MENTAL DISORDER ASSOCIATED WITH PRIMARY LUNG CARCINOMA

BY

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The association of bronchial carcinoma with cerebellar degeneration is now well known (Brain *et al.*, 1951; Henson *et al.*, 1954). Recently, too, attention has been directed towards the occurrence of neuropathy and myopathy in cases of carcinoma of the bronchus (Henson *et al.*, 1954; Heathfield and Williams, 1955) following the earlier reports of Wyburn-Mason (1948) and Denny-Brown (1948).

Mental deterioration, according to Brain *et al.* (1951), occurred as a fairly early symptom in three of their four cases, and was also described as a later feature in Greenfield's (1934) cases. In three out of five of the cases of Henson *et al.* (1954) which presented with predominantly cerebellar disorders, dementia, euphoria, and memory loss are also mentioned. In another case whose main disability was a polyneuritis (Case 9), dementia was an early finding. Reference occurs to "gross anxiety" in Case 19, where a myasthenic and myopathic picture developed in conjunction with carcinoma of the bronchus; later this patient was said to have become "mentally euphoric." Microscopical changes in the cerebral cortex have been ill defined or totally lacking; but here, as Brain *et al.* (1951) point out, "technical difficulties, especially the large area of cortex to be examined, make a histological assessment of the degree of degeneration in it difficult and uncertain."

In this paper three cases of severe mental disturbance are described, which either preceded or overshadowed the presence of bronchial carcinomas. All the cases occurred in males. Cerebral metastases were not found.

Case 1

A bricklayer aged 53 was admitted to the Maudsley Hospital on April 10, 1953. There was no family history of mental illness or any evidence of a previous breakdown. He was described as a man who had always worried over things, restless, and full of nervous energy, often depressed and pessimistic but never bad-tempered. For many years he had complained of dyspepsia, and had been given a careful diet by his wife. He was known to have no very strong feelings about religion. He rarely drank, but smoked about forty cigarettes a day.

His wife reported that he had become more depressed since September, 1952. He complained more of his stomach and visited his doctor frequently. He ate and slept poorly; many nights he did not retire, but dozed in an armchair. In December, 1952, he was noted to be "vacant" at times. He became quarrelsome and less sociable. Then he announced people were all against him, his workmates were plotting, and, he said, his family were trying to annoy him. On Boxing Day he suddenly became excited, and ran across the landing in the early hours of the morning, shouting that he must go to work. With some difficulty he was calmed down, and, in fact, after the Christmas holidays he returned to work.

In February, 1953, he again behaved strangely. He insisted that his wife should leave her work and go with him to Mitcham. When they arrived there he told her to meet him in an hour's time, and then wandered off. Next day (Sunday) he was still agitated, saying, "You can't trust anybody." His daughter had gone off to Sunday school, and, in the words of his wife, "that seemed to set him off talking about religion." He locked his wife and little girl in a room with him, made his wife sit still on a chair, and started reading the Bible and praying aloud. He kept calling out to "Lord Jesus" and scribbling on the walls. After his son had sent for the police the patient threw the Bible on the fire, then picked up the burning coals in his hands and rubbed them on his face, sustaining burns of his forehead. He was sent to an observation ward, and thence transferred to a mental hospital on February 16.

Examination there revealed a small, pale, sandy-haired man in good general health. On physical examination the only abnormality noted was a second-degree burn of the forehead with singeing of the hair. He was quite co-operative, and explained away the burn by stating that he had fallen asleep and slipped on to the fire. No delusions or hallucinations were recorded, and he was correctly orientated. The haemoglobin was found to be 104% and sedimentation rate 5 mm. an hour. He made steady improvement after his admission, no further abnormalities being observed. A diagnosis of paranoid schizophrenia was made. He soon returned to work, but had another "vacant" attack, became very restless, and had to be readmitted to the observation ward, "completely irrational, walking up and down and talking nonsense."

On admission to the Maudsley Hospital on April 10 he was found to be thin—weight 98 lb. (49 kg.)—anaemic (haemoglobin 52%), and with a cough. He had a pulse rate of over 100 a minute, but was afebrile. The liver was enlarged, with a hard irregular edge. No localizing signs were found in the chest or central nervous system. His mental state was thought to be normal apart from anxiety and some depression. He realized he had "said silly things to everybody in the room," seemed ashamed of his lapses, and was reluctant to speak of them. The E.S.R. was 68 mm. an hour, blood urea 24 mg. per 100 ml., and the W.R. negative. A chest radiograph on April 14 showed a mass at the right hilum. Tests for occult blood in the faeces were strongly positive. An E.E.G. showed a moderate diffuse abnormality of a non-specific kind without localizing features. These findings led to a tentative diagnosis of bronchial carcinoma with hepatic and cerebral metastases. The patient went rapidly downhill, and died 12 days later with terminal haemorrhage.

Post-mortem Findings

The right lung showed almost complete replacement of the middle lobe by a tumour, which extended into the upper lobe. The orifice of the right middle lobe bronchus was almost completely occluded by haemorrhagic necrotic material. The right main bronchus, 2 cm. from the carina, was stenosed owing to metastatic deposits in the adjacent lymph nodes. Invasion of the tracheobronchial lymph nodes on the right descended to the aortic and vena caval orifices in the diaphragm, that of the vena cava being partially stenosed.

There was considerable metastatic invasion of the superior mesenteric lymph nodes. The liver was bulky (2,625 g.) and contained numerous carcinomatous deposits.

The brain weighed 1,790 g. There was no external evidence of raised intracranial pressure, nor of secondary tumour deposits. The basal vessels and meninges were normal. After hardening in 10% formalin and sectioning, there was no evidence of secondary deposits or of hydrocephalus. The junction of the cortex and white matter was well defined, but the white matter was of creamy colour and consistency, and appeared rather bulky. This was associated with compression of the lateral and third ventricles, which were reduced to narrow slits.

Histological Appearances

The primary tumour was an anaplastic mixed oat- and round-cell carcinoma of the bronchus showing areas of haemorrhage and necrosis.

The cerebral cortex showed no abnormality of cyto-architecture. There was a moderate increase in astrocytic nuclei in the outer layer. In Holzer preparations a marginal gliosis could be seen in all regions of the cortex, but greatest in the occipital and inferior temporal areas and least in the frontal. This gliosis could be traced down to the middle of the third layer. The cortical neurones showed no evidence of ischaemia, neurofibril change, or pellagra. In the central white matter there was a fairly large increase in astrocytes with only a slight increase in the oligodendroglia.

Dilated perivascular spaces were conspicuous throughout the white matter, producing a fine honeycombed appearance, which was also present to a less extent in the cortex, particularly in the deeper layers. The caudate nucleus and putamen were normal. There was a perivascular increase in fibrous glia in the inner segment of the globus pallidus, and a light gliosis in the zona incerta. Holzer preparations showed a moderate fibrous gliosis throughout the centrum ovale, perivascular rather than diffuse in its distribution, and more intense in occipital than in temporal and orbital regions. A moderate subependymal gliosis could be traced from the third ventricle throughout the aqueduct to the floor of the fourth ventricle. There was a similar gliosis around both lateral ventricles.

Within the cerebellum, the cells of the Purkinje and granule layers were normal, but the two layers were separated by a clear interval, most pronounced over the convexities of the folia. There was a moderate increase of the Bergmann glia. Astrocytes were also increased in both the dentate nucleus and the central white matter.

The spinal cord, spinal nerve roots, and dorsal root ganglia were not available for examination.

Case 2

A millwright aged 43 was admitted to the Maudsley Hospital on June 7, 1951. There was no family history of mental illness or history of previous breakdown. The patient's wife had left him, after a rather unhappy marriage, in 1947, and since then he had been solitary and self-neglectful. He suffered from "chronic bronchitis" and was a very heavy cigarette smoker.

On November 25, 1950, he attended the Brompton Hospital for the first time, with a history of haemoptysis eight months previously. No abnormal physical signs were detected, but an x-ray film revealed abnormal shadowing at the right base. At a later visit (May 31, 1951) the chest film showed collapse of the right upper lobe, with a possible mass at the hilum.

He was admitted to an observation ward on June 2, having wandered away from his home, in a depressed and apathetic state. He refused to speak or to eat, stared, and rocked himself to and fro. He appeared to have lost his memory; but four days later, while still in the observation ward, his memory returned and he recognized his sister. On June 7, after admission to the Maudsley Hospital, he was found to be afebrile, and had diminished air entry and percussion note at the right apex. He was observed to limp on the left leg, but there were no abnormal neurological signs, apart from some tenderness of the calf muscles. The only mental abnormality was some lability of mood. His intelligence quotient on progressive matrices was 90 and on the Mill Hill vocabulary 105. The W.R. was negative and the E.S.R. 12 mm. an hour. An x-ray film of the chest showed collapse and consolidation of the right upper lobe, together with a mass extending upwards from the hilum. On July 4 lumbar puncture revealed a C.S.F. pressure of 100 mm. water. There was 55 mg. of protein per 100 ml., cells were not increased, the Lange curve was normal, and the W.R. was negative. Four separate E.E.G.s were recorded in July and were essentially normal.

The patient had alternating lucid and confused periods. In the latter his behaviour was strange, and he verberated—for example, he was constantly begging pardon (on one occasion over a period of 15 minutes) for dropping cigarette ash on the floor. He kept up a continuous nonsensical and disconnected chatter—on recovery claiming an amnesia for these confused periods. During July the suspicion of cerebral metastases led to repeated neurological examinations, but with negative results until July 30, when extensor plantar responses were observed, strongly on the right and less so on the left.

Mentally he continued to deteriorate. On one occasion echolalia was noted. In his confused phases his behaviour would become very disturbed; he would disarrange the bed, tear up letters, throw food about, etc. At the beginning of August he developed pyrexia for the first time. At the end of August his liver became palpable, and he developed finger- and toe-clubbing. He died on October 11, after developing mediastinal obstruction a few days previously.

Post-mortem Findings

The mucous membrane of the right main bronchus showed a smooth white elevation, and where the bronchus divided into upper and lower branches the mucosa had been penetrated by soft white tumour tissue. The growth extended into the right upper and middle lobes, the ventral part of the upper lobe being completely replaced by tumour which extended into the mediastinum surrounding the aorta. The upper lobe was adherent to the parietal pleura, which was thickened. Dilatation of the smaller bronchi and bronchioles in the right lower lobe was observed. There were two nodules of tumour in the position of the paratracheal lymph nodes. The liver showed two very large masses (approximately 6 cm. in diameter), and was peppered with smaller nodules of tumour.

Histological Appearances

The primary tumour was a carcinoma of the bronchus of small oat-cell type.

The brain weighed 1,360 g. There was no naked-eye evidence of metastases on sectioning. In all areas of the cerebral cortex the lamination was well preserved. The pyramidal cells of Ammon's horn were intact throughout, the only abnormality being a mild subependymal gliosis. In the thalamus the neurones were normal in form and number, but there was a light gliosis, particularly evident in the medial part of the structure and showing perivascular accentuation.

A constant finding in all parts of the subcortical white matter of the cerebrum was a mild but unequivocal fibrous gliosis, most conspicuous around blood vessels. A marginal gliosis of similar intensity was also to be seen in the cortex and could be traced down into the second lamina. Gliosis was also present in a subependymal situation in the lateral ventricles, the third ventricle aqueduct, and the floor of the fourth ventricle. The gliosis was rather more marked in the hippocampus, where it could easily be traced down through the layer of pyramidal cells, but was not present in the end folium.

No evidence of abnormality was found throughout the pyramidal system, other than a fine honeycombing which involved all the white matter but was rather less pronounced than in Case 1. The Purkinje cells and granule cells of the cerebellar cortex were normal in structure and numbers, but it was noticeable that the two layers were separated by a clear space, particularly over the summits of the folia. The neurones of the anterior and posterior horns of the cervical cord were normal, and there was no abnormality of myelination of the long tracts. Around the central canal a mild subependymal gliosis could be detected. The anterior and posterior nerve roots and all elements of the dorsal root ganglia presented normal appearances.

Case 3

A stockbroker aged 63 was admitted to the Bethlem Royal Hospital on January 8, 1953. No family history of mental illness was known. The patient had been invalided from the R.A.F. in the second world war with "spastic colitis." The history of the present illness as obtained from his wife was as follows. At the beginning of 1952 he slowed down in his activities and said he felt tired. When on holiday in the July he became what was described as "delirious," and was thought at the time to be suffering from heat exhaustion. On July 2 he sat up in bed suddenly, and talked incessantly to himself the whole night about past events, while fumbling with the bedclothes. In the morning he had a complete amnesia for his behaviour. After this his wife noted that he would quite suddenly fall asleep in his chair, or his memory would fail from time to time.

At the end of July he was examined, but there were no abnormal physical signs. The cerebrospinal fluid was normal in all respects. An air encephalogram was normal. About this time he had three major convulsions. The diagnosis was thought to lie between Alzheimer's disease and cerebral metastases from a carcinoma of the bronchus. An x-ray film of the chest in November revealed some shadowing at the right base. Between July and December his course was fluctuating, with lucid intervals lasting for a few days. However, before admission to the Bethlem Royal Hospital he had lost weight, did not ask for food, and became apathetic and incontinent.

On admission he looked old, and was restless and fumbling. There was a perioral tremor. He was incontinent of urine, lacked initiative, and required hand-feeding. He tended to wander about at night. His speech was observed to be indistinct; he diverged from the point, and questions had to be repeated. He perseverated at times. His mood was drowsy and apathetic, and his attention and concentration were greatly impaired. He was found to be correctly orientated.

He was very wasted, with a dorsal kyphosis, later shown to be due to neoplastic involvement of the fifth to the ninth thoracic vertebrae. He remained afebrile until March, 1953, after which there was slight pyrexia. No further abnormal physical signs were ever detected in the central nervous system. An x-ray film of the chest showed a mass in the left paratracheal region, and a left pleural effusion; there was a healing pathological fracture of a rib, and the neoplastic involvement of the vertebrae already mentioned. The sedimentation rate was 16 mm. an hour, haemoglobin 72% (11.2 g.% Haldane), and W.B.C. 7,300.

His mental state continued to show great fluctuation. He gradually became weaker physically, and died on March 20, about 2½ months after admission.

Post-mortem Findings

A large white irregular mass occupied the hilar region of the left lung, stenosing and infiltrating the main bronchus. Hilar and mediastinal glands were enlarged and adherent, and some showed central necrosis. The liver was enlarged and contained numerous secondary deposits. The brain weighed 1,390 g. In coronal slices there was no evidence of secondary tumour deposits, and the lateral and third ventricles were of normal size.

Histological Appearances

Sections of a secondary deposit in the liver presented the appearances of an oat-cell carcinoma of the bronchus with a marked tendency to alveolar arrangement within well-defined trabeculae.

Brain.—In all regions of the cortex examined the cyto-architecture was well preserved, and no significant changes were to be seen in individual neurones. A consistent finding was a moderate increase in astrocytic nuclei in the molecular layer corresponding to a moderate fibrous gliosis in Holzer and Mallory preparations. This was most marked in the

insula. Similar astroglial proliferation was also present in the subcortical white matter and corresponded to a light fibrous gliosis, largely perivascular in distribution and slightly greater in the temporal lobe than elsewhere. There was a honeycomb appearance of the white matter similar to that seen in Case 2. The Purkinje and granule cell layers of the cerebellum were normal but separated by a variable interval which, as in the other cases, was widest over the summits of the folia. In the central white matter of the cerebellar hemispheres there was dilatation of the perivascular spaces. The latter were the foci of origin of a light fibrous gliosis which could be traced through all parts of the white matter. A moderate subependymal fibrous gliosis was present in the lateral, third, and fourth ventricles, and was more extensive and intense in Ammon's horn, while not involving the end folium.

The spinal cord and peripheral nervous system were not available for examination.

Discussion

Clinically these three cases presented features of a toxic confusional psychosis running a fluctuating course. "Lucid intervals" occurred in all. There was no clear evidence of any neurological abnormality, and convulsions occurred only in Case 3. Mental changes preceded the signs of pulmonary neoplasm in Cases 1 and 3 by six and four months respectively. In Case 2 the striking psychotic features appeared some 14 months after the initial symptom (haemoptysis) of the lung growth.

It is noteworthy that the electroencephalogram in Cases 1 and 2 showed little abnormality and that the cerebrospinal fluid in Cases 2 and 3 was normal. Further, there was no evidence of severe secondary infection—for example, hectic fever, sweating, copious sputum, albuminuria, or leucocytosis. Peripheral neuropathy and myopathy were not clinically demonstrable, nor was involvement of the cerebellum. All cases showed extensive bronchial carcinomas of anaplastic type at necropsy, but without evidence of cerebral metastases or meningeal carcinomatous infiltration. In each case the liver contained extensive metastatic tumour deposits.

It is to be noted that there was no degeneration of the cerebellar Purkinje cells as described by Brain *et al.* (1951). In Case 2 the spinal cord, dorsal root ganglia, and nerve roots were normal, and in all three cases there was no pathological evidence of pellagra or of Wernicke's encephalopathy. The sparing of such vulnerable areas as the Sommer sector of Ammon's horn, the globus pallidus, the Purkinje cells of the cerebellum, and the neurones of the third cortical layer militates against the presence of an anoxic state *in vivo*. In Case 3 the contribution of convulsions to the histological appearances of the brain of a man of 63 cannot readily be assessed, but there was no evidence of the usual anoxic sequelae.

Evidence for Oedema.—A gross increase in brain weight was present only in Case 1, that of Case 2 was within normal limits, and that of Case 3 was rather above average weight for that age (see Table). Further, white matter of

Weight of Brain

Case	Age	Brain Weight	
		Actual	Normal (Rössle, 1923)
2	43	1,360 g.	1,361 g.
1	53	1,790 g.	1,338 g.
3	63	1,390 g.	1,306 g.

creamy colour and consistency was present only in Case 1. The histological features of the white matter, similar in type but varying in intensity in the three cases, could be consistent only with an oedema of very brief duration. Thus there was no pallor of the myelin sheaths or any other evidence of their breakdown. The honeycomb appearance was probably due to some increase in interfascicular fluid. The astrocytes of the white matter exhibited various degrees

of swelling, but amoeboid or other degenerate forms were not seen. The interfascicular oligodendroglia were swollen in all cases, but Greenfield (1942) has reported the normality of these cells in the presence of obvious oedema associated with cerebral tumour, granuloma, and abscess. The absence of any activation of the microglia confirmed the lack of damage to the myelin sheaths.

It must be concluded, then, that the honeycombing of the white matter together with the increased brain weight of one case must represent an increase in the inter-fibre fluid of the central white matter of such brief duration that myelin damage and its associated glial reactions have not yet occurred.

In view of the relationship between hepato-cellular disease and organic dementia (passing into coma) described by Sherlock (1955), the presence of extensive liver metastases in these three cases must raise the question of a possible connexion between the liver damage and the mental state. Such a connexion would imply that liver damage due to tumour deposits is to be regarded as a factor in the aetiology of the mental state distinct from the metabolic effects of the primary growth itself. Further, psychiatric disorders in malignant disease may be present in the absence of liver metastases (Brierley, unpublished cases; Meerloo, 1944).

The precise nature of the metabolic disorder associated with bronchogenic carcinoma remains elusive, and there is, as yet, little to replace the suggestion of Denny-Brown (1948) that carcinomas may produce some metabolite which interferes with the metabolism of vitamins. The very pleomorphism of the neurological and psychiatric manifestations of carcinoma of the bronchus, with a neuropathological picture ranging from apparent normality to severe cell loss—for example, cerebellum—must imply a complex pathogenesis. A factor of some importance here may be the normal involutional process. This is suggested by the fact that in Cases 1 and 2 the marginal, subependymal, and white-matter gliosis could well be regarded as typical involutional change occurring at a presenile age (43 and 53 years). The interrelationship of involutional change, metabolic disorder due to carcinoma, and liver damage, and their contributions to the genesis of the psychiatric picture, cannot be assessed, but it is possible that in the presence of carcinoma involutional changes could be accelerated, and in the present cases might have contributed some structural basis for the mental changes.

The various instances of the association of carcinoma with psychiatric symptomatology have been well reviewed by Fischer-Williams *et al.* (1955), and the above three cases show that mental symptoms can also occur in the absence of cerebral metastases, meningeal infiltration, peripheral neuropathy, or myopathy. In view of the higher incidence of carcinoma in the older age groups, the possibility of a hidden neoplasm deserves consideration in middle-aged and elderly subjects admitted to observation wards of mental hospitals suffering from a subacute organic reaction.

Summary

Three cases of carcinoma of the bronchus in patients aged 53, 43, and 63 years are presented.

In Cases 1 and 3 psychotic features preceded symptoms due to the growth, and in Case 2 they occurred 14 months after the initial symptom of haemoptysis.

The psychiatric symptoms were non-specific and resembled a fluctuating toxic confusional psychosis in which "lucid intervals" were well marked. There were no associated neurological signs.

In all cases cerebral metastases or meningeal infiltration were absent. Liver metastases occurred in all three.

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REFERENCES

- Brain, W. R., Daniel, P. M., and Greenfield, J. G. (1951). *J. Neurol. Neurosurg. Psychiat.*, 14, 59.
Denny-Brown, D. (1948). *Ibid.*, 11, 73.
Fischer-Williams, M., Bosanquet, F. D., and Daniel, P. M. (1955). *Brain*, 78, 42.
Greenfield, J. G. (1934). *Ibid.*, 57, 161.
— (1942). *Proc. roy. Soc. Med.*, 35, 525.
Heathfield, K. W. G., and Williams, J. R. B. (1955). *Brain*, 77, 122.
Henson, R. A., Russell, D. S., and Wilkinson, M. (1954). *Ibid.*, 77, 82.
Meerloo, A. M. (1944). *J. Amer. med. Ass.*, 126, 558.
Rösle, R. (1923). *Wachstum und Altern*. München.
Sherlock, S. (1955). *Proc. roy. Soc. Med.*, 48, 479.
Wyburn-Mason, R. (1948). *Lancet*, 1, 203.

FAILURE TO PREVENT CONGENITAL SYPHILIS

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Congenital syphilis is an eminently preventable disease provided the maternal infection is recognized in time to be adequately treated. As acquired syphilis in the expectant mother is so often clinically latent, its recognition must usually depend on the result of serological testing for syphilis. Amongst many others, Morton (1954) has stated that antenatal Wassermann-testing offers the best hope of the early eradication of congenital syphilis and has emphasized the need for close co-operation by all concerned in antenatal care if a high percentage of antenatal Wassermann-testing is to be achieved.

What progress has been made towards this goal? With venereologists in the lead persistent education over the past quarter-century has achieved much success in making a blood test for syphilis a routine measure in the majority of antenatal clinics of hospital and local public health authorities in England. The taking of this routine blood test for syphilis in expectant mothers was much facilitated by the introduction of rhesus-testing in 1947, and at that time it seemed that the goal of a blood test for syphilis as a routine in all expectant mothers would soon be realized. However, following the introduction of the National Health Service in 1948, the general practitioner has taken over the antenatal care of an increasing proportion of expectant mothers and, unfortunately, there is evidence that in few of such cases is antenatal blood-testing carried out. Thus in 1952, Macfarlane (quoted by Morton, 1954) found that on Tyneside, with an estimated 31,705 births (including stillbirths), of 15,812 (50%) antenatal Wassermann tests performed only 491 (3%) were made by general practitioners, who, according to the local executive councils, were remunerated for the care of 15,178 pregnancies.

In the area served by the Manchester Regional Hospital Board (Abstract of Statistics for the year ended December 31, 1954, p. 16 and Appendix Table vii) the 40,945 hospital births were 60% (Table I) of the total births in a home population estimated by the Registrar-General to be 4,379,760.

It might appear, therefore, that if, as at present, antenatal testing is seldom carried out in that proportion (about half) of all expectant mothers supervised by general practitioners, examples of congenital syphilis