Encephalitis associated with carcinoma

Central hypoventilation syndrome and cytoplasmic inclusion bodies

ALLEN M. KAPLAN AND HIDEO H. ITABASHI¹

*From the Departments of Pathology, Neurology and Pediatrics,
Harbor General Hospital, Torrance, California, U.S.A.*

SYNOPSIS A case of encephalitis associated with a remote and occult oat cell carcinoma is presented in which the main clinical features were progressive dementia and central hypoventilation syndrome. The only significant anatomical lesions within the known anatomical substrate of respiration affected the locus caeruleus on both sides. It is speculated that the degeneration of the locus caeruleus was responsible for the central hypoventilation syndrome. Hitherto undescribed neuronal intracytoplasmic eosinophilic inclusions were found in an isolated lesion of the insular cortex. Electron microscopy failed to disclose viral particles in the regions of neuronal degeneration.

One of the less common but diagnostically challenging of the remote, nonmetastatic, neurological complications of carcinoma is an encephalitis clinically manifested as progressive dementia and pathologically seen as changes predominantly localized within the limbic system (Brain *et al.*, 1951; Charatan and Brierley, 1956; Brierley *et al.*, 1960; Brain and Norris, 1965; Henson *et al.*, 1965; Morton *et al.*, 1966; Corsellis *et al.*, 1968). However, the pathological lesions may be widespread or localized to various other levels of the central nervous system from the cerebral cortex outside the limbic system (Morton *et al.*, 1966) down to the upper thoracic spinal cord (Case Records of the Massachusetts General Hospital [Case 42—1970], 1970). In most instances there have been close correlations between the encephalitic lesions and the clinical syndromes such as exemplified in 'limbic encephalitis' associated with a remote carcinoma.

Central hypoventilation syndrome is an uncommon disorder of various aetiologies such as poliomyelitis (Sarnoff *et al.*, 1951; Garlind and Linderholm, 1958; Plum and Swanson, 1958; Strieder *et al.*, 1967), infarcts (Plum and Alvord, 1964; Devereaux *et al.*, 1973), brain-stem tumour (Plum, 1970), and of unknown cause

(Seriff, 1965). Where anatomical studies were available, the lesions were in the brain-stem and in particular the medulla. In this report, we present a case in which the predominant clinical findings were those of progressive dementia and central hypoventilation syndrome, and evidence is presented to suggest that lesions of the locus caeruleus may play a role in this latter syndrome.

The aetiology of encephalitis associated with carcinoma remains unknown, but a pathogenesis dependent on an opportunistic viral infection remains an attractive hypothesis (Störting *et al.*, 1962; Henson *et al.*, 1965; Case Records of the Massachusetts General Hospital [Case 42—1970], 1970). In this regard, intranuclear inclusion bodies have been noted previously within oligodendrocytes (Glaser and Pincus, 1969) and neurones (Norris *et al.*, 1970). Therefore, an effort was made to find inclusion bodies and viral particles in the case reported here.

CASE REPORT

A 61 year old black foundry worker was admitted to Harbor General Hospital on 23 July 1972. He was well until about 14 months before admission when he developed arthralgias involving large joints without swelling and symptoms of progressive emphysema which forced him to leave his job. About a year later, he was noted to have poor recent memory, increased

¹ Address for reprint requests: Dr Itabashi, Department of Pathology, Harbor General Hospital, 1000 West Carson Street, Torrance, California 90509, U.S.A.

periods of sleeping, combined with occasional hallucinations, difficulty with gait, and vague symptoms of neck stiffness and photosensitivity. The family had also noted an unilaterally large pupil and a 13.6 kg (30 lb) weight loss over the year before admission. He was brought to the hospital because of gradually increasing somnolence and a rapidly progressive mental deterioration. The patient had no previous major medical or surgical problems. He had smoked one-half to one pack of cigarettes per day during most of his life. The patient's father died of lung carcinoma, and his mother died of cancer of the breast.

Physical examination on admission showed a cachectic man in no acute distress. Blood pressure was 150/100 mmHg, heart rate 92 per minute, respirations 22 per minute, and temperature 37°C. On mental examination, the patient was moderately somnolent and disoriented in time and place. He was unable to name the President of the United States or recall any previous presidents. He could not calculate beyond adding 2 plus 2. His attention span was short, and an anomic aphasia was noted. Cranial nerve

examination revealed a right exophoria and anisocoria, the right pupil measuring 7 mm and the left 4 mm. Both pupils reacted normally to light, and the remaining cranial nerves were intact. There was no papilloedema. His gait was not wide-based or grossly ataxic, but he was reported to be 'unsteady'. Generalized muscle wasting was present but with normal tone, and a left arm drift was observed. Sensory examination was normal. Tendon reflexes in the arms were brisk on the right compared with the left. They were normally active in the legs bilaterally, but a Babinski sign was noted on the right side at times.

Admission laboratory studies included the following: haemoglobin of 11.2 g/100 ml; haematocrit 34.5%; white blood cell count 5,000/mm³ with shift to the left. Skull and chest radiographs were normal. Blood electrolytes on the day of admission were as follows: sodium 150 mEq/l.; potassium 2.9 mEq/l.; chloride 103 mEq/l.; and bicarbonate 36 mEq/l. Other serum chemical estimations, including blood urea nitrogen, glucose, calcium, phosphorus, uric acid, cholesterol, total protein, bili-

FIG. 1. Graph illustrating the blood PCO₂, PO₂, and pH in the top portion. Normal range for blood pH and PCO₂ is indicated by stippled zones. The administration of oxygen with and without the use of respirator is indicated in the lower portion. Note the trend toward CO₂ retention with acidosis reversed by assisted ventilation.

FIG. 2. High power view of portion of periaortic lymph node replaced by oat cell carcinoma. H and E, $\times 510$.

rubin, alkaline phosphatase, acid phosphatase, lactic dehydrogenase, and SGOT, were all within normal range. There was 9% retention on sulphobromophthalein test. Echoencephalography showed no midline shift, and brain and liver scans were normal. Bilateral carotid and vertebral angiograms were normal. Lumbar puncture revealed an opening pressure of 210 mm of cerebrospinal fluid (CSF) with a closing pressure of 70 mm. The CSF was clear and contained three lymphocytes per mm^3 and three erythrocytes per mm^3 . CSF glucose was 100 mg/100 ml and total protein 88 mg/100 ml. The VDRL was nonreactive, and the colloidal gold curve read 1122332200. An electroencephalogram showed mild to moderate generalized slowing without focal abnormality. Bronchoscopy was performed and revealed no evidence of mass or obstruction, and cytology was negative for malignant cells.

During his one month of hospitalization, his course was complicated by multiple problems including pneumonia which resolved and recurred, labile blood pressure with periodic hypertension and

hypotension (200/120 to 60/0 mmHg), hypothermia $28.5^{\circ}\text{--}36.1^{\circ}\text{C}$, and biochemical abnormalities including hyperglycaemia and hyponatraemia. Although a single serum potassium value on admission was low, subsequent daily determinations were within normal range. Multiple chest radiographs showed mild persistent right lower lobe pneumonia. Five days after admission the patient developed an acute respiratory failure characterized by hypoventilation with carbon dioxide retention, acidosis, and hypoxaemia despite oxygen supplementation (see Fig. 1). The patient required assisted ventilation and was intubated early, but ultimately a tracheostomy was performed. Although observed to have hypoventilation off the respirator, it was stated that 'periodically, he can take deep inspiration on command'. Another observer wrote: 'respirations occasionally shallow, but patient responds to verbal commands to take deep breaths'. At no time was the patient completely apnoeic when tested off the respirator. No clinical seizures were noted throughout the hospital course. The patient's neurological examination showed no dramatic changes and his mental impairment persisted. He died on 25 August 1972 after an illness lasting 15 months.

NECROPSY FINDINGS General necropsy examination showed no obvious pulmonary neoplasm, but the periaortic lymph nodes contained metastatic tumour consistent with oat cell carcinoma (Fig. 2). Later careful dissection of the lungs failed to show a primary neoplasm. There was a right lower lobe pneumonia with areas of consolidation, and there was no evidence of emphysema. Incidental findings included bilateral adrenal and renal adenomata, mild generalized arteriosclerosis, pseudomembranous tracheitis, multiple prostatic infarcts, and chronic thyroiditis.

NEUROPATHOLOGICAL EXAMINATION The brain weighed 1,280 g after formalin fixation. The leptomeninges and dura mater appeared normal. The cerebral hemispheres were symmetrical without gross evidence of cortical atrophy or oedema. The base of the brain as well as the cranial nerves was normal. Cerebral arteries showed minimal atherosclerosis without major anomalies. Coronal sections revealed mild symmetrical ventricular dilatation. The hippocampal formations were small and contained thin brownish lines corresponding to hippocampus proper consistent with atrophy. The adjacent temporal horns were dilated, and a small greyish lesion was noted in the lateral wall of the left temporal horn. Sections of the cortex, central white matter, thalamus, basal ganglia, cerebellum, and

FIG. 3. Hippocampal formation shows total loss of neurones in end plate of hippocampus proper and scattered surviving neurones in dorsal cell band and Sommer's sector. Note the perivascular cuffs indicated by arrows. Nissl stain, $\times 12$.

brain-stem showed no gross lesions or evidence of metastasis.

Microscopically, the significant histological findings were localized severe neuronal loss, profuse astroglial hypertrophy and proliferation, microglial proliferation, perivascular cuffs of lymphocytes, rare neuronophagia, and myelin degeneration in the zones of neuronal loss. The hippocampal formation on both sides showed total loss of neurones in the end plate and dorsal cell band and scattered neurones surviving in Sommer's sector, fading into less

apparent loss in the subiculum and the adjacent cortex of the parahippocampal gyrus (Fig. 3). Profuse fibrillary astrogliosis and glial fibrosis replaced the zones of neuronal loss accompanied by microglia and rare phagocytes (Fig. 4a). The astrocytes in the zones of lesser involvement such as the subiculum were appreciably more plump and microglia more rod-shaped (Fig. 4b). Rare neuronophagia was noted in some areas (Fig. 4c). Microglial proliferation appeared to be the most subtle change, as it gradually disappeared in the lateral half of the parahippo-

TABLE
SUMMARY OF HISTOLOGICAL CHANGES

Anatomical areas	Histological changes				Comments
	PV cuff	Neuronal loss	Microglia	Astrogliosis	
Cerebral cortex	+	++	+	++	Only in insula and periamygdaloid cortex
Basal ganglia	0	0	0	0	
Thalamus	++	+	+	+	Only in dorsal medial nucleus and nucleus centrum medianum
Hypothalamus	++	0	0	0	
Hippocampus	+++	+++	++	+++	Similar but less severe changes in amygdala
Midbrain	+	+	+	++	
Pons	++	+++	++	++	Periaqueductal grey and nucleus of inferior colliculus
Medulla	++	0	++	++	
Cerebellum	0	0	0	0	Neuronal loss localized to region of locus caeruleus
Spinal cord	+	0	0	+	
					Especially in inferior olives

0 = no change; + = mild; ++ = moderate; +++ = severe.

FIG. 4. Four panels showing characteristic histological changes in various affected areas: (a, top left) severe neuronal loss in Sommer's sector of hippocampus proper with profuse astroglia; (b, top right) astroglial hypertrophy and microglial proliferation in subiculum; (c, bottom left) neuronophagia in the dorsal nucleus of the raphe of the midbrain; (d, bottom right) perivascular cuff of lymphocytes with surrounding astroglia. H and E, $\times 115$, $\times 375$, $\times 440$, $\times 110$ respectively.

FIG. 5. Four examples of neuronal intracytoplasmic inclusion bodies in cerebral cortex (arrows). Note the polar displacement of the nucleus in each instance and the degenerated appearance of the cells. *H* and *E*, $\times 715$.

campal gyrus. Capillaries and larger vessels were cuffed with lymphocytes throughout the affected areas (Fig. 4d). The dentate fascia showed similar changes of severe neuronal loss and astrogliosis. The fimbria and alveus showed little evidence of myelin loss, although the severely affected hippocampus was devoid of myelinated fibres. The overlying meninges contained only rare lymphocytes, and the ependymal lining of the adjacent temporal horn was intact.

In the amygdaloid complex of nuclei and periamygdaloid cortex, neuronal loss was diffuse but less conspicuous than in the hippocampus, but there was a striking hypertrophy of astrocytes throughout the area. A diffuse microglial proliferation was a prominent feature along with scattered perivascular cuffs of lymphocytes.

Except for an isolated focus confined to a portion of a single gyrus in the insular cortex, liberal samp-

ling of other cortical areas showed no change. The affected area showed partial loss of neurones, especially in the external pyramidal layer, with reactive fibrillary astrogliosis and the presence of elongated rod cells. Rare neurones at the margins of the zone of degeneration contained irregular, granular, eosinophilic, centrally located cytoplasmic inclusion bodies with margination of the Nissl substance and displacement of the nucleus to one side (Fig. 5). The inclusions were sometimes irregularly shaped coarse masses and in other cells finely granular. No intranuclear inclusion bodies were present. Sparse but definite lymphocytic infiltrations were noted in the overlying meninges and around blood vessels within the surrounding brain substance. The basal ganglia were free of abnormality. The thalamus, on the other hand, showed focal areas of astroglial and microglial proliferation and perivascular cuffs

FIG. 6. *Tegmentum of rostral pons showing severe loss of neurones in locus caeruleus bilaterally (arrows) without other abnormality aside from small perivascular cuffs. H and E, $\times 20$. Insert shows detail of locus caeruleus which is virtually devoid of neurones and contains pigment droplets indicated by arrow. H and E, $\times 120$*

of lymphocytes with mild to moderate neuronal loss in portions of the dorsomedial nucleus and nucleus centrum medianum. In the midbrain, there was microglial proliferation, astroglial hypertrophy, perivascular cuffs, and rare neuronophagia involving the nucleus of the inferior colliculus and the dorsal nucleus of the raphe. In the pons, there was localized but severe neuronal loss of the locus caeruleus bilaterally accompanied by extracellular pigment deposits and astrogliosis (Fig. 6). The vessels of the surrounding areas showed perivascular cuffs. The dorsal and ventral tegmental nuclei and the superior central tegmental nucleus showed normal neuronal populations with no reactive changes. No perceptible neuronal loss was appreciated in the medulla with the possible exception of the inferior olivary nuclei where astroglial hypertrophy was accompanied by microglial proliferation. Fibrillary astrocytes were prominent along the floor of the fourth ventricle but without perceptible neuronal loss. There was no evidence of increased vascularity anywhere along the floor of the fourth ventricle, and the medial and lateral medullary reticular formations were free of abnormality. Randomly scattered perivascular cuffs, sometimes quite heavy, were present throughout the

medulla but most prominent around the inferior olives. Rare perivascular cuffs were noted in the spinal cord without other change. The cerebellum was normal. The histological changes at the various levels of the central nervous system are summarized in the Table.

ELECTRON MICROSCOPY Small blocks of formalin fixed tissues were removed from the dorsal cell band and end plate of the hippocampus from sections adjacent to those showing neuronal degeneration obtained at necropsy. Minced blocks were washed in the sucrose-cacodylate buffer and post-fixed in 1% osmium tetroxide fixative, dehydrated through graded ethanol and propylene oxide, and embedded in Epon. Thin sections stained with lead citrate were examined under the Hitachi HU-11C electron microscope.

As expected, there was poor preservation of cell membranes and organelles, and cell relationships and identifying details were lost; however, oligodendrocytes and astrocytes were identifiable by their nuclear size and shape and closely packed fine glial fibrils associated with the latter. No neurones were identified. No particles of viruses were found.

DISCUSSION

ENCEPHALITIS ASSOCIATED WITH CARCINOMA Greenfield (1934) described two elderly patients with subacute spinocerebellar degeneration one of whom had an associated bronchial carcinoma. This patient was a 57 year old man who presented with shooting pains in the legs who then developed weakness of the legs, ataxia, hyporeflexia, and a rapidly progressive dementia over a seven month period. His spinal fluid was under normal pressure, but it contained 120 mononuclear cells per mm³, a total protein of 45 mg/100 ml, and a 'strongly positive globulin reaction'. Pathologically, the cerebellum showed widespread loss of Purkinje cells with reactive Bergmann's gliosis with no apparent loss of granule cells. No inflammatory changes were noted in the cerebellum other than in the dentate nucleus, which was 'degenerated' with an excess of microglia. Severe neuronal loss and microglial proliferation were noted in the subthalamic body. Perivascular cuffing with lymphocytes was widespread throughout the brain-stem and spinal cord, but they were also noted in the cornu ammonis and 'under the Rolandic cortex'. The condition of the hippocampal formation was not further detailed. In his conclusion, the author did not relate these degenerative and inflammatory changes of the central nervous system to the carcinoma.

Brain *et al.* (1951) described three patients with dementia, of whom two were found to have perivascular cuffing in the medulla, cerebellum, and spinal cord, mainly in the meninges of the latter two areas, but the authors attributed this inflammatory change to a 'reaction to rapidly degenerating nervous tissue'.

Charatan and Brierley (1956) reported three patients with symptoms resembling a 'toxic confusional psychosis' who had oat cell carcinoma. Two of the three patients presented with psychosis preceding the discovery of the pulmonary neoplasm. However, no convincing histological changes were demonstrated to account for the dementia.

Brierley *et al.* (1960) described three cases of subacute encephalitis mainly affecting the limbic areas occurring in later adult life. In one case, a neoplasm was demonstrated in association with the encephalitis, although it was suspected but

not found in one other case. In the case with the neoplasm, mediastinal and hilar lymph nodes were replaced by oat cell carcinoma, but, as in our case, no primary lesion was found in the lung. This patient (case 2) was a 58 year old man who developed an illness lasting 11 weeks beginning with respiratory symptoms and depression, terminating in a rapidly progressive dementia. The CSF contained 24 cells per mm³ (97% lymphocytes), total protein of 90 mg/100 ml, and colloidal gold curve of 5555554321. Widespread but not generalized inflammatory and degenerative changes of neurones were noted throughout the brain, characterized by perivascular cuffs of round cells and astroglial and microglial proliferation. These changes were most severe in the parahippocampal gyrus, subiculum, Ammon's horn, amygdaloid complex of nuclei, and insular cortex. Although the authors commented on the possible association of the encephalitis with the presence of carcinoma in one of their cases, they concluded, 'it seems most unlikely that this finding is in any way related to the encephalitis but its occurrence should be noted'. As to the pathogenesis of the encephalitis, a viral aetiology was suspected on the basis of the histological appearance, but the authors concluded that virological studies were necessary to substantiate the pathogenesis. Subsequently, additional case reports strengthened the association between encephalitis and carcinoma (Henson *et al.*, 1965; Corsellis *et al.*, 1968). Various authors favoured a degenerative theory (Verhaart, 1961; Ulrich *et al.*, 1967), a viral theory (Störting *et al.*, 1962; Henson *et al.*, 1965; Yahr *et al.*, 1965), and an immunological one (Russell, 1961).

Our patient presented with multiple manifestations of the remote effects of carcinoma, and, although an occult neoplasm was strongly suspected, it was not demonstrated until the post-mortem examination. These symptoms included arthralgias, a rapidly progressive mental deterioration, and unexplained weight loss. There was a paucity of abnormal laboratory findings. Generalized slowing on the electroencephalograph (EEG), anaemia, and a CSF total protein of 88 mg/100 ml were noted.

A review of 28 previously reported cases (Greenfield, 1934; Brain *et al.*, 1951; Charatan and Brierley, 1956; Brierley *et al.*, 1960; Verhaart, 1961; Störting, 1962; Henson *et al.*,

1965; Yahr *et al.*, 1965; Morton *et al.*, 1966; Corsellis *et al.*, 1968; Glaser and Pincus, 1969) disclosed the following findings which may be useful in clinical diagnosis. This disorder occurred most frequently between the ages of 50 and 70 years (21 of 28 cases) with the youngest being 39 years of age and the oldest 80 years. There was no definite sex preponderance, with the males affected in 15 of 28 cases. The course of the disease varied between 2½ months to 24 months. Mental symptoms in general occurred in 23 of 28 cases and included confusion, agitated depression, hallucination, disorientation, and most commonly memory impairment.

Neurological examination revealed no consistent characteristic constellation of signs other than dementia, but the findings of other overlapping neuromuscular syndromes, especially those of peripheral sensory neuropathy, and cerebellar degeneration (Greenfield, 1934; Brain *et al.*, 1951) were present.

Abnormal elevation of CSF protein was noted in 14 of the 22 cases studied, and leucocytes in the spinal fluid were increased in eight of 22. Although not characteristic, abnormalities in the EEG were noted in six of the eight cases studied. Where performed, radiographic contrast studies of the brain were normal.

Among other possibilities, the diagnosis of encephalitis with a remote carcinoma should be strongly suspected in an afebrile patient presenting with a rapidly progressive mental deterioration in middle or late life, with or without other neurological signs, elevated protein and increased cells in the CSF, nonspecific EEG abnormality, and normal cerebral radiographic contrast studies.

CENTRAL ALVEOLAR HYPOVENTILATION Our patient had an interesting clinical syndrome of hypoventilation which was related to the primary problem of encephalitis only by the selective anatomical involvement by this process in the brain-stem. Peripheral causes of hypoventilation such as mechanical respiratory dysfunction, metabolic causes, and pulmonary obstructive diseases were minor if present, and a recurrent right lower lobe pneumonia was not considered severe enough to account for the entire problem. The history of 'emphysema' was not confirmed clinically or at postmortem

examination. Although hypoventilating at rest, the patient could take deep breaths on command. These findings led to a diagnosis of central alveolar hypoventilation syndrome. Only to the extent that our patient could voluntarily improve his respirations could the term 'Ondine's curse' be applied to his respiratory disorder (Severinghaus and Mitchell, 1962; Mellins *et al.*, 1970).

Anatomical studies of patients with central alveolar hypoventilation syndrome have been few, and the causes have been varied. These causes have included bulbar poliomyelitis (Sarnoff *et al.*, 1951; Plum and Swanson, 1958), brain stem tumour (Plum, 1970), infarcts of the brain-stem (Plum and Alvord, 1964; Devereaux *et al.*, 1973), bilateral high cervical cordotomy (Belmusto *et al.*, 1963), and various encephalitides—for example, Western equine encephalitis and von Economo's epidemic encephalitis (Garland and Linderholm, 1958). Where anatomical studies were performed, the lesions have been localized to the medullary levels in such areas as the region around the floor of the fourth ventricle (Seriff, 1965), lateral medullary tegmentum (Devereaux *et al.*, 1973), and ventral lateral medullary reticular formation (Plum and Swanson, 1958).

The classical view of the central regulation of respiration has placed the primary respiratory centres in the medullary reticular formation with a capacity for autorhythmic activity (Pitts, 1946; Oberholzer and Tofani, 1960). In turn, these centres are under higher level controls from pontine centres, diencephalon, and various cortical areas. The two known pontine centres are the 'pneumotaxic centre' localized to the rostral dorsolateral pontine tegmentum (including the locus caeruleus) and the 'apneustic centre' occupying a more extensive region in the middle and caudal pons (Ngai and Wang, 1957; Wang *et al.*, 1957; Oberholzer and Tofani, 1960). Destruction of the locus caeruleus *in man* associated with various pathological states such as diabetic coma, pernicious anaemia, and arteriosclerosis was accompanied by a respiratory disorder characterized by a normal rhythm but with deepening of the inspiratory and expiratory phases (Hess and Pollack, 1924). These cases showed no abnormality of the vagal nuclei and the medullary reticular formation, and Hess

and Pollack held that the locus caeruleus is a respiratory centre.

The apneustic centre exerts a tonic inspiratory and rhythmic influence on the medullary inspiratory centre, and apneustic respiration develops when the inhibitory (expiratory) influence of the pneumotaxic centre is abolished (Breckenridge and Hoff, 1953; Oberholzer and Tofani, 1960). Bilateral destruction of the locus caeruleus caused apneusis in cats, and stimulation caused expiratory pauses before vagal section and inspiratory pauses after vagotomy (Johnson and Russell, 1952). Degeneration studies indicate that the locus caeruleus exerts its influence on the medullary respiratory centres through the lateral tegmentoreticular tract (Johnson and Russell, 1952; Russell, 1955). Examination of the brain-stem in our patient failed to uncover any appreciable neuronal loss in the medulla; however, the locus caeruleus on both sides showed severe degeneration. In the presence of these discrete destructive lesions of the locus caeruleus, and in the absence of any major medullary or other brain-stem lesions, it would appear that the locus caeruleus and its connections to the medullary reticular formation mediated through the lateral tegmentoreticular tract could have played an important role in this patient's hypoventilation syndrome. However, this conclusion remains speculative, inasmuch as the part played by the limbic and cortical lesions and the meaning of the mild but definite fibrillary astrogliosis along the floor of the fourth ventricle cannot be properly assessed.

PATHOLOGICAL FINDINGS INCLUDING INTRACYTOPLASMIC INCLUSION BODIES The pathological changes and the clinical picture of encephalitis have not always been very well correlated. On the other hand, there are well-documented cases in which severe changes within the limbic system have been associated with dementia. Macroscopically, no distinctive changes were present, although slight cortical atrophy, mild ventricular dilatation, and a brownish discolouration within the hippocampal formation have been described (Verhaart, 1961; Corsellis *et al.*, 1968). Leptomeninges have been grossly normal. Typically, microscopic changes include perivascular cuffs of lymphocytes, focal neuronal loss, neuronophagia, microglial nodules, and

diffuse microglial and astroglial proliferation (Brierley *et al.*, 1960; Henson *et al.*, 1965; Corsellis *et al.*, 1968). Although these changes are widespread, they are most prominent within the limbic system (Brierley *et al.*, 1960; Verhaart, 1961; Störing *et al.*, 1962; Henson *et al.*, 1965; Corsellis *et al.*, 1968), certain cortical areas (Brierley *et al.*, 1960; Morton *et al.*, 1966), and brain-stem (Henson *et al.*, 1965). One paper (Glaser and Pincus, 1969) described intranuclear inclusion bodies in oligodendrocytes and occasional neurones in a patient with a remote carcinoma. Norris *et al.* (1960) reported a patient who had progressive blindness and amyotrophy for 2½ years. Metastases were also found in the pancreas and lymph nodes with histology resembling oat cell carcinoma, but no primary pulmonary neoplasm was found. In the latter respect, this patient was similar to ours in whom oat cell carcinoma was found in the periaortic lymph nodes with no primary tumour in the lung. These authors reported 'diffuse motor neurone degeneration, with lymphocytic cuffing of small blood vessels' without further details as to the levels of the involvement of the central nervous system. No inclusion bodies were demonstrated by light microscopy. However, electron microscopic studies of material removed from the medulla and spinal cord contained intranuclear particles measuring 25–30 μm in diameter suggestive of viral particles. To our knowledge, the neuronal intracytoplasmic inclusions found in our case have not been noted previously. Such inclusion bodies suggest viral aggregates, but electron microscopic demonstration and virological studies are needed to clarify this finding. Electron microscopic examination of our material failed to uncover any particles suggesting viruses, but sampling was limited.

We thank Mr Edgar Davis for his assistance with the photography and Mrs Elaine Jones for preparation of the manuscript.

REFERENCES

- Belmusto, L., Brown, E., and Owens, G. (1963). Clinical observations on respiratory and vasomotor disturbances as related to cervical cordotomies. *Journal of Neurosurgery*, **20**, 225–232.
- Brain, W. R., Daniel, P. M., and Greenfield, J. G. (1951). Subacute cortical cerebellar degeneration and its relations to carcinoma. *Journal of Neurology, Neurosurgery, and Psychiatry*, **14**, 59–75.

- Brain, Lord, and Norris, F. H., Jr (eds.) (1965). *The Remote Effects of Cancer on the Nervous System*. Grune and Stratton: New York.
- Breckenridge, C. G., and Hoff, H. E. (1953). Ischemic and anoxic dissolution of the supramedullary control of respiration. *American Journal of Physiology*, **175**, 449–457.
- Brierley, J. B., Corsellis, J. A. N., Hierons, R., and Nevin, S. (1960). Subacute encephalitis of later adult life. Mainly affecting the limbic areas. *Brain*, **83**, 357–368.
- Case Records of the Massachusetts General Hospital (Case 42—1970) (1970). *New England Journal of Medicine*, **283**, 806–814.
- Charatan, F. B., and Brierley, J. B. (1956). Mental disorder associated with primary lung carcinoma. *British Medical Journal*, **1**, 765–768.
- Corsellis, J. A. N., Goldberg, G. J., and Norton, A. R. (1968). 'Limbic encephalitis' and its association with carcinoma. *Brain*, **91**, 481–496.
- Devereaux, M. W., Keane, J. R., and Davis, R. L. (1973). Automatic respiratory failure associated with infarction of the medulla. *Archives of Neurology (Minneapolis)*, **29**, 46–52.
- Garlind, T., and Linderholm, H. (1958). Hypoventilation syndrome in a case of chronic epidemic encephalitis. *Acta Medica Scandinavica*, **162**, 333–349.
- Glaser, G. H., and Pincus, J. H. (1969). Limbic encephalitis. *Journal of Nervous and Mental Disease*, **149**, 59–67.
- Greenfield, J. G. (1934). Subacute spino-cerebellar degeneration occurring in elderly patients. *Brain*, **57**, 161–176.
- Henson, R. A., Hoffman, H. L., and Urich, H. (1965). Encephalomyelitis with carcinoma. *Brain*, **88**, 449–464.
- Hess, L., and Pollack, E. (1924). Zerebrale dyspnöe. *Medizinische Klinik*, **20**, 1422–1425.
- Johnson, F. H., and Russell, G. V. (1952). The locus coeruleus as a pneumotoxic center. (Abstract.) *Anatomical Record*, **112**, 348.
- Mellins, R. B., Balfour, H. H., Jr, Turino, G. M., and Winters, R. W. (1970). Failure of automatic control of ventilation (Ondine's curse). Report of an infant born with this syndrome and review of the literature. *Medicine (Baltimore)*, **49**, 487–504.
- Morton, D. L., Itabashi, H. H., and Grimes, O. F. (1966). Nonmetastatic neurological complications of bronchogenic carcinoma: the carcinomatous neuromyopathies. *Journal of Thoracic and Cardiovascular Surgery*, **51**, 14–29.
- Ngai, S. H., and Wang, S. C. (1957). Organization of central respiratory mechanisms in the brain stem of the cat: localization by stimulation and destruction. *American Journal of Physiology*, **190**, 343–349.
- Norris, F. H., Jr, McMenemey, W. H., and Barnard, R. O. (1970). Unusual particles in a case of carcinomatous neuronal disease. *Acta Neuropathologica (Berl.)*, **14**, 350–353.
- Oberholzer, R. J. H., and Tofani, W. O. (1960). The neural control of respiration. In *Handbook of Physiology. Section 1. Neurophysiology*. Vol. 2, pp. 1112–1129. Edited by J. Field, H. W. Magoun, and V. E. Hall. American Physiological Society: Washington.
- Pitts, R. F. (1946). Organization of the respiratory center. *Physiological Reviews*, **26**, 609–630.
- Plum, F. (1970). Neurological integration of behavioural and metabolic control of breathing. In *Breathing*, pp. 159–181. A Ciba Foundation Symposium. Edited by R. Porter. Churchill: London.
- Plum, F., and Alvord, E. C., Jr (1964). Apneustic breathing in man. *Archives of Neurology*, **10**, 101–112.
- Plum, F., and Swanson, A. G. (1958). Abnormalities in central regulation of respiration in acute and convalescent poliomyelitis. *Archives of Neurology and Psychiatry*, **80**, 267–285.
- Russell, D. S. (1961). Encephalomyelitis and 'carcinomatous neuropathy'. In *Encephalitides*, pp. 131–135. Edited by L. van Bogaert, J. Radermecker, J. Hozay, and A. Lowenthal. Elsevier: Amsterdam.
- Russell, G. V. (1955). The nucleus locus coeruleus (dorso-lateral tegmentum). *Texas Reports on Biology and Medicine*, **13**, 939–988.
- Sarnoff, S. J., Whittenberger, J. L., and Affeldt, J. E. (1951). Hypoventilation syndrome in bulbar poliomyelitis. *Journal of the American Medical Association*, **147**, 30–34.
- Seriff, N. S. (1965). Alveolar hypoventilation with normal lungs: the syndrome of primary or central alveolar hypoventilation. *Annals of the New York Academy of Sciences*, **121**, 691–705.
- Severinghaus, J. W., and Mitchell, R. A. (1962). Ondine's curse—failure of respiratory center automaticity while awake. (Abstract.) *Clinical Research*, **10**, 122.
- Störing, G. E., Hauss, K., and Ule, G. (1962). Zur topischen Diagnostik des amnestischen Symptomenkomplexes. *Psychiatria et Neurologia*, **143**, 161–177.
- Strieder, D. J., Baker, W. G., Baringer, J. R., and Kazemi, H. (1967). Chronic hypoventilation of central origin. A case with encephalitis lethargica and Parkinson's syndrome. *American Review of Respiratory Disease*, **96**, 501–507.
- Ulrich, J., Speiss, H., and Huber, R. (1967). Neurologische Syndrome als Fernwirkung maligner Tumoren. *Schweizer Archiv für Neurologie, Neurochirurgie und Psychiatrie*, **99**, 83–100.
- Verhaart, W. J. C. (1961). Grey matter degeneration of the C.N.S. in carcinosis. *Acta Neuropathologica (Berl.)*, **1**, 107–112.
- Wang, S. C., Ngai, S. H., and Frumin, M. J. (1957). Organization of central respiratory mechanisms in the brain stem of the cat: genesis of normal respiratory rhythmicity. *American Journal of Physiology*, **190**, 333–342.
- Yahr, M. D., Duvoisin, R. C., and Cowen, D. (1965). Encephalopathy associated with carcinoma. *Transactions of the American Neurological Association*, **90**, 80–86.