degrees of visual disturbance are much more difficult to detect. Hemianopia is often reported by an owner as blindness of one eye (the side being related to that of the lost visual field) but the exact nature of the deficiency may be established on the basis of the animal's reaction to blink and fixating reflexes.

Papillœdema, indicative of raised intracranial pressure, was reported in 10 of the 21 animals and there is evidence that the eye opposite to the side of the tumour is more seriously affected (the Foster-Kennedy syndrome). Ophthalmoscopic examination may also be useful in the detection of nystagmus. The excursion of the nystagmic movement associated with vestibular damage may increase over a period of time but the magnification afforded by the ophthalmoscope is often useful in seeing fine, residual movements.

Tumours of the medulla, brain stem and cerebellum are frequently meningiomas or sarcomas. These may result in damage of cranial nerves and lead to paralysis of the extrinsic ocular muscles, to ptosis, pupillo-dilatation and to neurogenic atrophy of muscles of mastication and of the tongue.

Convulsions are an additional distressing feature. Most commonly they arise when the neoplastic process involves the pyriform or hippocampal cortex, but they may also occur when a tumour invades the hypothalamus or pituitary which in turn may cause hypoglycæmia. Other signs of hypothalamic involvement include vomiting, diabetes insipidus, and Cushing's syndrome which in the dog is seen as progressive adiposity, alopecia and genital atrophy.

The diagnosis of brain tumours in the dog is complicated by the occurrence of a granulomatous form of encephalitis in the older animal which is often accompanied by manifestations of blindness, dullness and of vestibular disturbance (signs reminiscent of those of neoplasia). The diseases may be caused by the virus of canine distemper (Lincoln *et al.* 1971, Lincoln *et al.* 1973) but the illness is of a protracted nature unlike the acute encephalitis associated with distemper in the younger animal.

Primary tumours of the central nervous system also occur in the spinal cord. These include a variety of gliomas but more commonly schwannomas involving the nerve roots and, in the author's experience, especially nerve roots of the brachial plexus. As these nerve-root tumours expand, they gradually encroach on the substance of the spinal cord and lead to clinical manifesta-

tions difficult to differentiate from those caused by prolapse of a cervical intervertebral disc. Both conditions may cause considerable pain, with reluctance to move the head and protective spasm of the neck muscles. Both tumour and prolapsed disc may cause peripheral nerve dysfunction, with flaccid paralysis of the affected foreleg and neurogenic atrophy as well as hind-leg paralysis because of pressure necrosis of the cord. However, remissions can be expected with a prolapsed disc whereas tumour progresses to its fatal outcome.

The morphological differentiation of primary neoplasms of the CNS in the dog is complex. Many tumours such as meningiomas, schwannomas, oligodendrogliomas and glioblastomas resemble closely their counterparts in man. But in the case of many gliomas and of a wide range of meningeal sarcomas and neoplastic reticuloses no human tumours appear to be analogous, and this has led to much confusion in classification (*see* Lüginbühl *et al.* 1968).

Attempts have been made to remove tumours from the canine brain and no doubt success will follow improvement in diagnosis and surgical technique. However, surgery is likely to have a limited application only because many of the gliomas are extremely invasive.

Conclusion: A wide variety of tumours of the brain occur in the dog, most commonly in the Boxer breed. Tumours may arise from the subependymal plate which may influence the parts of the brain destroyed and hence the pattern of clinical signs. Because of the small capacity of the dog's skull, vital neurological structures are quickly destroyed and the time course of these events is much shorter than in man. The high incidence of tumours in the Boxer would suggest that this breed might afford a useful model for clinical treatment using, for instance, cytotoxic agents.

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Detection of Intracranial Tumours with Special Reference to Immunodiagnosis

Although knowledge of the mechanisms involved in the blood-brain barrier remains inadequate there can be no doubt about its significance in clinical oncology. On the one hand it appears to exclude effective concentrations of most cytotoxic agents; on the other, it is frequently breached by neoplastic cells leading to meningeal leukæmia or intracerebral metastasis formation. Yet it can be exploited. Radioisotope scanning depends on localized breaches of the barrier in the vicinity of intracerebral tumours. The evidence indicates that the new capillaries associated with tumour formation lack the tight junctions, the so-called zonulæ occludentes, which are found between the endothelial cells of normal brain capillaries (Long 1970, Brightman *et al.* 1970, Shuttleworth 1972).

The importance of early diagnosis of both primary and secondary brain tumours is self-evident, for if treatment is to be effective in this anatomical site the lesion must be detected before irreversible damage has been incurred. Brain scans provide little or no information about the morphological nature of the lesion and both surgical resection and biopsy of cerebral lesions carry potentially severe penalties. The purpose of this paper is to draw attention to evidence which indicates that the blood/brain barrier provides a basis for biochemical and immunochemical methods for the detection of tumour-associated substances arising from tumours within the central nervous system (CNS).

One example, already tested to a limited degree, was proposed by Paoletti *et al.* (1969). Desmosterol (24-dehydrocholesterol) is present in the cerebrospinal fluid (CSF) of some patients with gliomas. This substance is the precursor of cholesterol, and is present in large amounts in developing brain but only in small amounts in normal mature brain. Its concentration is increased by CNS tumours and the amount of desmosterol in CSF is further increased in these patients by the administration of triparanol which blocks its conversion to cholesterol. Positive results in 60–80% of patients with gliomas were confirmed by Weiss *et al.* (1972), who considered the test to be potentially useful in patients with indecisive brain scans.