J. clin. Path., 1976, **29**, 520-529

Spindle-cell tumours and hypoglycaemia

P. R. MILLARD, D. W. JERROME, AND G. H. MILLWARD-SADLER

From the Department of Pathology, Radcliffe Infirmary, Oxford

SYNOPSIS The light microscopy and clinical features of two patients with extrapancreatic tumours and hypoglycaemic episodes are described—together with the electron microscopy findings in one patient. The primary tumour of one patient arose within the skull and later metastasized to the liver, while the other patient had a locally recurrent intrathoracic tumour. Neither the intracranial origin nor the ultrastructural features support the concept of a mesothelial origin for these tumours, and they should be referred to as spindle-cell tumours associated with hypoglycaemia. There are ultrastructural similarities between these neoplasms and those of the pancreatic β cells.

Lowbeer (1961) collected 25 examples of large extrapancreatic non-epithelial tumours associated with hypoglycaemia, and Leger *et al* (1963) refer to a similar group of 39 patients. Azzopardi (1966) added three further examples, but none of the patients in any of these reviews had a primary intracranial tumour. Also no mention is made in these reports of electron microscopic appearances. The ultrastructural features could help in tracing the cell of origin of these tumours which remains a subject of debate based on little objective evidence (Leger *et al*, 1963; Boshell *et al*, 1964). Two further examples of large spindle-cell neoplasms coincident with hypoglycaemia are presented and the ultrastructure of one is described.

Observations

CLINICAL FEATURES

Case 1

Mrs M. P. (1939-70) was admitted on 11 November 1966 in a semicomatose state with weakness of the left arm and face and gross ataxia. She was 20 weeks pregnant. There was a history of an acute transient right-sided blindness in March 1966 and the development of worsening headaches and vomiting. Her husband had noticed that she had failing memory and slurring of speech. After admission her conscious level improved but the left pupil became fixed and dilated. A ventriculogram and carotid angiogram showed a vascular tumour filling the posterior part of the floor of the right middle cranial fossa. This was removed on 18 November and postoperative recovery was satisfactory. The operative findings were considered to be insufficient to account entirely for the patient's symptoms but no blood sugar levels were measured during this illness. After the birth of the child a course of radiotherapy was given. She remained well although with a residual right lower motor neurone facial palsy. A second child was born in December 1969.

In the following February she noticed increasing tiredness, blurring of vision which often occurred at mid-day, and morning sweats. On 16 March 1970 she was found comatose and covered in sweat but afebrile. There was a flaccid tetraparesis with bilateral extensor plantar responses and uniformly diminished reflexes but no meningism or papilloedema. The liver was enlarged. The neurological signs were disproportionate with her conscious level which spontaneously improved during the day and was rapidly corrected with 20% intravenous dextrose and a Horlicks drink. The blood sugar immediately before this treatment was 8 mg/dl of blood. Investigation of the hypoglycaemia included fasting blood sugars, a glucose tolerance test, a glucogen stimulation test, insulin assay, liver and pancreatic scan, abdominal aortogram, skull *x*-ray and gamma encephalogram, liver function tests, and a liver biopsy. No lesions were found in the brain or pancreas. Severe hypoglycaemia was confirmed and rounded vascular deposits taking up selenomethionine were demonstrated in the liver. Tests of liver function were within normal limits and tumour was included in the liver biopsy. No evidence of dissemination of tumour to other sites was found and after removal of the patient's own liver an orthotopic liver transplant was performed.

The immediate postoperative recovery was un-

Received for publication 11 November 1975

eventful, but later a bile leak developed and repeated attempts to correct this failed. She died 82 days after the operation with a severe chest infection.

Case 2

Mrs N. R. (1907-73) worked from 1948 to 1953 as a secretary next door to an asbestos factory. A symptomless right-sided lesion was recorded on a chest *x*-ray in 1961 but was not investigated. She became progressively unwell during 1967 with shortness of breath and loss of one stone (6·4 kg) in weight. A six-pint, sterile, right-sided pleural effusion was drained and malignant cells were identified. By the following October she was having attacks of unconsciousness of 15 min to 24 h and was becoming aggressive and confused and slurring her speech. The pleural effusion had recurred but there were no abnormalities in the cerebrospinal fluid or in carotid angiograms. A blood sugar level of 40 mg/dl of blood was recorded during one of these attacks and there was a marked improvement following intravenous glucose. Investigations for hypoglycaemia included fasting blood sugars, a glucose tolerance test, and a glucagon stimulation test, a tolbutamide tolerance test and insulin assay (these results are discussed by Spry *et al* (1968)). Resection of the right intrathoracic tumour was undertaken on 27 November 1967 and the postoperative recovery was uneventful.

During 1968-73 she developed dizziness which was most marked after exertion. Blood sugar levels remained within normal limits but did reach 55 mg/dl of blood after a fast of 72 hours. A chest *x*-ray during 1970 showed a further right-sided mass which slowly increased in size. In June 1973 because of the progressive worsening of the dizziness she was reinvestigated for hypoglycaemia, but no abnormality apart from the intrapleural tumour was found. At this time there was a slight slurring of speech, an ataxic gait, and a decrease in power of the proximal muscles of the lower limbs. The mass in the chest had increased in size and was removed on 6 July 1973 together with the lower lobe of the right lung. Postoperatively she was difficult to wean from the respirator and developed pulmonary oedema, a chest infection, and pulmonary emboli. She died 12 days after the thoracotomy.

PATHOLOGY

Tissues were fixed in 10% neutral buffered formalin solution, and 5 μm sections were stained with Harris' haematoxylin and eosin and by special staining procedures including reticulin preparations. Tissues (1 mm^3) for electron microscopy were fixed in phosphate buffered 4% glutaraldehyde (pH 7·4) at 0-4°C followed by washing in phosphate buffer and post fixation in phosphate buffered 1% osmium tetroxide at 0-4°C. The blocks were processed and embedded in Araldite. Sections were double stained with 2% aqueous uranyl acetate and lead citrate and examined with a Philips EM 200. Necropsy included inspection of the thoracic and abdominal viscera and of the brain.

Case 1

The intracranial tumour consisted of lobulated fragments measuring up to 6·5 × 6·0 × 4·5 cm with firm pale grey surfaces which included round nodules. Light microscopy showed a cellular spindle-cell tumour (fig 1). The cells were uniform but with many mitoses and little cytoplasm. They were arranged in loose interweaving bundles supported by reticulin and separated by numerous capillaries (fig 2). The diagnosis of angioblastic meningioma was made.

The liver biopsy specimen and the features in the tumour in the hepatectomy specimen were comparable to one another and to those above. The liver nodules were rounded and sharply demarcated from the investing liver with firm homogeneous white surfaces (fig 3). At necropsy there was jaundice, oedema of the legs, multiple recent abdominal surgical incisions, and an ileostomy. The transplanted liver was bile stained and all the vascular anastomoses were intact and patent. Parts of the common bile duct were necrotic and there was a fistula associated with the enteroenterostomy formed from a jejunal loop anastomosed to the fundus of the gall bladder. The stomach had a perforated ulcer infiltrated by fungus and a fibrinous exudate covered the peritoneal cavity and gut. Discrete areas of necrosis were seen in the pancreas and small friable vegetations were adherent to the mitral valve cusps. Thrombus occluded both femoral and external iliac veins. The lungs were oedematous with many small arteries occluded by embolus infiltrated by a Candida and Aspergillus species. Cytomegalovirus inclusion bodies were present in the alveoli. A single paratracheal lymph node was replaced by tumour like that in the patient's own liver. A superficial cyst, 3 cm diameter, containing clear fluid was found adjacent to the right Sylvian fissure but there were no other changes in the brain or skull.

Case 2

The tumour removed at the first thoracotomy (1270g) had lobulated firm white surfaces with small scattered foci of necrosis. It was very cellular with numerous blood vessels and abundant fibrous tissue. Within the fibrous tissue there were moderate numbers of uniform spindle cells while in other areas the cells were markedly pleomorphic and often

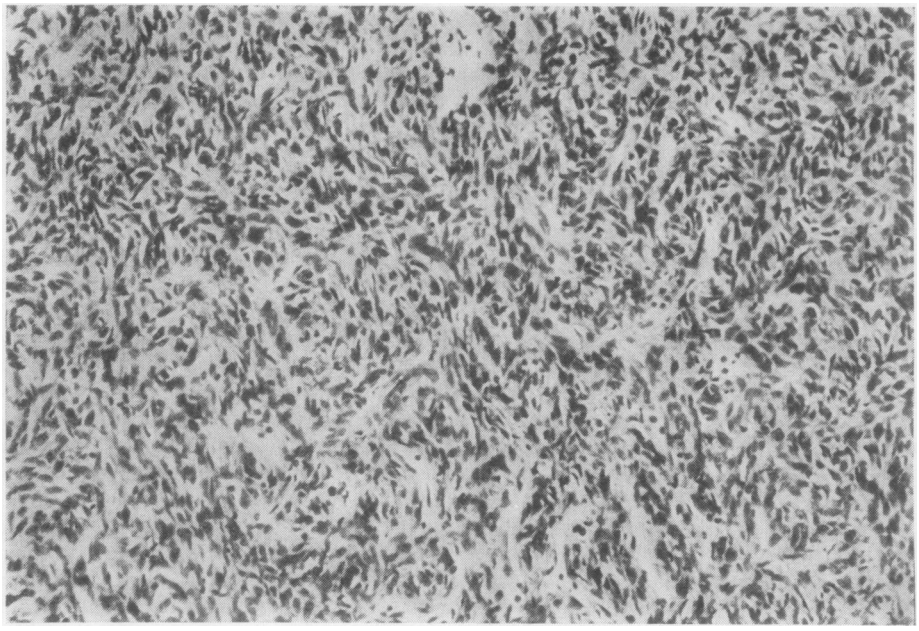

Fig 1 *Case 1. Intracranial tumour with interweaving spindle-cell pattern. Haematoxylin and eosin × 43.*

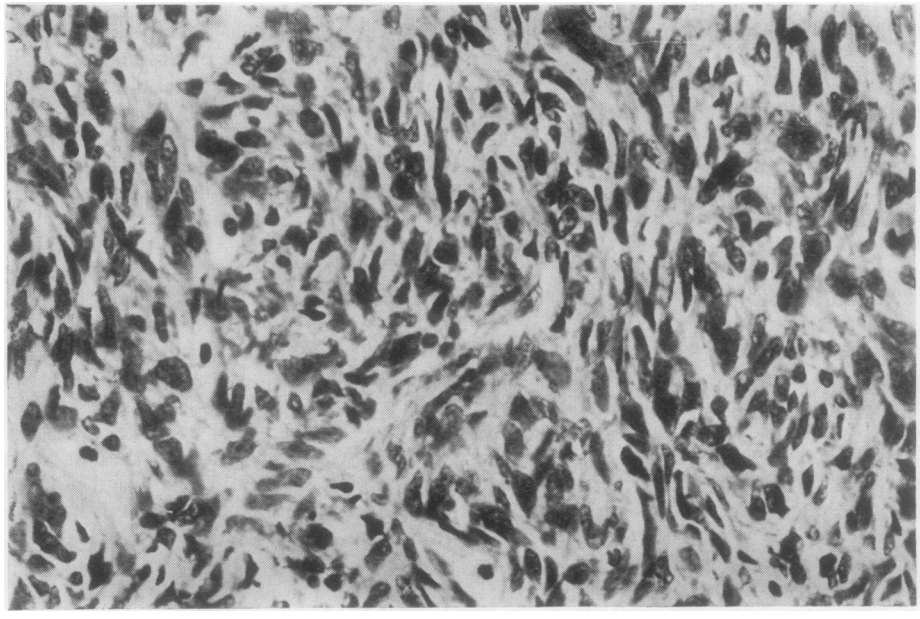

Fig 2 *Case 1. High-power view of spindle-cell tumour cells of figure 1. H and E × 104.*

harboured bizarre nuclei. A moderate number of mitoses were present. The cells were in bundles intimately intertwined among the supporting vascular and reticular framework (fig 4). The tumour mass (278 g) removed at the second thoracotomy was essentially similar (figs 5 and 6).

Electron microscopy of the recurrent tumour mass revealed two types of cell which were arranged in

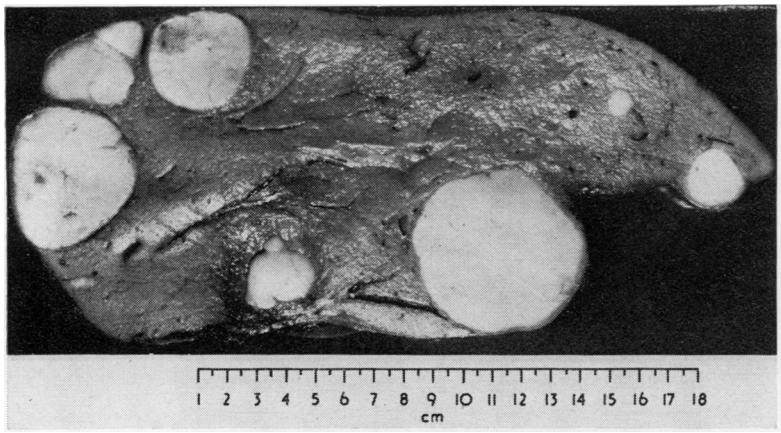

Fig 3 *Case 1. Parasaggital section of liver with circumscribed tumour nodules separated by abundant normal liver.*

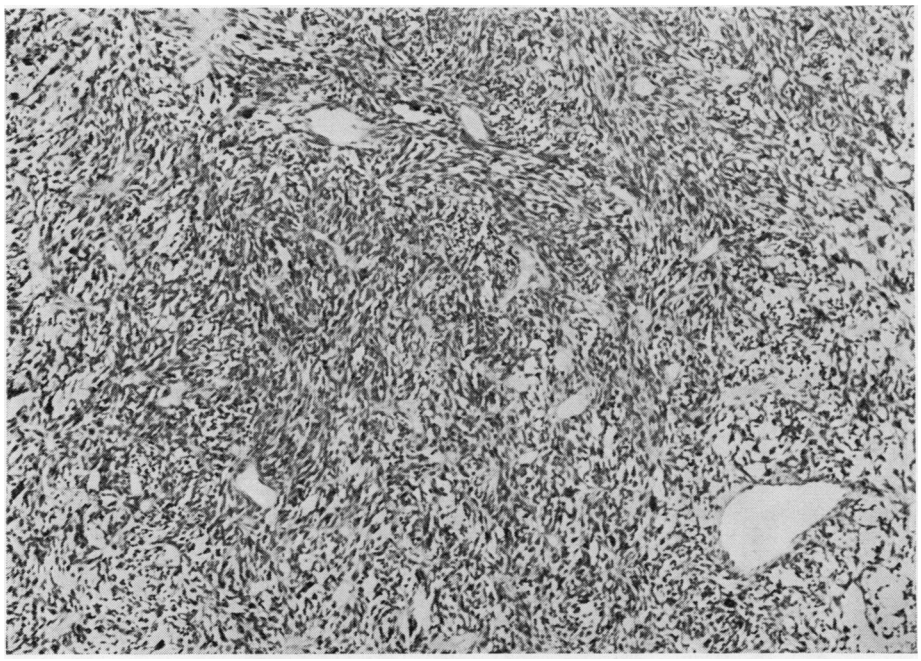

Fig 4 *Case 2. Original intrathoracic tumour with interweaving spindle-cell pattern—compare with figure 1. H and E × 14.*

groups with some separation by vascular channels, collagen, and reticulin (fig 7). These two types occurred in apparently equal proportions although their distribution was variable in any one field. One type of cell had a darkly staining large, irregularly indented nucleus. The cytoplasm was scanty and was occupied by mitochondria, dilated rough endoplasmic reticulum, and Golgi apparatus, but there were no microvilli or granules (fig 7). The other type of cell had a paler staining nucleus but was of a similar size although with a greater amount of cytoplasm. Occasional microvillus-like processes projected from the plasmalemma. The cytoplasm contained mitochondria, undilated rough endoplasmic reticulum, Golgi apparatus, and many fine filaments (fig 8). In some of these cells a few dense granules of variable diameter and surrounded by a closely apposed single limiting membrane were also seen (figs 7

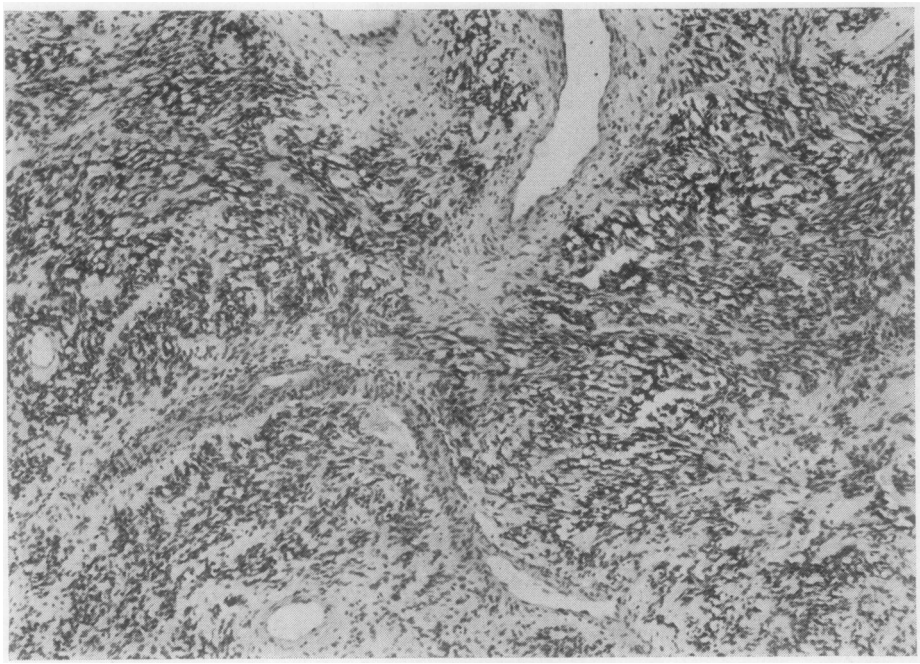

Fig 5 *Case 2. Recurrent tumour with similar features to those in figures 1 and 4. H and E × 14.*

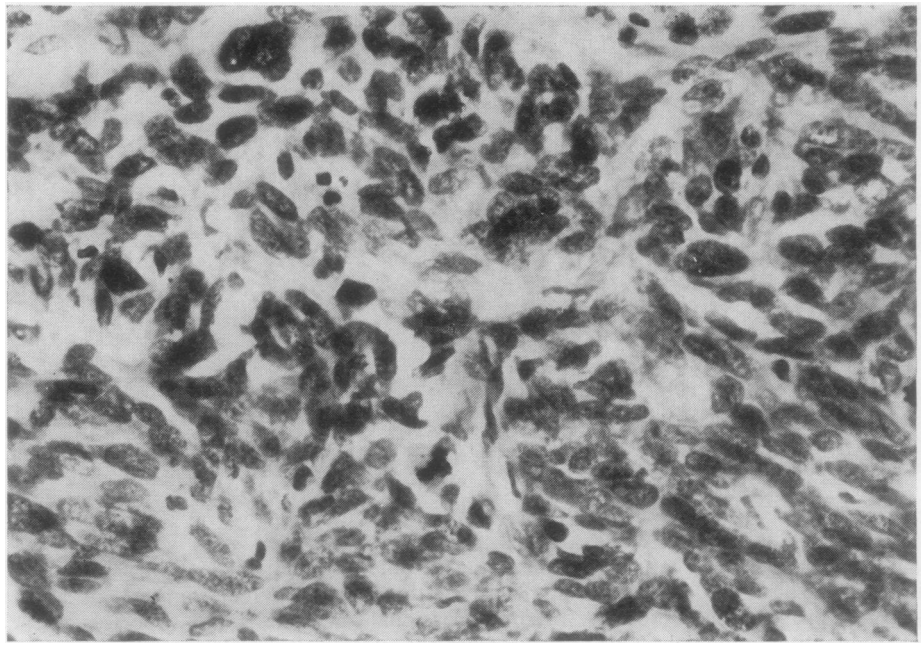

Fig 6 *Case 2. High-power view of recurrent spindle-cell tumour with abnormal mitosis lower centre. H and E × 85.*

and 9). A solitary giant cell was found among these two main groups of cells.

At necropsy the fingers of both hands were clubbed and there was bilateral leg oedema. The right thoracotomy incision was healing and there was an open tracheostomy. The lower lobe of the right lung had been removed and the other lobes of both lungs were oedematous with emboli in some

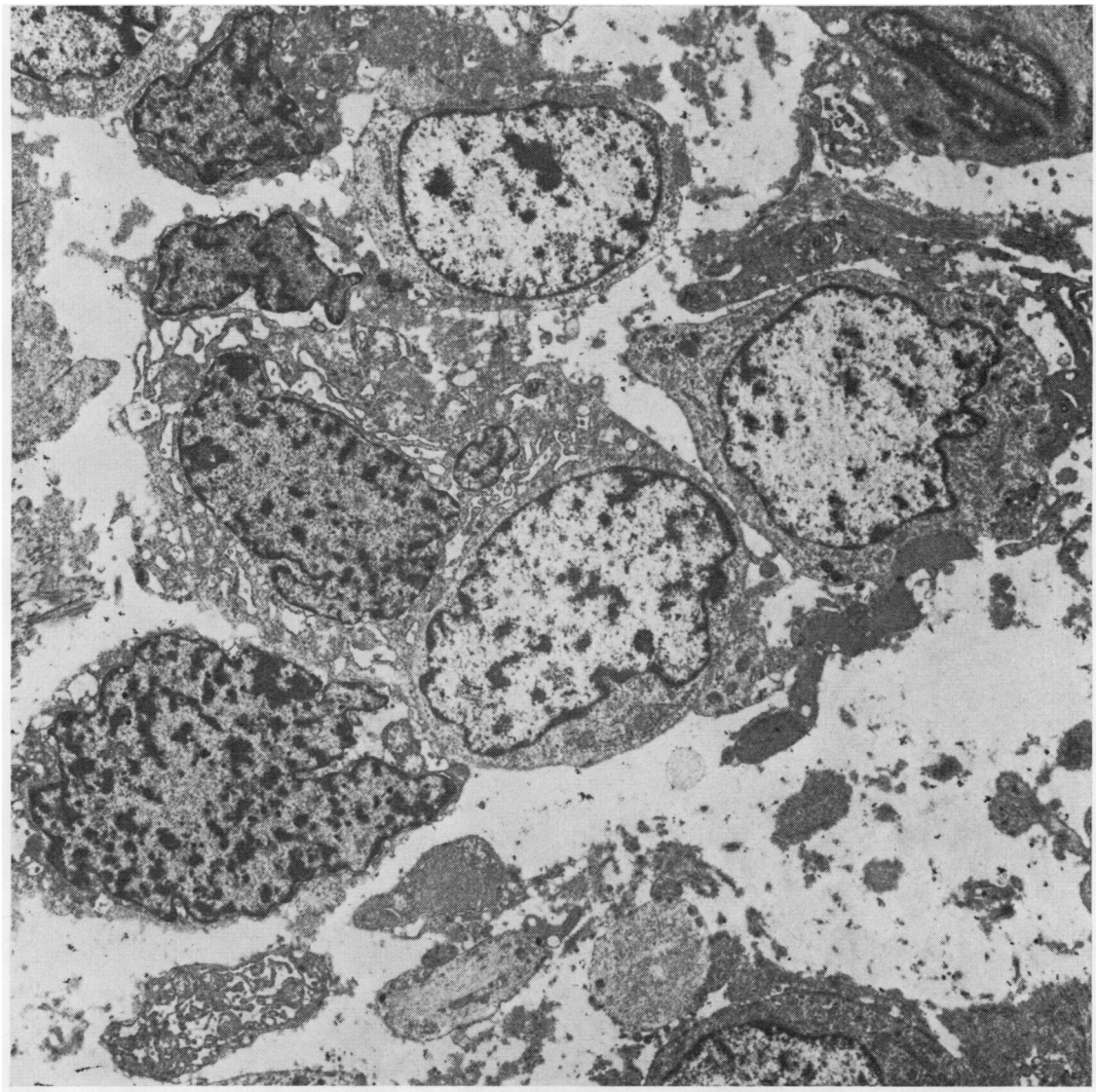

Fig 7 *Dark and light tumour cells with a few granules in the light cell on the right-hand side.* × *3955.*

smaller arteries. Small granular vegetations were loosely adherent to the mitral and aortic valves, and partly occlusive thrombus occupied the inferior vena cava from the right femoral vein to the junction of both renal veins. The liver was fatty, and small areas of necrosis were seen in the pancreas. No localized lesions or metastatic tumour were found in any of the other organs including the brain.

Discussion

Extracranial spread of meningeal tumours is well documented (Simpson, 1957; Kruse, 1961) but neither of these reports includes examples of hypoglycaemia co-existent with a primary intracranial tumour or with their extracranial metastases. Case 1 may provide such an example, although without pre-

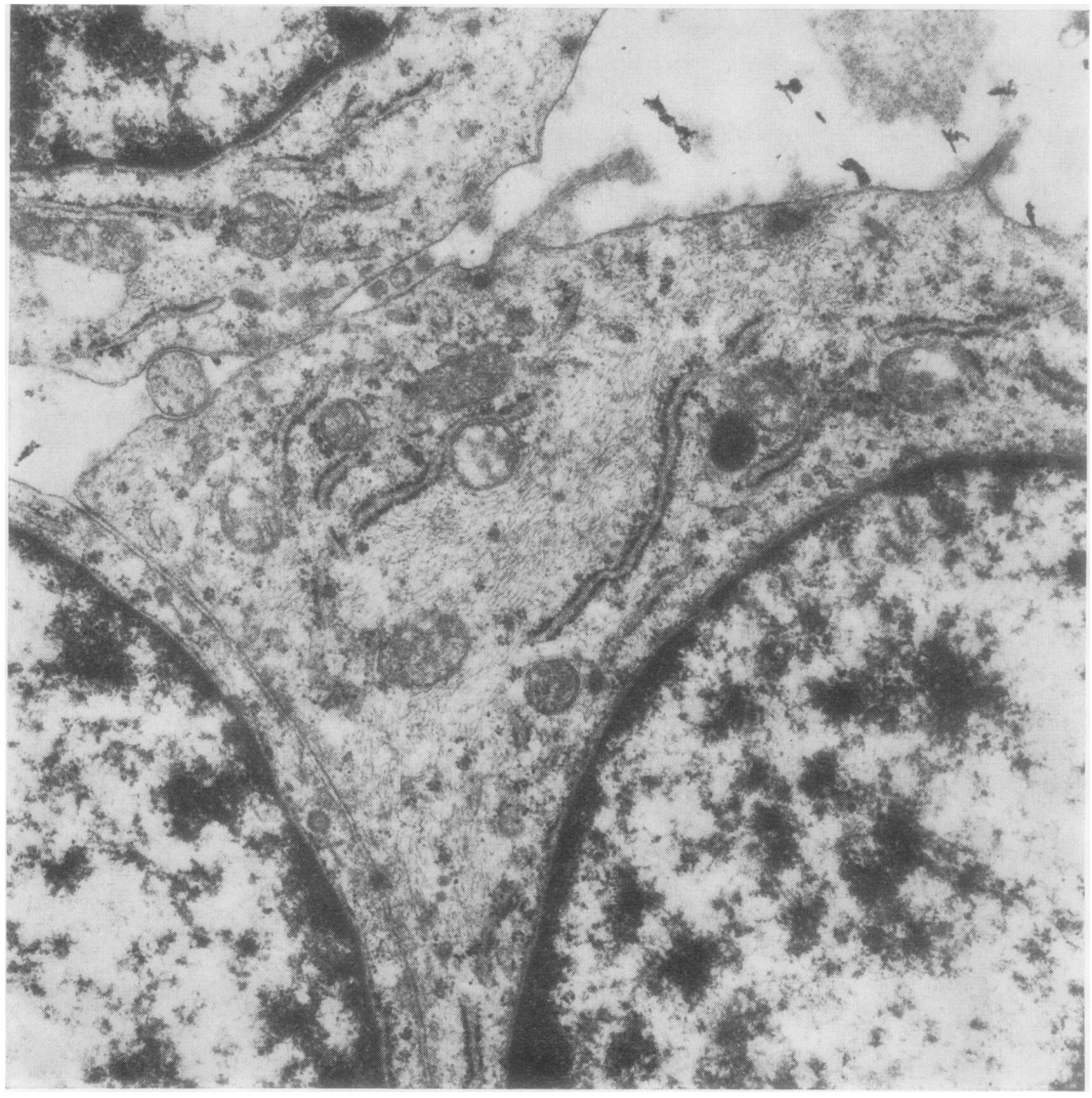

Fig 8 *Light nuclear staining cell with abundant fine filaments, rough endoplasmic reticulin, and mitochondria. Two microvilli extend from the plasmalemma (upper centre and upper right).* × *30 360.*

operative blood sugar levels absolute proof is lacking. Hypoglycaemia and this intracranial tumour could have accounted for the clinical state of the patient since the impression following the operative findings was that the size and position of the tumour alone were insufficient to explain satisfactorily the clinical observations. Among Simpson's (1957) 12 patients with tumours diagnosed as angioblastic meningiomas no extracranial spread developed and in none was there any evidence of local tumour recurrence . Kruse (1961) encountered a single example of extracranial spread among his eight similar cases. The possibility must be considered that case 1 had had two primary tumours, intracranial and hepatic, only the hepatic neoplasm inducing hypoglycaemia, or that the hepatic lesions were metastatic from a further extracranial site. The macroscopic distribution and appearances of the intrahepatic lesions (fig 3) and the failure at necropsy to find an alternative primary site are against these

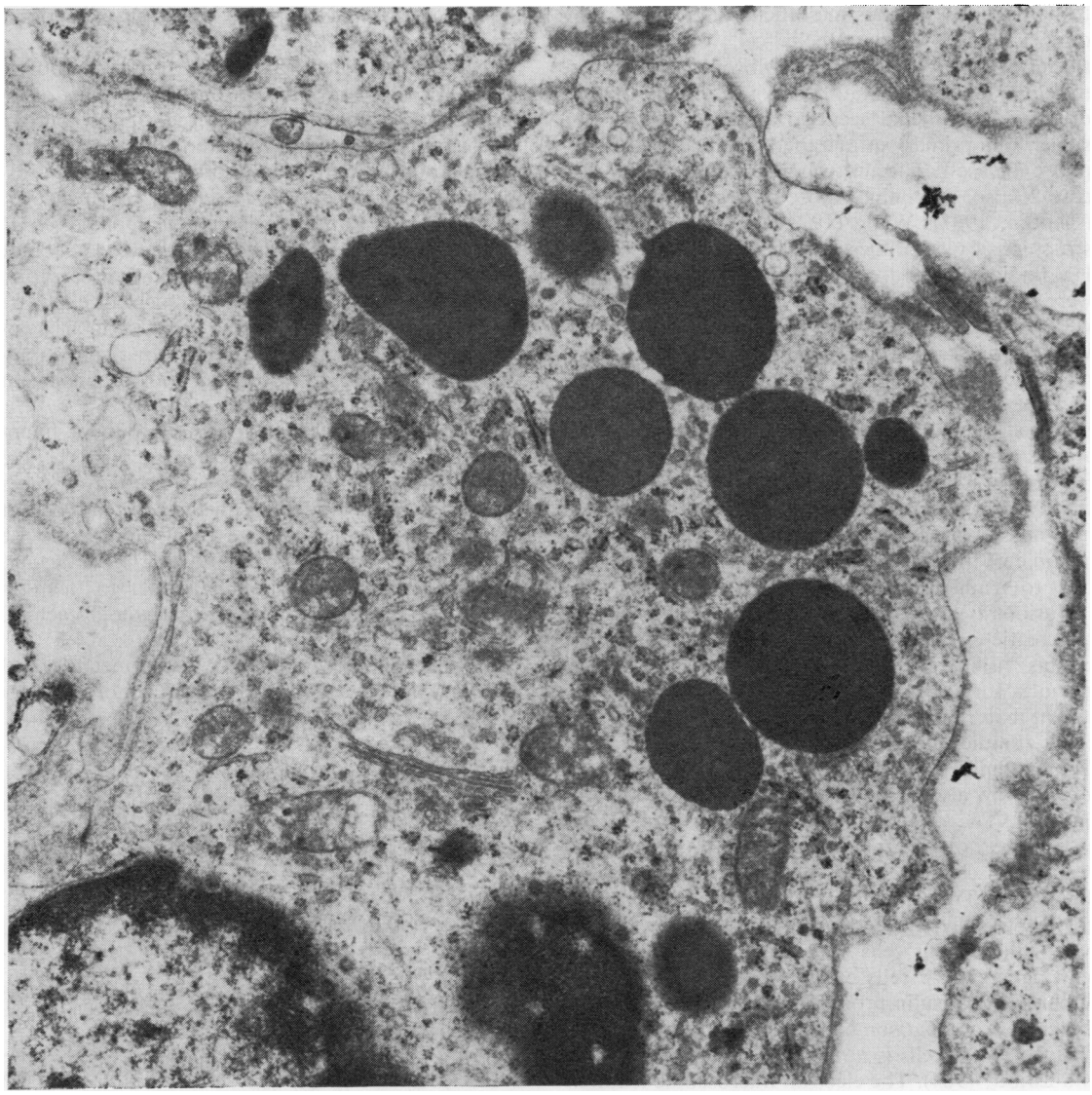

Fig 9 *Light nuclear staining cell with dense granules in the cytoplasm.* × *23 000.*

hypotheses. Further, the histological similarity between the intracranial and the intrahepatic growth also favours the view that the liver lesions represented metastases from the intracranial tumour. The mode of spread appeared to be vascular but, in view of the lymph node involvement at necropsy, lymphatic dissemination is also implicated. This lymph node metastasis could alternatively have arisen from dissemination during liver transplantation and the subsequent surgery.

The course and light microscopy findings in case 2 are like those in the patients reviewed by Lowbeer (1961) and Azzopardi (1966). These patients had large extrapancreatic tumours which were usually retroperitoneal but also developed in other sites. On light microscopy spindle cells were predominant in a vascular fibrous stroma, and all the patients experienced hypoglycaemic episodes. Azzopardi (1966) considers the behaviour and appearance of these tumours as typical of a fibroblast and the structure

to be that of a 'fibrous mesothelioma'. This terminology implies a mesothelial-cell origin. Mesothelial cells may be facultative fibroblasts and these tumours fibroblastic but the concept that the cell origin is mesothelial seems discredited by the possibility of a primary intracranial or even hepatic neoplasm in case 1. The electron microscopic features of case 2, also, are unlike those of normal fibroblasts (Rhodin, 1967). Wang (1973) described the ultrastructure of pleural mesotheliomas in four patients. His findings differ from ours in that two cell types were not recognized, and the cells from his patients were distinguished by either many brush-like microvilli or by pseudopod extensions of their cytoplasm. Only a few microvilli were apparent and only in some of the tumour cells of case 2. If the assumption that the similarity between the primary growth and its recurrence applies to the electron microscopy features is correct then the tumour of case 2 is not closely akin to those described by Wang (1973) and may not be a true mesothelioma. The granules found in some of the tumour cells are also in marked contrast to Wang's observations.

Various types of granule are found in the cells of pancreatic islets and within some pancreatic neoplasms (Like, 1967; Greider *et al*, 1970). These granules form a heterogeneous group but there are salient features to those in normal β and α cells. The β cell granules have a clear area dividing the granule from its limiting membrane while the granules in the α cells show a wide spectrum of diameter within any one cell. The granules in the recurrent tumour of case 2 are not separated from their limiting membrane by a clear space but do demonstrate variable diameters. The functional effect of the original growth was hypoglycaemia and any similarity between the tumour cells and normal cells should be with pancreatic β cells but ultramicroscopic studies of pancreatic insulin-producing tumours have shown that a close comparison between the tumour granules and those of β cells is not always apparent (Greider and Elliott, 1964). The electron microscopic features in case 2 are therefore consistent with an insulin-secreting growth, and the small number of granules may account for the clinical difficulty in producing hypoglycaemia. It is likely that patients with marked hypoglycaemia have a greater number of granule-containing cells in their tumours. These comments imply a close similarity between the tumours of case 2 and tumours of β-cell origin. Further support for this lies in the comparable ultrastructure of an insulinoma described by Greider and Elliott (1964) and the recurrent neoplasm of case 2. This insulinoma included similar granules and was formed of both light and dark cells. However, we have not investigated the characteristics of the granules in case 2 or demonstrated that they have any functional significance.

The variance noted between the tumours reported by Wang (1973) and those in this report must query a mesothelial origin and discredit their present nomenclature. The term mesothelioma has become synonymous with growths secondary to asbestos exposure (Hourihane, 1964; Selikoff *et al*, 1965; Mortimer and Campbell, 1968; McDonald *et al*, 1970) but there is insufficient evidence to include either of the patients in this report in that category. Case 1 had no history to suggest such an exposure and case 2, who had worked adjacent to an asbestos factory, was thoroughly investigated by the Pneumoconiosis Panel but no adequate proof of significant asbestos exposure was found.

No suitable appellation for this group of hypoglycaemic producing tumours arises from these observations, and the findings in these two cases cast considerable doubt on the validity of that at present in use. Until a more precise origin of the growths is defined it may be more descriptively exact, although cumbersome, simply to refer to them as spindle-cell tumours associated with hypoglycaemia.

We should like to thank the many medical and technical staff of both Oxford and Cambridge who have given their help.

References

Azzopardi, J. G. (1966). Systemic effects of neoplasia. In *Recent Advances in Pathology*, 8th edition, edited by C. V. Harrison, pp 146-153 Churchill, London.

Boshell, B. R., Kirschenfeld, J. J., and Soteres, P. S. (1964). Extrapancreatic insulin-secreting tumor. *New Engl. J. Med.*, **270**, 338-341.

Greider, M. H., Bencosme, S. A., and Lechago, J. (1970). The human pancreatic islet cells and their tumors. 1. The normal pancreatic islets. *Lab. Invest.*, **22**, 344-354.

Greider, M. H. and Elliott, D. W. (1964). Electron microscopy of human pancreatic tumors of islet cell origin. *Amer. J. Path.*, **44**, 663-678.

Hourihane, D. O' B. (1964). The pathology of mesotheliomata and an analysis of their association with asbestos exposure. *Thorax*, **19**, 268-278.

Kruse, F., Jr. (1961). Hemangiopericytoma of the meninges (angioblastic meningioma of Cushing and Eisenhardt): clinicopathologic aspects and follow-up studies in 8 cases. *Neurology*, **11**, 771-777.

Leger, L., Sors, C., Dubost, C., Magdelaine, M., Lejeune, J., Roseau, E., and Lemaigre, G. (1963). Les hypoglycémies des tumeurs mésenchymateuses extra-pancréatiques. *Presse méd.*, **71**, 219-222.

Like, A. A. (1967). The ultrastructure of the secretory cells of the islets of Langerhans in man. *Lab. Invest.*, **16**, 937-951.

Lowbeer, L. (1961). Hypoglycemia-producing extrapancreatic neoplasms. *Amer. J. clin. Path.*, **35**, 233-243.

McDonald, A. D., Harper, A., El Attar, O. A., and McDonald, J. C. (1970). Epidemiology of primary malignant mesothelial tumors in Canada. *Cancer (Philad.)*, **26**, 914-919.

Mortimer, R. H. and Campbell, C. B. (1968). Asbestos ex-

posure and pleural mesotheliomas. *Med. J. Aust.*, **2**, 720-722.

Rhodin, J. A. G. (1967). Organisation and ultrastructure of connective tissue. In *The Connective Tissue*, edited by B. M. Wagner and D. E. Smith, p. 1. Williams and Wilkins, Baltimore.

Selikoff, I. J., Churg, J., and Hammond, E. C. (1965). Relation between exposure to asbestos and mesothelioma. *New Engl. J. Med.*, **272**, 560-565.

Simpson, D. (1957). The recurrence of intracranial meningiomas after surgical treatment. *J. Neurol. Neurosurg. Psychiat.*, **20**, 22-39.

Spry, C. J. F., Williamson, D. H., and James, M. L. (1968). Pleural mesothelioma and hypoglycaemia. *Proc. roy. Soc. Med.*, **61**, 1105-1107.

Wang, N. S. (1973). Electron microscopy in the diagnosis of pleural mesotheliomas. *Cancer (Philad.)*, **31**, 1046-1054.

Reports and Bulletins prepared by the Association of Clinical Biochemists

The following reports and bulletins are published by the Association of Clinical Biochemists. They may be obtained from The Publishing Department, British Medical Journal (ACB Technical Bulletins), B.M.A. House, Tavistock Square, London WC1H 9JR. Overseas readers should remit by British Postal or Money Order.

SCIENTIFIC REPORTS (price £1·00/$2.00 each)

3 Automatic Dispensing Pipettes: an assessment of 35 commercial instruments September 1967 P. M. G. BROUGHTON, A. H. GOWENLOCK, G. M. WIDDOWSON, and K. A. AHLQUIST

4 An Evaluation of five Commercial Flame Photometers suitable for the Simultaneous Determination of Sodium and Potassium March 1970 P. M. G. BROUGHTON and J. B. DAWSON

SCIENTIFIC REVIEWS (price £1·00/$2.00 each)

1 The Assessment of Thyroid Function March 1971 F. V. FLYNN and J. R. HOBBS

2 Renal Function Tests Suitable for Clinical Practice January 1972 F. L. MITCHELL, N. VEALL, and R. W. E. WATTS

3 Biochemical Tests for the Assessment of Feto-placental Function May 1975 C. E. WILDE and R. E. OAKEY

TECHNICAL BULLETINS (price £1·00/$2.00 each)

9 Determination of Urea by AutoAnalyzer November 1966 RUTH M. HASLAM

11 Determination of Serum Albumin by AutoAnalyzer using Bromocresol Green October 1967 B. E. NORTHAM and G. M. WIDDOWSON

13 An Assessment of the Technicon Type II Sampler Unit March 1968 B. C. GRAY and G. K. MCGOWAN

14 Atomic Absorption Spectroscopy: an outline of its principles and a guide to the selection of instruments May 1968 J. B. DAWSON and P. M. G. BROUGHTON

15 A Guide to Automatic Pipettes (2nd edition) June 1968 P. M. G. BROUGHTON

16 A Guide to Automation in Clinical Chemistry May 1969 P. M. G. BROUGHTON

17 Flame Photometers: a comparative list of 17 instruments readily available in Britain August 1969 P. WILDING

19 Spectrophotometers: a comparative list of low-priced instruments readily available in Britain May 1970 C. E. WILDE and P. SEWELL

20 Quantities and Units in Clinical Biochemistry June 1970 P. M. G. BROUGHTON

21 Filter Fluorimeters: A comparative list of 18 instruments September 1970 H. BRAUNSBERG and S. S. BROWN

22 Bilirubin Standards and the Determination of Bilirubin by Manual and Technicon AutoAnalyzer Methods January 1971 BARBARA BILLING, RUTH HASLAM, and N. WALD

23 Interchangeable Cells for Spectrophotometers and Fluorimeters September 1971 S. S. BROWN and A. H. GOWENLOCK

24 Simple Tests to Detect Poisons March 1972 B. W. MEADE *et al.*

25 Blood Gas Analysers May 1972 K. DIXON

26 Kits for Enzyme Activity Determination September 1972 S. B. ROSALKI and D. TARLOW

27 Assessment of Pumps Suitable for Incorporation into Existing Continuous Flow Analytical Systems November 1972 A. FLECK *et al.*

28 Routine Clinical Measurements of Transferrin in Human Serum September 1973 K. DIXON

29 Control Materials for Clinical Biochemistry (5th edition) September 1973 J. F. STEVENS

30 Notes on the Quality of Performance of Serum Cholesterol Assays September 1973 S. S. BROWN

31 Determination of Uric Acid in Blood and in Urine July 1974 R. W. E. WATTS

32 A Survey of Amino Acid Analysers Readily Available in the United Kingdom September 1974 J. E. CARLYLE and P. PURKISS

33 Definitions of some Words and Terms used in Automated Analysis November 1974 A. FLECK, R. ROBINSON, S. S. BROWN, and J. R. HOBBS

34 Measurement of Albumin in the Sera of Patients January 1975 LINDA SLATER, P. M. CARTER, and J. R. HOBBS

35 Investigation of the Validity of Temperature Correction Factors for Serum Aspartate and Alanine Transaminases March 1975 S. B. ROSALKI *et al.*

36 Factors Influencing the Assay of Creatinine, November 1975 J. G. H. COOK