THE JOURNAL OF NEUROLOGY AND PSYCHOPATHOLOGY

Vol. XVI.

APRIL, 1936

No. 64

Original Papers

MULTIPLE METASTATIC TUMOURS IN THE BRAIN ARISING FROM PRIMARY BRONCHIAL CARCINOMA *

By

W. E. CARNEGIE DICKSON, AND C. WORSTER-DROUGHT, LONDON

THE clinical and pathological investigation of multiple metastatic tumours of the brain arising from primary bronchial carcinomas is full of snares and pitfalls for the neurological physician, surgeon and pathologist; and, although bronchogenic carcinoma with secondary growths in the brain produces a now fairly well recognized and not uncommon syndrome, its diagnosis is still sometimes made only in the post-mortem room; and even there difficulties may occasionally arise in its recognition.

Ten years ago, in a text-book¹ for which one of us, together with Professor J. M. Beattie, was responsible, the statement was made that 'Primary tumours of the lung are extremely rare. Osteomas, chondromas, and sarcomas occur, but the most usual primary tumours are columnar-celled cancers—originating, probably, from some part of the bronchi or from the mucous glands'; while under the heading 'Tumours of the Brain' we merely stated that 'Secondary cancer is also rare.' Similarly, Ewing, in the third edition (1928) of his book, *Neoplastic Diseases*, p. 851, gives the frequency of primary malignant tumours of the lung at about 1 per cent. of all cancers, his statistics being taken from between 16,000 and 17,000 autopsies on cancer cases.

These statements now require modification, as both in our own experience and in that of others, the frequency of bronchial carcinomas—whether they are described as such or as 'Oat-celled Sarcoma of the Mediastinum'^{2 3}: as 'Tumours of the Mediastinum and Lung'⁴: as 'Primary Lung Tumours,'⁵

* Communicated at Meetings of the Neurological Section of the Royal Society of Medicine, London, May 17, 1934, and February 21, 1935. From the West End Hospital for Diseases of the Nervous System, London.

or as 'Primary Carcinoma of the Lung' ⁶—has increased remarkably during the last ten years, not only in this country but on the continent of Europe and in America and elsewhere. Recent writers give figures up to 15 per cent. or more, and Percival Bailey, ⁷ writing in America, gives this increasing frequency of carcinoma of the lung as 7 to 10 per cent. of all carcinomas, and the age incidence as especially between 40 and 60. The marked tendency for such bronchogenic carcinomas to produce metastases in the brain is indicated by figures such as 37, 41, and 47 per cent. in various recorded series of such cases.

Papers dealing with the histological aspect of the subject have, as is natural, been written mainly from the point of view of those interested in the lung condition rather than in its neurological aspects. Practically all recent writers dealing with the pathology of these tumours are agreed that they are of the nature of carcinomas arising from the bronchial mucous membrane. Shennan ⁴ of Aberdeen gives an excellent description of the naked-eye and histological appearances of such intrathoracic tumours but in the main portion of his paper makes no special reference to the frequency of cerebral metastases. In an appendix, however, in giving the details of some of his 31 cases, he mentions one (Case 16) in which there were such secondary nodules in the brain, the tumour being histologically a columnar-celled papilloma, occurring in a male aged 62. Dr. Norah Schuster in her paper on the 'Ætiology and Pathology of Primary Lung Tumours' ⁵ gives details of 62 such cases, and draws attention to the occurrence of metastases in the brain in which, she states, 'they are nearly all small-cell tumours,' previously often mistaken for, or designated as, 'sarcomas.' She also points out that histologically these metastatic tumours not infrequently show varied appearances in different parts—a finding with which our own experience fully agrees. Dr. Schuster makes the valuable suggestion that, as the cells of bronchial tumours may secrete mucin, the investigation of such cases should include the use of some specific stain for that substance, such as Mayer's mucicarmine, a suggestion which we have found extremely useful.

From a statistical point of view, the paper on 'Primary Carcinoma of the Lung' by S. Levy Simpson ⁶ gives much valuable information. In his analysis of 139 cases occurring at the London Hospital, 19 are recorded as having metastases in the brain. This writer also calls attention to the frequency with which the clinical diagnosis has been missed; of 66 erroneously diagnosed cases, found at post-mortem to be carcinoma of the lung, there was what he terms a 'cerebral group' of 13, of which seven had been diagnosed clinically as primary cerebral tumour. For the clinical diagnosis of such cases Simpson calls attention to the significance of general wasting, dyspnoea, bronchitis, hæmoptysis, hoarseness, offensive breath (bronchiectasis) and leucocytosis. As regards latency of symptoms, some of the other records are also striking. Sehert, ⁸ in a series of 204 cases of tumour of the lung, found that only six had been diagnosed during life, and Wells ⁹ in 11 cases found only one diagnosed.

During the past two years we have had, at the West End Hospital for Diseases of the Nervous System, seven patients who on post-mortem examination were found to have died from multiple metastatic tumours of the brain arising from primary bronchial carcinomas. For purposes of comparison, Dr. Norah Schuster has kindly placed at our disposal five of her cases occurring at the Royal Chest Hospital, City Road, and our colleague, Dr. McMenemey, has provided us with two similar cases from another hospital.

Perhaps the most notable feature of the majority of these cases has been the extreme latency of the lung symptoms. In our seven West End Hospital cases, a point of interest was that all occurred in middle-aged to elderly males (with ages of 43, 45, 47, 55, 56, 61, and 64 years). McMenemey's cases were also both males, while Schuster's five cases were all females (with ages of 29, 33, 41, 42 and (?)). Both series occurred in mixed hospitals, showing that one should not make any broad generalizations with regard to age, sex, etc., from a small series of cases. It is possible, however, that in the female cases, which occurred mostly in earlier middle-age, the symptoms of the lung condition were sufficiently pronounced to cause patients to seek advice and treatment at a chest hospital; whilst in the male cases, the lung condition tended to remain more or less latent or was believed to be merely some degree of 'chronic bronchitis,' and was often completely masked by the symptoms produced by the cerebral metastases, thus causing the patients to be sent to a hospital for nervous diseases.

In the first two cases of the latter series occurring in males which we investigated, the histological appearances of the cerebral metastatic tumours were pronouncedly *papillomatous* in character, and, moreover, some of the tumours occurred actually in, or in continuity with, the choroid plexuses of the lateral ventricles. On perusing the literature of similar cases, we found several apparently identical examples of such tumours described as 'multiple malignant papillomatous tumours of the choroid plexus'; but, judging by the findings in some of our post-mortem examinations and granted that other less likely sources can be excluded, we are inclined to suspect that not a few of these have in reality been cases of multiple metastatic growths secondary to some perhaps quite inconspicuous and undetected primary bronchial carcinoma, such as is illustrated in our second case. Quite a number of cases recorded by surgical writers, especially in America, and described as 'malignant tumours of the choroid plexus' may equally well have been cerebral metastases from bronchial carcinomas. Walter E. Dandy,¹⁰ in his recently published book entitled *Benign Encapsulated Tumors in the Lateral Ventricles of the Brain*, and, in the chapter dealing with 'Invasive and Malignant Tumors of the Lateral Ventricles,' makes the following statement, with which we fully agree :

'Microscopic diagnosis in the seas in other tumours attains increasing value only after correlation with the gross observations and especially with the ultimate results following extirpation. Neither the gross nor microscopic appearance of the tumour

is as yet an infallible guide concerning the character of the tumour and at times both together fail in the task, the life history of the growth being the final test.'

The two cases of malignant tumour which Dandy records as arising from the choroid plexus *early in life* we believe to be in all probability accurately thus diagnosed; but, from our recent experience of cases such as he describes in older patients, we have grave doubt as to the accuracy of the statement (p. 31) that the case recorded by Le Blanc (1866) was 'an unquestioned malignant tumour of the choroid plexus'; and we are equally uncertain about the accuracy of the diagnosis in the other cases of middle-aged to elderly patients reported by many of the older writers such as Spät¹¹ (1882), Bielchowsky and Unger¹² (1906, in a female aged 43, with multiple tumours both in cerebrum and cerebellum), and others. In fact we regard the diagnosis of primary malignant tumour of the choroid plexus as distinctly open to question, and we venture to suggest that in particular the history of Atlee's case¹³ (1907), which Dandy quotes in some detail (p. 31), is almost pathognomonic of multiple secondary bronchogenic carcinomatous nodules in the brain. Dandy's account of this case is as follows:

'Atlee of Lancaster, Pennsylvania, removed a seemingly encapsulated tumour from the right Rolandic area. A splendid temporary result followed its enucleation, for the patient, who was a physician, regained his motor and sensory functions. Histological examination revealed the characteristic duplication of the choroid plexus. Doubtless the tumour was a metastatic nodule because it was cortical and not intraventricular. Another interesting feature that especially engaged the attention of Dr. Mills, who reported the case with Atlee, was paralysis of the vocal cord on the contralateral side. Dr. Mills collected many reports from the literature to prove that the paralysis was of central and not peripheral origin. We now know from extirpation of a cerebral hemisphere that paralysis of the vocal cord does not follow. Recently Dr. Atlee advised me that his patient died several months after operation from symptoms that were referred to the thorax. It was his belief that the patient died as the result of metastases from the original cerebral tumour—probably an adenocarcinoma of the choroid plexus.'

That the intrathoracic condition was the primary one and that the (presumably) multiple cerebral tumours were secondary to a bronchial carcinoma we regard as more than probable—in fact almost a certainty. Involvement of the left recurrent laryngeal nerve by mediastinal spread of the lung tumour probably accounted for the laryngeal paralysis described as occurring in the case. Temporary improvement from the relief of pressure may well have occurred after the incomplete removal of the easily enucleable tumour mass, but the inevitable regrowth from the shell of infiltrating malignant cells that remained lining the operation cavity occurred later with a fatal result. In these cases, such cerebral metastatic tumours are almost invariably multiple and the presence of the primary growth in the lung, as well as secondary metastases in the lungs themselves and in other organs, may also contribute to a rapidly fatal issue. In 1933, Hall and Fentress¹⁴ described very fully a case which they considered to be one of 'Papilloma

Choroideum with Diffuse Central Nervous System Metastases,' any or all of the illustrations and descriptions of which might quite well have been taken from one or other of our own series of bronchogenic cases; and we suggest that, in the sections of the metastases in the central nervous system of their case, the presence of mucin might possibly have been demonstrated by appropriate methods, especially in the papilliferous cystic tumours filled with coagulated fluid. In their clinical history of this case, these writers say that a radiogram of the chest showed a circumscribed area in the upper lobe of the left lung with striations passing from it into the surrounding lung-tissue, an appearance which was interpreted by the radiologist as a possible metastasis; but they further state that this suspicion was not confirmed by the post-mortem findings. They do not, however, give details of any histological examination of the pulmonary lesion. In several of our own cases we should certainly have failed to find the often quite inconspicuous little nodule of bronchial carcinoma, perhaps in connection with a secondary or a tertiary division of a bronchus, had we not previously been convinced that some such tumour must be present because of the naked-eye characters of the multiple cerebral metastases, or from the microscopical findings in the puncture-fluids obtained from the larger mucus-containing cysts which were often present. The old routine method of examining a lung at autopsy by a single slice from the outer side to the root may perhaps reveal even a comparatively small tumour if it chanced to be situated in one of the primary bronchi at or near the root, or, if situated at the periphery of the lung where the tumours are often larger and more easily found; but, except for a lucky chance, the plane of section is almost certain to miss a small and sometimes single nodule of tumour if such be present in the body of the lung farther from the hilum. A search for the possible presence of this small tumour may demand a combination of careful palpation with the fingers and the laborious slitting up of the bronchi seriatim from the root outwards into all the lobes of the lungs. In cases of multiple tumours of the brain it is a wise precaution, even if nothing obvious is found in the lungs at the post-mortem itself, to preserve these organs for further detailed examination. Where nodules or patches of old fibrotic change due to pneumoconiosis (the occupation of one of our patients was that of plasterer), chronic tuberculosis, or old syphilitic interstitial pneumonia are present, the difficulty of finding a small nodule of tumour is greatly increased. From our more recent experience of searching for some such very small tumour in the lung, we are by no means surprised that we may ourselves in the past have missed finding them, or that the presence of a small bronchial tumour has not been detected in many of the cases in the literature of multiple cerebral tumours which have not infrequently, we believe, been erroneously described and recorded as 'malignant papillomatous tumours of the choroid plexus.' References to other cases are given in Hall and Fentress' paper,¹⁴ but, on looking up the original articles, a similar suspicion as to their having been in reality metastases from carcinoma of the

lung, or less probably from some other site of origin, arises in one's mind. The literature is so full of such cases that we cannot refer to them in detail, but two further difficulties in connexion with many of the records also call for passing notice. In some otherwise excellent papers upon pulmonary and mediastinal tumours, whether described as papillomatous or 'oat-celled' sarcomatous growths, there is in the majority of the cases no note of the brain having been examined; from the opposite point of view, post-mortem examinations limited to the head may lead to similar fallacious findings from lack of any data as regards the possible presence of some primary tumour in the lung, breast, prostate, gastrointestinal canal or elsewhere.

Of surgical writers on the subject, Percival Bailey of Chicago is one of the comparatively few who seem to be fully alive to the fact that, in the case of elderly patients, especially males, the headache, confusion and other symptoms suggestive of cerebral tumour are not infrequently due to the presence of metastases, often multiple, secondary to tumours in distant organs, and on p. 355 of his recent book *Intracranial Tumors* he ⁷ writes :—

'Primary bronchogenic carcinoma of the lung so commonly metastasizes to the brain, and does it so often before the primary tumour has given symptoms, that it should always be looked for in any patient of middle age, or beyond, who develops rather rapidly symptoms of an infiltrating tumour of the brain, especially if the signs of intracranial hypertension are not marked or there is a pronounced mental confusion.'

On p. 361 he also makes the statement, with which we entirely agree, that :—

'The primary pulmonary tumour in its early stages is difficult to recognize, and may have remained entirely symptomless, until after the cerebral metastases are well developed. And these tumours are so numerous that any patient who develops symptoms of intracranial tumour rather rapidly in middle life or later should have a careful examination of the chest, including a roentgenogram, whether pulmonary symptoms are present or not.'

Carcinomas of the lung have been described as occurring in three forms—nodular, lobar, and diffusely infiltrating—but for our present purpose and with regard to the primary focus in the lung, our own series of cases falls conveniently into three main types as follows :—

- I. Sclerosing bronchial type, usually at or near the root of the lung.
 - II. Primary growth, often small, occurring in connexion with a secondary or tertiary bronchus.
 - III. Larger and sometimes massive tumour at the periphery of the lung.
- To illustrate these, we select the following cases :—

I. SCLEROSING BRONCHIAL TYPE

Case I.—J. H. W., age 55, admitted to hospital on September 29, 1933, under the care of Dr. L. R. Yealland, complaining of headache, difficulty in walking and pain in the chest.

History.—Bronchitis on and off for three years with excessive yellow sputum and occasional hæmoptysis, no tubercle bacilli being found. Pain in the chest at times and lassitude for last 18 months. Headache and giddiness for past 12 months and occasional vomiting for six months. His temperament was said to have changed and he had become extremely irritable and at times difficult to manage. No previous illnesses of importance.

Condition on Admission.—Pupils small but equal and reacted normally. Papilloedema (4D) practically equal on the two sides with small hæmorrhages in the neighbourhood of the disc. Slight nystagmus to left. Other cranial nerves normal. No definite sensory loss. Right armjerks increased as compared with left. Spasticity of both legs about equal on the two sides. Knee- and anklejerks brisk and about equal. No ankle clonus. Plantars—right extensor, left flexor. Abdominal reflexes present and equal. Gait somewhat ataxic but coordination otherwise normal.

Heart normal. Blood pressure 110/70. Respiration slow but equal on the two sides. Impairment of percussion note at apex of right lung with patchy bronchial breathing. Generalized crepitations and rhonchi over chest.

Cerebrospinal fluid: Small lymphocytes 2 per c.mm. Total protein 0.08 per cent. Globulin a trace in excess. Wassermann and Kahn reactions negative. Lange's colloidal gold curve 0012100000.

Subsequent Progress.—The patient became increasingly drowsy and died 11 days after admission without further change beyond the development of weakness of the lower half of the right side of face.

Post-mortem Examination.—Body extremely emaciated. Dura firmly adherent to inner surface of skull-cap, with some exaggeration of the parasagittal Pacchionian bodies. The cerebral convolutions were much flattened, and, at the centre of the outer border of the under surface of the left temporo-sphenoidal lobe, there was a large tumour coming to the surface, where it measured 30 mm. × 30 mm., about the size of a small tangerine orange. It occupied the greater part of the interior of the left temporo-sphenoidal lobe, its surface being level with the general surface of the brain and showing a somewhat lobulated or puckered appearance, rather resembling miniature convolutions, but, on section, showing a fine spongy texture, light greyish brown in colour, and tending to crumble on being cut, its general appearance being much like that of the choroid plexuses. Its margins were fairly discrete and it was easily broken away from the surrounding brain tissue but tending to leave a thin crumbling layer of tumour attached to the latter. On a series of horizontal sections of the brain being made, fairly numerous similar but smaller tumours—some two dozen in all—were found, varying in size from a hazelnut downwards. These were situated in both occipital and both frontal lobes, in both cerebellar hemispheres and elsewhere. The most interesting tumour, however, was found in connexion with the postero-superior wall of the body of the right lateral ventricle, which it was invading, being also continuous in front with, and very much resembling in texture, the hyperplastic right lateral choroid plexus (see fig. 1).

In connexion with some of these tumours, cysts had developed, many of them numerous and of small size but here and there larger, e.g. that shown in the white matter of the left occipital lobe (fig. 1). These cysts were

CASE I.

FIG. 1.—Horizontal section through the hemispheres showing several of the metastatic papillomatous tumours—one of them in continuity with the hyperplastic right lateral choroid plexus, invading the ventricular wall and corpus callosum. The nodule in the left occipital lobe shows the development of a cystic cavity not part of the ventricle. This photograph illustrates the appearances which simulate and may be mistaken for malignant papillomatous tumour of the choroid plexus itself.

CASE I.

FIG. 2.—Horizontal section through cerebellum, showing numerous secondary nodules of the spongy papillomatous tumour. In connexion with the largest of these growths several cysts of considerable size have developed, the contents of which much resemble mucoid sputum.

CASE I.

FIG. 3.—Section through the upper lobe of the right lung showing the eparterial bronchus blocked with tumour. The surrounding whitish tissue is mostly fibrotic, of older standing than the neoplastic condition. Immediately above and to the left of the blocked bronchus is a recently thrombosed branch of the pulmonary artery, above and below which are enlarged carbon-pigmented lymph-nodes also containing secondary tumour growth.

CASE I.

FIG. 4.—A low power photograph showing the malignant papillomatous tumour arising from the bronchial mucous membrane, filling the lumen and infiltrating outwards through the wall of the bronchus between two of its cartilages. van Gieson and hæmatoxylin. $\times 100$.

filled with thick colourless and comparatively clear mucoid-looking material, like raw white of egg, swelling and becoming somewhat opaque on fixation with formalin. The largest of these cysts was found in the left cerebellar hemisphere, measuring slightly over 30 mm. in its greatest diameter, the adjoining tumour from which it had developed and several smaller cysts being shown in fig. 2, in which several other smaller nodules of spongy tumour are shown in both cerebellar hemispheres and also in the choroid plexus of the fourth ventricle. The various choroid plexuses were voluminous and hyperplastic, their appearance being somewhat suggestive of the ' villous hyper-

CASE I.

FIG. 5.—Low power of spreading margin of tumour in right frontal lobe, showing the combined cystic and papillomatous structure. Mallory's stain for connective tissue. $\times 32$.

trophy' described by L. E. Davis¹⁵ in 1924 as occurring in many cases of hydrocephalus.

In the thorax there were firm old fibrous adhesions of the right lung to the chest wall, especially over the upper lobe and its junction with the middle lobe. On palpating the root of the right lung, there was a firm nodulated mass suggestive of possible tumour, but found to be due mainly to an old fibrotic condition spreading outwards into the lung-tissue from the root. On dissection, the eparterial bronchus was found to be the seat of a stenosing carcinoma (fig. 3), and the surrounding lung-tissue showed a mixture of fibrosis resembling a silicosis (the patient's occupation had been that of plasterer) and the infiltrating malignant tumour. A few small, firm, pea-like nodules, found microscopically to be a mixture of fibrosis and tumour, were also scattered elsewhere in the lower part of the upper lobe and in the middle lobe. No caseation or other evidence of tuberculosis could be made out with the naked eye. Several moderately enlarged lymph-nodes at the root

showed a mottled mixture of opaque white metastatic tumour and black carbon-pigmented fibrotic tissue. The whole of the upper lobe was collapsed, congested and intensely oedematous, and there was recent thrombosis of the larger branches of the pulmonary artery to this lobe. The rest of the right lung and also the left lung showed chronic bronchitis with thickening and peribronchial fibrosis and scattered small nodules of tumour. The right lower lobe and most of the left lung also showed marked emphysema.

The heart was extremely soft and flabby, its chambers dilated and the myocardium showing a mixture of fatty degeneration and brown atrophy

CASE I.

FIG. 6.—Low power view of the nodule of tumour involving the choroid of the right lateral ventricle and the neighbouring portion of the ventricular wall. The general appearance of the tumour was suggestive of choroid plexus, from which it was at first believed to have originated. Hæmatoxylin and eosin. $\times 32$.

with a considerable degree of atheroma of the aorta, aortic cusps and coronary arteries, especially the right.

Abdomen.—Except for one small nodule of tumour, 4 to 5 mm. in diameter, in the medulla of the left suprarenal, opaque pearly-white in colour and slightly granular when its cut surface was examined with a hand-lens, no metastases were found, the suprarenal itself not being appreciably enlarged. The liver and kidneys showed merely fatty degeneration and chronic venous congestion and the only other abnormality found was a moderate-sized hydrocele of the right testicle, with no naked eye evidence of tumour.

Microscopically.—The lumen and walls of the right eparterial bronchus, just as it entered the lung tissue, and its main branches were the seat of a

malignant papillomatous tumour arising from the bronchial mucous membrane (fig. 4). In some parts of its structure, the tumour was loose and 'feathery,' in others more densely packed, and, where it was invading already fibrosed lung-tissue, almost resembling a scirrhus cancer in structure. Most of the latter areas showed marked increase of carbon and also the presence of particles of stone-pigment, this condition having probably preceded the occurrence of the tumour and being apparently of the nature of a silicosis. In some of these areas there was also a considerable degree of chronic

CASE I.

FIG. 7.—Low power view of the spreading margin of the tumour involving the right lateral choroid plexus, showing the general papilliferous structure of the tumour. The outermost layer of columnar epithelium is, however, suggestive of its bronchial origin, and when stained with mucicarmine, gives the specific stain for mucin. At the infiltrating margins, the tumour appears to carry outwards its own delicate connective-tissue stroma and blood-vessels, many of which show a dilated sinus-like structure. Hæmatoxylin and eosin. $\times 100$.

irritation—small round-celled infiltration with lymphocyte-like cells. The secondary growth in the bronchial glands gave a similar picture, the looser 'feathery' papillomatous characters being best seen where papilliferous cysts had developed, and in other parts the tumour-cells being mixed with much carbon-pigmented and fibrotic tissue. The small nodule in the left suprarenal also consisted of typical malignant papilloma.

As we are writing from the neurological standpoint, the histology of the multiple malignant tumours in the brain may be described a little more fully, and this is most satisfactorily done by referring to the accompanying illustrations and their annexed descriptions. Figs. 5, 6, 7 and 8 are low-power

microphotographs of the spreading margins of the nodule of secondary growth involving the choroid plexus and wall of the right lateral ventricle and show appearances which might easily mislead one into the belief that the tumour had actually arisen as a primary tumour of the choroid plexus itself. This is perhaps particularly so in the case of fig. 6. Fig. 8 is more suggestive of a tumour arising from a mucous membrane or a gland lined by columnar epithelial cells, and, when the tissue was stained with mucicarmine, the presence of mucin, which would naturally not be present in a tumour arising from the choroid plexus, could be demonstrated in it. Figs. 5 and 6 show the tendency to the formation of papillomatous cysts, which may

CASE I.

FIG. 8.—Low power view of a secondary nodule in the frontal lobe, showing a typical metastasis of the bronchial papillomatous carcinoma. van Gieson and hæmatoxylin. $\times 100$.

vary in size from microscopic up to large naked-eye cysts such as those shown in figs. 1 and 2.

Although *blepharoplasten* might be expected in cells derived from the originally ciliated bronchial epithelium, we were unable, by Bailey's neutral ethyl violet orange G, and other special methods, to demonstrate their presence in the papillomatous cells of the tumours either in the brain or in the lung itself, and we are therefore not inclined to stress a negative finding in this respect as of great importance. Similarly no cilia were themselves detected at the free margins of any of the cells.

II. SMALL AND INCONSPICUOUS GROWTH IN RELATION TO A SECONDARY BRONCHUS

Case II.—A. S., male, age 47, was admitted to hospital on December 29, 1934.

History.—He had felt quite well until two months previously, viz. October 1934, when he became rather quiet in manner and seemed tired, especially in the mornings. No complaint of headache at that time. A month before admission he had stopped working because he felt ill but had no very definite complaint. His appetite then failed and his speech became vague and indistinct: he made irrelevant answers and seemed at times to be rather confused and complained of severe headache. At the same time he had several painful boils, the largest being on the neck and at the vertex of the head.

Condition on Admission.—Pupils central, equal and reacted to light and on accommodation. Both fundi showed papilloedema. No nystagmus. Slight weakness of lower half of face on right side. Some degree of aphasia. Sensation as far as could be tested appeared normal. Upper limbs: normal. Right leg spastic, kneejerks exaggerated and right anklejerk greater than left. Double extensor plantar response. Right lower abdominal reflex absent. With finger-nose test some ataxia on right side. Sphincters: double incontinence.

Heart normal, blood-vessels not thickened. Blood pressure 130/96. Respiratory system: an area at the base of right lung showed increased resonance with loud expiration and impaired percussion note. X-ray examination of chest: no abnormality detected. Cerebrospinal fluid showed pressure 170 mm. Queckenstedt test normal. Cells: 8 small lymphocytes per c.mm. Total protein 0.05 per cent. Globulin faintest detectable trace. Wassermann and Kahn reactions negative. Lange's colloidal gold curve 0121000000. Blood Wassermann and Kahn reactions negative.

Blood: leucocytes 8,200 per c.mm. Films showed moderate but distinct anisocytosis, but otherwise nothing of note.

Subsequent Progress.—A lesion of the left frontoparietal region was diagnosed. The physical signs in the right lung, though scanty, suggested the possibility of a bronchial carcinoma, and an X-ray examination was carried out. This however was reported negative. In view of the recent history of several boils the possibility of cerebral abscess was also considered and, as the papilloedema was increasing, a left-sided subtemporal decompression was carried out by Mr. C. P. G. Wakeley. Death occurred two days later on January 7, 1935.

Post-mortem Examination.—The body was poorly developed and showed considerable emaciation.

On opening up the recent left-sided subtemporal decompression area there was considerable flattening of the cerebral convolutions, the temporo-sphenoidal lobe on this side having a 'baggy' feeling and appearance. Some turbid fluid aspirated through a needle after deep insertion in this region and examined in fresh wet preparations (see fig. 9) showed numerous obviously malignant tumour-cells, mostly small and rounded in shape, but sometimes oat-shaped, and occasionally somewhat columnar. Several clumps of cells showed a suggestion of radial arrangement, such as one might expect in a papillomatous tumour, but with no trace of any connective-tissue cores. These were sufficiently suggestive of the structure found in some other cerebral metastases from bronchial tumours to warrant a provisional diagnosis of 'metastases (probably multiple) in the brain from a primary bronchial

CASE II.

FIG. 9.—Fluid aspirated from cystic tumour in temporo-occipital lobe. A fresh wet preparation stained with methylene blue showing clumps of epithelial cells, suggesting fragments of papillomatous tumour. Some of the cells are oat-shaped, others small-round. From these and other similar preparations a diagnosis of malignant tumour (probably multiple) secondary to a bronchial carcinoma was suggested. Methylene blue. $\times 400$.

CASE II.

FIG. 10.—Horizontal section of the cerebral hemispheres above the level of the corpus callosum. A metastatic tumour of considerable size is seen in the outer and posterior part of the left frontal lobe.

carcinoma,' this being confirmed by the further examination of the brain after removal and fixation. At the level of the upper surface of the corpus callosum, in the left frontal lobe and occupying its posteroexternal portion there was an irregularly rounded tumour, the size of a walnut, mainly in the white but also encroaching upon the inner aspect of the grey matter (fig. 10). The cut surface of this tumour showed the distinct spongy and crumbling character suggestive of a papillomatous tumour secondary to bronchial carcinoma. The central portion of the tumour also showed some patchy yellow necrosis and in its lower part there were some small mucus-containing cysts. In the temporosphenoidal lobe there was a similar but rather smaller tumour showing the same spongy texture and the presence of a considerable

CASE II.

FIG. 11.—Naked-eye photograph of left lung, showing the two cut halves of a small primary bronchial carcinoma on one of the main branches of the bronchus to the upper lobe. The tumour is only about the size of a pea, but is surrounded by some chronic induration and fibrosis.

amount of thick sputum-like mucus, from the aspirated contents of which the provisional diagnosis of tumour secondary to bronchial carcinoma had been made. A third nodule, about the size of a marble (15 to 20 mm. in diameter) was found in the centre of the right cerebellar lobe, mainly amongst the leaves of grey matter.

The heart was extremely soft, flabby and atrophied, with marked fatty infiltration of the right ventricle, the myocardium of the left ventricle being also atrophied and showing fatty degeneration. The coronary arteries showed distinct thickening and patches of atheroma.

Both lungs showed a considerable degree of emphysema of their apices and borders. There was well-marked chronic bronchitis with chronic

CASE II.

FIG. 12.—A fresh wet teased preparation of the brain substance at the margin of the temporosphenoidal tumour, showing infiltration by groups of malignant epithelial cells among the glial fibres. Toluidin blue. $\times 400$.

CASE II.

FIG. 13.—Low power view of margin of secondary tumour in temporosphenoidal lobe, showing the loose feathery arrangement of the epithelial cells, somewhat suggestive of a catarrhal bronchitic exudate. Hæmatoxylin and eosin. $\times 100$.

congestion, thinning and catarrh of the bronchial mucous membrane, with also some slight, more or less diffuse dilatation of many of the smaller bronchi.

In the left lung there was found, in the upper part of the lower lobe, a

x

small hard firm nodule-like mass, about the size of a small pea, situated about 2 inches from the root. This had the appearance of a small nodule of tumour in connexion with a medium-sized bronchus and around this nodule was some radiating fibrosis and carbon-pigmentation (fig. 11).

The bronchial and other mediastinal lymph-nodes showed congestion and some excess of carbon-pigmentation, but no obvious naked-eye evidence of tumour.

No nodules of new growth were found in the liver, spleen, pancreas, kidneys, gastrointestinal tract, bladder or prostate, or in any of the lymph-nodes.

Microscopically.—Teased fresh wet preparations of the brain-substance from the margins of the temporosphenoidal tumour (fig. 12) showed small groups of infiltrating malignant epithelial cells among the glial fibres, etc., and, as already noted above, the mucoid fluid aspirated from the cystic portions of this tumour also showed epithelial cells the characters of which suggested that they were derived from a papillomatous bronchial or other carcinoma.

Sections of the small primary bronchial carcinoma itself (fig. 13) showed the epithelial cells arranged in a loose, 'feathery' manner, with, here and there, a suggestion of papillomatous structure, but most of the cells were oat-shaped to slightly columnar. The same loose feathery arrangement of the epithelial cells was found in sections of the temporosphenoidal tumour, in some parts almost suggestive of a 'catarrhal bronchitic exudate'; while in other metastases, e.g. that in the frontal lobe, the papilloma-like structure was more in evidence.

III. MASSIVE PRIMARY GROWTH AT PERIPHERY OF LUNG

Case III.—G. A. W., male, age 56, admitted to hospital on July 5, 1934.

History.—This patient had been seen and examined by one of us in January 1926—over nine years before. He was then complaining of lack of mental concentration and shakiness on excitement, of four months' duration. He showed no evidence of organic disease either of the nervous or other systems. The heart was normal and blood-pressure 140/80. The blood gave a weak positive Wassermann reaction.

He was then lost sight of until the day before his admission to hospital.

Condition on Admission.—Mentally confused, used words in their wrong places and had little or no memory for recent events. He stated that he had no complaints excepting headaches which he 'had had for years.'

Pupils: small but equal, reacted normally. Bilateral papilloedema (1.5 D). Slight nystagmus to left. Other cranial nerves normal. Upper limb reflexes brisk and equal. Right knee- and anklejerks greater than left. Plantars: right extensor, left indefinite. Abdominal reflexes absent. Incoordination of right arm. Heart normal, blood-pressure 118/70. Some dulness over upper lobe of left lung with diminished breath and voice sounds. Cerebrospinal fluid: 26 cells per c.mm., practically all small lymphocytes with an occasional small endothelial cell. Total protein 0.06 per cent. Globulin: a trace in excess. Wassermann reaction weak positive. Lange 5553210000. Blood Wassermann reaction weak positive.

Subsequent Progress.—The patient became increasingly confused, drowsy and

incontinent. Death occurred a few days after admission. The fact that this patient was undoubtedly a syphilitic subject and probably suffering from early dementia paralytica obscured the diagnosis. The chest condition was suspected on account of the physical signs but his mental condition precluded an X-ray examination.

Post-mortem Examination.—The body, unlike that of our other cases in which emaciation was a notable feature, was well developed and well nourished with distinct excess of adipose tissue.

Head.—The skull-cap was dense and heavy and to it the subjacent dura was firmly adherent. The whole brain was extremely soft and its convolu-

CASE III.

FIG. 14.—Horizontal section through cerebral hemispheres, showing two large coalescing metastatic nodules of the bronchogenic carcinoma in the left frontal lobe, etc. The choroid plexuses of the lateral ventricles show well-marked hyperplasia.

tions much flattened. The left frontal lobe showed a condition of 'baggy softening' with breaking down of the cerebral substance anteroexternally. During removal, a large soft necrotic dark reddish mass of tumour mixed with bloodclot began to protrude at this area, and the whole brain was at once placed in fixative.

On horizontal section after fixation, two large coalescing masses of malignant tumour were found infiltrating and replacing most of the left frontal lobe and the area of the caudate nucleus, etc. (fig. 14), producing great bulging of the anterior half of the left hemisphere and pushing some of its structures well beyond the middle line to the left and also backwards. The anterior and larger mass of tumour had a loose necrotic spongy texture with extensive hæmorrhage into it. The smaller posterointernal mass was

x 2

somewhat whiter in colour but also finely spongy to granular in texture, and also showed patchy hæmorrhages. The lateral ventricles showed considerable dilatation—the right as a whole, the left only above the level of the tumour which bulged into the roof of its anterior horn, the interior of which was invaded. Another considerable mass of tumour was found in the postero-external and inferior aspects of the left temporosphenoidal lobe and a smaller metastasis about the size of a hazelnut was present in the central white matter of the right cerebellar hemisphere (fig. 15). These showed a varie-

CASE III.

FIG. 15.—Base of the brain with portions of left temporosphenoidal lobe and cerebellum cut away, showing large metastatic tumour in the former, and smaller nodule in the centre of the right lobe of the cerebellum.

gated, somewhat granular, whitish and pinkish-white appearance mixed with hæmorrhage and some necrosis.

The heart was small, soft and flabby, and showed an extreme degree of fatty infiltration, especially of the right ventricle, with marked atheroma of the aorta and coronary arteries and patchy thickening of the aortic cusps and anterior cusp of the mitral valve.

Both lungs were extremely œdematous and congested and, in the lower part of the upper lobe of the left lung, there was a large firm nodular mass about the size of a medium-sized orange (fig. 16), over which there was old dense fibrous thickening of the pleura, but without adhesion to the chest-wall.

On section, this mass showed a granular, yellowish-white necrotic appearance throughout its central part, but at the periphery it was less opaque and showed a zone of pinkish-white tumour-like tissue. This was the

only mass suggestive of tumour growth in the lungs, nothing being detected towards the roots indicative of neoplasm.

In the abdomen, there was a small secondary growth, about the size of a pea, in the spleen immediately beneath the capsule on the diaphragmatic surface towards its upper pole. No nodules of tumour were found in the liver, but in and greatly distending the left suprarenal body was a soft mass of tumour about the size of a small orange. A minute metastasis was found in the right suprarenal, but none in the pancreas or kidneys.

CASE III.

FIG. 16.—Naked-eye photograph of the primary tumour in the lower part of the upper lobe of the left lung.

Microscopically.—The histological appearances in sections of the primary lung tumour and of the metastases in the brain and suprarenal, etc., were all practically identical, the epithelial cells being loosely arranged in feathery masses and the individual cells often separated from one another by clear mucoid fluid. These cells, even in section, showed an appearance suggestive of the exudate of an acute catarrhal bronchitis. All the tumours showed numerous patchy areas of necrosis and hæmorrhage, the surviving tumour-cells being arranged in zones immediately around the numerous, rather

delicate, thin-walled blood-vessels, which were sometimes dilated and sinus-like. Some of these phenomena were perhaps associated with the pre-existing syphilitic element in this case.

The three foregoing cases may be taken as representative of the three groups into which we have divided the cases of bronchogenic carcinoma which we have encountered. We give, therefore, only a brief synopsis of our remaining cases and need refer only to some of the points in which they differ from the cases already described.

Case IV.—A. A., male, age 64. This patient was under the care of Mr. C. P. G. Wakeley. There was a clinical history of inability to concentrate and loss of memory,

CASE IV.

FIG. 17.—High power view of margin of tumour showing the surrounding brain tissue invaded by a papilloma-like process, with central vascular core and radially arranged bronchial epithelial cells. Hæmatoxylin and eosin. $\times 400$.

with vomiting and failure of vision. He was admitted to hospital (January 4, 1934) in a condition of stupor.

The physical signs pointed to the presence of a cerebral tumour of the right parietal lobe. A large right temporal decompression was performed and an inoperable tumour found in the temporosphenoidal lobe. After some temporary improvement, the patient died six weeks later.

Post-mortem Examination.—(Limited to head.)—*Brain.*—The right cerebral hemisphere was much larger than the left and showed large spongy metastatic growths in the temporosphenoidal and frontal lobes.

Microscopically.—These tumours showed the feathery and papillomatous appearances characteristic of bronchogenic carcinomatous metastases which are illustrated in fig. 17.

Case V.—H. S. H., male, age 45, admitted under the care of Dr. L. R. Yealland with symptoms of cerebral tumour—severe headaches, failure of memory and gradually increasing coma, death occurring about a fortnight after admission.

Post-mortem Examination.—(Limited to head.)—A poorly developed and somewhat emaciated adult male. Marked general flattening of the cerebral convolutions with ‘baggy’ softening and bulging in the centre of the

CASE V.

FIG. 18.—Horizontal section through the cerebral hemispheres, showing some of the spongy metastatic growths.

outer surface of the right temporosphenoidal lobe, in which there was a large spongy and extensively cystic metastatic malignant tumour which had burrowed downwards and inwards and had become adherent to the upper surface of the tentorium cerebelli about its centre (figs. 18 and 19). Some of the contents of this, aspirated for immediate examination, were mucoid and sputum-like and, microscopically, showed numerous columnar or cigar-shaped epithelial cells suggestive of a bronchitic exudate, together with little clumps of cells, evidently fragments of papillomatous tumour, from which the provisional diagnosis of a bronchial carcinoma was made (fig. 20). On serial horizontal section, about a dozen soft spongy tumours were found throughout the brain, varying in size from that of a pea up to that of a tangerine orange, the largest being that already described, in which cystic projec-

CASE V.

FIG. 19.—Under surface of horizontal section through the cerebral hemispheres, showing some of the spongy metastatic growths. That on the left side posteriorly in the occipital and temporosphenoidal lobes is, at a lower level, extensively cystic, and from it the 'catarrhal' and sputum-like fluid shown in fig. 20 was obtained.

CASE V.

FIG. 20.—Fresh wet contents of a large cystic tumour in the inner part of the substance of the left temporosphenoidal lobe, which burrowed towards the pineal region, where it became adherent to the tentorium cerebelli. The aspirated contents of this were mucoid and resembled sputum in consistency and appearance. Microscopically, as shown here, it suggested an admixture of small fragments of papillomatous tumour and bronchial catarrhal cells. Toluidin blue. $\times 100$.

tions from the lower part of the occipital and temporosphenoidal lobes were found. There was also a smaller nodule in the left lobe of the cerebellum, among the cortical leaves, towards its posterointernal part.

Case VI.—E. W., male, age 61, admitted under the care of Dr. L. R. Yealland in January, 1933, complaining of diminishing vision and headache.

History.—He was stated to have been well until five months previously to admission when he had a 'stroke' and 'saw coloured lights,' with impairment of

CASE VI.

FIG. 21.—Under surface of a horizontal section through cerebral hemispheres showing the large metastatic tumour invading the right occipital lobe, pushing its way forwards and compressing the posterior horn, the posterior part of which is seen as a slit-like cavity in front of it towards the middle line. The tumour has also burrowed its way forwards into the body of the right lateral ventricle as far as the origin of the descending horn. An irregular nodule of the tumour is also seen in connexion with the anterior horn of the same ventricle, showing the development of a cyst-like cavity filled with mucus. A smaller subcortical nodule is seen on the left side, towards the posterior part of the parietal lobe. (Note.—This is a photograph of the under surface of this portion of brain and the sides therefore appear reversed.)

sight on looking to the left. He suffered from frontal and occipital headaches—the former mostly on the right side.

Condition on Admission.—Pupils small, central but irregular. Reaction to light normal. The right visual field was slightly diminished to the right, the left absent on the left as far as the fixation point. The fundi showed papilloedema.

The cerebrospinal fluid showed a slight, but distinct, yellowish tint but no frothing. Cells 2 per c.mm.—small lymphocytes. Total protein 0.12 per cent. Globulin in slight excess.

Lange 0012210000. Wassermann and Kahn reactions negative, as also in the blood. A leucocyte count gave 15,300 per c.mm. (polymorphs 68.5 per cent. ; lymphocytes

13.0 per cent. ; monocytes 18.5 per cent. ; eosinophils and basophils 0.0 per cent.). Blood urea 51 mgm. per cent.

Progress.—The patient grew steadily worse, developing patchy dulness in the lung with much secretion, which he was unable to expectorate. He became very emaciated, with frequent attacks of vomiting and further deterioration of vision, death occurring on May 18, 1933. The provisional diagnosis was one of right occipital lobe tumour.

Post-mortem Examination.—As shown in the accompanying photograph (fig. 21), a large malignant tumour was found occupying most of the right occipital pole. On section, this was variegated in appearance, some parts

CASE VI.

FIG. 22.—Occipital tumour : high power view showing the actively phagocytic and highly vacuolated tumour-cells, some of which contain numerous englobed red blood corpuscles. Some of the larger vacuoles when empty simulate the appearance of transverse sections of capillaries, with the nucleus stretched and pushed to one side and the cytoplasm reduced to a thin peripheral ring. Hæmatoxylin and eosin. $\times 400$.

being pearly rather opaque white, others dark red and hæmorrhagic, and yet others showing old-standing blood-pigmentation together with mottled areas of necrosis. The tumour was much firmer than the surrounding brain-tissue and did not show the crumbling spongy appearance of the majority of our cases of bronchogenic carcinoma—perhaps because of the distinct tendency to reversion to squamous epithelium. Anteriorly, this tumour involved the posterior horn and body of the right lateral ventricle, being continuous with the choroid plexus. Another fairly large nodule with considerable cystic development was found in connexion with the anterior horn of the same ventricle, while a subcortical nodule was present on the other side towards the junction of parietal and occipital lobes.

(DR. NORAH SCHUSTER'S CASE.)

FIG. 23.—High power view of portion of infiltrating malignant tumour of the bronchial mucous membrane, showing the tendency to reversion to squamous epithelium, lining cystic spaces with papillomatous ingrowths into them. Mayer's mucicarmine. $\times 400$.

(DR. McMENEMEY'S CASE.)

FIG. 24.—High power view of metastasis in suprarenal, showing the small round-cells which gave rise to the diagnosis of small round-celled sarcoma. The spaces, however, are lined at the periphery by epithelial cells similar to those found upon the papillomatous processes seen in sections of the primary lung tumour and the cerebral metastases from it. Hæmatoxylin and eosin. $\times 400$.

The microscopical appearances are shown in fig. 22. The chief interest of this case lay in the fact that, although some parts of the tumour were distinctly papillomatous in structure, there was a tendency of the tumour-cells to show a reversion to a squamous type of epithelium, a metaplastic change not uncommon in the primary bronchial carcinomas themselves. The individual cells of this tumour were highly phagocytic, not only to red blood-corpuscles and leucocytes, but also to other tumour-cells, the remains of which, in all stages of digestion, could be found in the digestive vacuoles (see fig. 22). When stained by Mayer's mucicarmin method, numerous globules and granules of mucin could be demonstrated in the cytoplasm of the cells, particularly in those which had been englobed by other tumour-cells.

It is interesting to note that in three of Schuster's cases varying degrees of this metaplasia to squamous cells were found in some parts of both primary and secondary tumours (fig. 23) which might otherwise have been labelled small round-celled tumours. As a typical example of the latter we show a microphotograph (fig. 24) from the case of a man (age 43), for which we are indebted to our colleague Dr. W. H. McMenemey, who found it labelled with a diagnosis of 'small round-celled sarcoma' among some old microscopical preparations in one of his hospitals. This was from a metastasis in the suprarenal body, similar tumours being found in the lung in which they show characteristically papillomatous structures, the primary tumour being a bronchial carcinoma.

CLINICAL COMMENTARY

It is noteworthy that all our patients were males and came under observation purely on account of cerebral symptoms at a neurological hospital. Their ages varied between 43 and 64 years, the average age being 53. In Levy Simpson's ⁶ series of 139 cases of bronchial carcinoma the average age was 48; 111 were males and 28 females (four to one). The majority of observers place the ratio as three males to one female affected. Metastases of the brain occurred in 19 of Levy Simpson's 139 cases, and in 11 of the 19 the primary bronchial growth was not detected clinically. In Ormerod's ¹⁶ series of 27 cases at Brompton and Westminster Hospitals 23 were in males and four in females. Improved X-ray technique and the use of lipiodol, bronchoscopy and the histological examination of a biopsy specimen have greatly facilitated the diagnosis of such cases.

Chest symptoms were inconspicuous or practically absent in all but two of our cases. One of these patients had complained of a cough for 18 months and the other of a slight cough for only a few weeks. In the former case (sclerosing bronchial type of tumour), suggestive signs were found in the upper lobe of the right lung, but in the second case only a few râles at the bases were apparent. In two other cases signs were detected in the lungs in the absence of symptoms. In one case (Case II) with a small primary tumour on a secondary bronchus, an X-ray examination was carried out with

negative results. The second case (Case III) showed definite signs in the left upper lobe.

When sputum is available from cases of suspected bronchial carcinoma, suitable specimens should be examined for the presence of malignant cells, preferably by fresh wet staining methods, for which purpose we have found toluidine blue one of the most useful dyes.

In all cases headache was a prominent symptom, also mental symptoms such as confusion, lack of concentration, failure of memory and disorientation. In three cases a definite change of temperament was noted.

Papilloedema was found at some stage of the illness in all cases. Nystagmus was present in three, but, apart from weakness of the lower half of one side of the face (as part of a hemiparesis) in two cases, other cranial nerves were not affected. The deep reflexes were unequal in all cases; both plantar reflexes were extensor in four and one in the remainder.

The blood pressure was uniformly low, the highest pressure recorded being 130/96. The latter was also the highest diastolic pressure—in a man of 47. The lowest was 110/65. It is of interest to note that in the two patients with the lowest pressures—110/65 and 118/70—a large metastasis was found in the left suprarenal body in each case.

As regards the cerebrospinal fluid, no definite increase in cells was found in any case with the solitary exception of the patient (Case III) showing evidence of previous syphilis. In this example, 26 small lymphocytes per c.mm. were present, but, in addition, the Wassermann reaction was weakly positive and the Lange reaction showed a curve of parietic type. This increase in lymphocytes, therefore, was more probably a result of the syphilitic infection than of the cerebral neoplasms. Increase in the total protein was only moderate except in one case. In this latter the amount was 0.12 per cent. The lowest was 0.04 per cent., figures from 0.06 to 0.08 per cent. occurring in the remaining cases.

In cases submitted to operation—owing to the exact nature of the tumour being doubtful—there is always the possibility of a definite diagnosis being made by the examination of puncture-fluid aspirated from one of the more superficial cystic tumours (see Pathological Commentary).

In general, the clinical symptoms and signs indicate lesions of the frontal or temporosphenoidal lobes and/or of the cerebellum in which situations the larger tumours were found to occur.

PATHOLOGICAL COMMENTARY

From the pathological standpoint, perhaps the most interesting and important problem in connexion with this series of cases has been the question of excluding the possibility of the diagnosis of choroid papilloma. Many of the cases with this diagnosis described in the literature, especially in middle-aged to elderly patients, in our opinion, have been typical examples of

cerebral metastases derived from a primary bronchial carcinoma. We have already drawn attention to the latency of the symptoms, especially in males.

In our series of cases, the largest of these cerebral metastases have usually been in the temporosphenoidal and frontal lobes and in the cerebellum. We have also emphasized the fact of their presence in, and continuity with, the choroid plexuses themselves in an appreciable number of cases. These are obviously due to the implantation of embolic malignant cells in the choroid vessels. In this connexion it is interesting to recall that an infective disease, meningococcal meningitis, in an analogous manner, probably results from the meningococci being carried by the bloodstream to the choroid plexuses, from which the infection is carried by way of the ventricular chain to the surface of the brain.¹⁷

Secondary growths of the bronchogenic carcinoma, in almost every case, were also found in the suprarenal medulla, which may from this point of view be regarded as a part of the nervous system.

Histologically, both the primary bronchial carcinomas and the secondary growths in the brain and other organs usually show, in whole or in part, an appreciable and often a marked tendency towards the development of a papillomatous structure. The tumour-cells often retain a considerable capacity for secreting mucus, and cysts of varying size filled with sputum-like material may develop, not infrequently giving a baggy feeling to the overlying surface of the brain. It is often not a difficult matter to obtain some of their contents through a puncture-needle. The presence of fragments of papillomatous tumour and numerous cigar-shaped, columnar or tailed epithelial cells resembling those of a catarrhal bronchitis may facilitate the diagnosis. Mucin may often be demonstrated, whereas in the contents of somewhat similar tumours secondary to carcinoma of the breast we have found numerous fatty granules and globules almost suggestive of an imperfect attempt at milk secretion.*

The naked-eye appearances of the secondary tumours are usually characteristic. They are spongy and friable and are easily enucleated, but leave a thin ragged layer of malignant cells in the wall of the cavity. The tumours in which squamous-celled metaplasia has occurred tend to be firmer in consistency, less spongy, and may show a variegated appearance on section (Case VI).

We have emphasized the great variability of the naked-eye appearances of the primary bronchial tumours in the lungs. Some of these in the larger bronchi near the root or in the lung tissue at the periphery of the organs are easily found, but others in an intermediate position, e.g. in connexion with

* The diagnosis of these and other cerebral tumours, primary and secondary, by means of fresh wet preparations of exploratory puncture-fluids formed the subject of a separate paper communicated by one of us to the Second International Neurological Congress, London, 1935 (*Congress Abstracts*, p. 101).

secondary or tertiary divisions of the bronchi, may be inconspicuous and are easily overlooked.

In conclusion, we desire to thank our colleagues, especially Dr. L. R. Yealland, Dr. T. R. Hill, Dr. W. H. McMenemey, Dr. Norah Schuster and Mr. C. P. G. Wakeley for kindly allowing us to include some of their clinical and pathological material. Also, we have to acknowledge the valuable technical help of Messrs. J. Ottewill and K. Osborne and of Miss M. I. Wilson in the laboratory.

SUMMARY

1. Cases of multiple metastatic tumours of the brain secondary to primary bronchial carcinoma are described and analysed. As regards the primary focus in the lung, the cases fall into three main types: (1) sclerosing bronchial growth, (2) primary growth in connexion with a secondary or tertiary bronchus, and (3) large tumour especially at the periphery of the lung.

2. The increased incidence of such cases in recent years, the latency of symptoms of the primary bronchial focus and the liability for cerebral symptoms to dominate the clinical picture in males are confirmed.

3. In the brain, metastases are liable to occur especially in the frontal and temporosphenoidal lobes and in the cerebellum. The suprarenal medulla is also a frequent site of such secondary growths.

4. The symptoms include headache, mental confusion, defects of memory and occasionally a change of temperament. Papilloedema is invariably present, together with changes in the deep reflexes of the limbs and an extensor plantar reflex—bilateral or unilateral.

5. We emphasize the definite tendency for bronchogenic carcinoma, both primary and secondary, to be papillomatous in its histological characters.

6. Attention is drawn to the frequent occurrence of metastases in the choroid plexuses. From a perusal of the literature, we consider that many cases in which this has occurred have been described erroneously as examples of malignant papilloma of the choroid plexus.

7. Cysts often develop in connexion with the cerebral metastases, and these usually contain mucin, tests for which materially assist in the diagnosis.

8. The observation is made that puncture-fluids aspirated from such cysts may resemble sputum and that fresh wet films may show fragments of the papillomatous processes as well as malignant epithelial cells resembling the cells of a catarrhal bronchitis.

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