PARAPLEGIA DUE TO RADIATION MYELITIS FOLLOWING THE TREATMENT OF CARCINOMA OF THE BRONCHUS BY RADIOTHERAPY. REPORT OF TWO CASES

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INTRODUCTION

THE adverse effects of irradiation on nervous tissue have been known for some time. As early as 1930 Fischer and Holfelder reported the onset of focal epilepsy in a patient 7 years after irradiation of a rodent ulcer of the scalp, and described necrosis of cortical tissue accompanied by hyaline thickening of the small blood vessels in a biopsy taken from the irradiated area of the cerebrum of this patient. There have since been numerous accounts of brain damage following therapeutic irradiation of scalp and brain lesions, *e.g.* Wachowski and Chenault (1945) described extensive brain damage in six patients whose brain tumours had been treated by high-voltage radiation therapy. One of the fullest descriptions is that of Pennybacker and Russell (1948) in which they describe five cases of post-irradiation brain necrosis, the most prominent histological features being collagenous thickening, fibrinoid necrosis and thrombosis in small vessels. More recently Peck and McGovern (1966) have described necrosis of the brain in three cases of acromegal treated by irradiation. They found necrosis with delayed glial response and vessels showing endothelial proliferation, hyalinisation of the walls and thrombosis.

Spinal cord damage following X-ray therapy was first recorded by Ahlbohm in 1941, and first reported with histopathological detail by Stevenson and Eckhardt in 1945 when they described a 'myelomacia' of the cervical cord following irradiation of a naso-pharyngeal lymphoepithelioma. A number of other papers have since appeared with accounts of radiation myelopathies, *e.g.* Greenfield and Stark (1948), Boden (1948), Boden (1950), Malamud *et al.* (1954), Friedman (1954), Itabashi *et al.* (1957), Dynes and Smedal (1960), Pallis *et al.* (1961), Kozuka *et al.* (1964), Verjaal (1964), Raskind and Bagshaw (1966), Reagan *et al.* (1968), Maier *et al.* (1969), Tan and Khor (1969).

Most accounts concentrate on clinical details or irradiation dosage and tissue tolerances, and most refer to cervical lesions following the irradiation of pharyngeal, laryngeal, or neck-region lesions, or to lumbar-cord lesions following irradiation of the para-aortic nodes in patients with testicular tumours. Very few of the cases reported have autopsy proof of the absence of spinal cord metastases and even fewer have any account of the histopathology of the spinal cord. An exception is the paper by Phillips and Buschke (1969) in which they give the pathological findings of Drs. Lee and Malamud in the spinal cord of a man who developed clinical myelitis about one year after irradiation of a bronchial carcinoma. They describe necrosis with little gliosis, sparse gitter cells and no inflammation. Wallerian degeneration was present above and below the lesion. They note that vascular changes were minimal.

In this present communication it is the object of the author to present the findings, including histopathology, in two cases of paraplegia, apparently due to radiation myelopathy following the treatment of bronchial carcinoma, which were examined personally by autopsy.

Case Report (1). Mr. J. J. K., an Irish foundry foreman and a heavy smoker, had several bronchitic episodes from the age of 57. In February 1965, when he was 64, he developed extensive myocardial infarction necessitating two admissions to hospital. A chest radiograph at this time showed patchy consolidation in the upper lobe of the right lung. In November 1965, following a series of episodes of bronchitis, he was admitted to the Chest Unit of Tindal Hospital, Aylesbury, for investigation. Bronchoscopy and bronchial biopsy revealed a non-keratinising squamous carcinoma of the right main bronchus. In view of his recent myocardial infarction he was regarded as an unsuitable candidate for surgery. He was therefore referred to the Radiotherapy Department of The Churchill Hospital, Oxford. A course of treatment was begun on 14 December 1965 and lasted for 42 days during which time the tumour received a dose of 3500 rads given as 7 doses. The spinal cord was not shielded and Dr. Frank Ellis estimated that the cord in the region of the tumour received some 4200 rads. (Figure 1 shows diagrammatically the vertebral bodies and spinal cord segments in relation to the bronchi.)

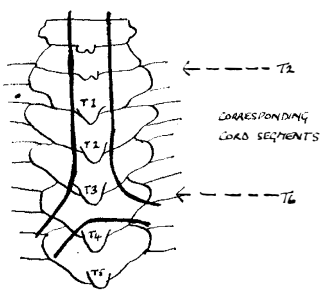

FIG. 1

Line diagram to show the relationship of the bronchi to the vertebral bodies and spinal cord segments.

Following radiotherapy there was some clinical and radiological improvement and, apart from some dull pain in the right shoulder and arm, he was fairly well until January 1967 when he developed severe constipation. A few days later he had a feeling of coldness in the right leg. The leg became heavy and weak until it dragged when he walked. He then developed an area of numbness in the right side of the lower abdomen. He did not complain at this time of any weakness or sensory disturbance in the left leg. He was referred to the Department of Neurosurgery, Oxford, for investigation. Neurological examination showed weakness in the right leg with weakness in dorsiflexion of the foot and almost absent knee flexion. There was increased tone in the right lower limb and bilateral clonus was worse on the right. The plantar responses were equivocal. A belt of hypo-aesthesia was detected at the level of T8. A lumbar puncture was normal and a myelogram showed no evidence of block. Radiographs of the spine showed no evidence of metastases.

After discharge his condition became steadily worse and he was readmitted to Tindal Hospital in March 1967. He now had a modified Brown-Sequard syndrome with motor loss predominantly in the right leg and sensory loss below segmental levels T9 and T10. He had already developed sacral and ischial pressure sores. In spite of the negative findings on radiography of the spinal column it was assumed that he, in fact, had a metastatic tumour deposit pressing on the cord and he was treated as a terminal case. He gradually deteriorated, becoming completely paraplegic, and died in June 1967.

Autopsy Findings. Autopsy was carried out on 13.6.67. The body was that of a thin man with extensive deep pressure ulcers of the sacrum, buttocks, trochanteric regions, and heels. There was an old occlusion in the anterior descending coronary artery and extensive fibrosed infarction of the anterior wall of the left ventricle. The oesophagus was tethered by fibrosis to mediastinal structures. A serous effusion of 1200 mls. was in the right pleural cavity. The right main bronchus showed an area of irregu-

larity and scarring of the epithelial surface of its antero-lateral wall. The right upper lobe was collapsed, fibrotic, and showed peripheral pneumonic changes. There was no macroscopic evidence of residual tumour in the bronchus or lung. However, microscopic study of tissue taken from the right main bronchus revealed several small areas of squamous carcinoma external to the bronchial cartilage and surrounded by fibrosis. No lymph node deposits were found either macroscopically or microscopically.

The brain was of normal appearance both externally and on coronal slicing, there being no evidence of tumour. The spinal canal was opened and examined. No evidence of tumour was found in the vertebral bodies or spinal canal.

The spinal cord was examined after fixation in formalin. There was some opacity of the arachnoid matter posteriorly. The spinal arteries and veins appeared normal. Transverse cuts were made at every segmental level. These revealed a white change suggestive of Wallerian degeneration in the posterior columns above the level of T8 and in the lateral corticospinal tracts below segment T11. Segments T9 and T8 were grossly abnormal with extensive softening of the posterior columns and a haemorrhagic appearance of the grey matter.

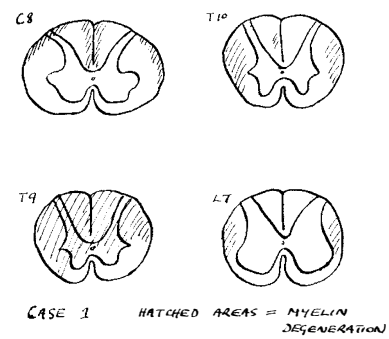

FIG. 2

Case 1.—Diagram to show the extent of myelin degeneration in the spinal cord at various levels.

Histopathological examination of sections taken at several levels in the spinal cord confirm the presence of Wallerian degeneration of the ascending tracts above T9 and of the descending tracts below the same level. The areas of reduced uptake of myelin stain at varying levels in the cord are shown diagrammatically in Figure 2.

Figure 3 illustrates the severe disruption of internal structure of segment T9. There is extensive necrosis and demyelination with only a few anterior horn neurones and some anterior column white matter remaining. In the necrotic areas in the lateral columns there are many compound granular corpuscles. The most striking features of the histology of this region of the cord are the relatively little inflammatory response to the extensive necrosis, and the presence of many small blood vessels, apparently, arteries whose walls show marked collagenous thickening and prominent endothelial cells. These appearances, which are most prominent in the Van Gieson preparations, are shown in the accompanying photomicrographs Figures 3-6. Neither macroscopically nor microscopically was there any evidence of thrombus, embolus or tumour.

Case Report (2). Mrs. R. G. was a hypertensive housewife with a past history of smoking cigarettes. She presented in December 1968, at the age of 64, with increasing dyspnoea and an haemoptysis, and was admitted to the Chest Unit at Tindal Hospital in January 1969. Chronic bronchitis and emphysema with poor respiratory function were noted. Radiology, bronchoscopy, and bronchial biopsy revealed a neoplasm in the right main bronchus which was 'flapping' over to the left. Histologically this was a poorly differentiated non-keratinising squamous carcinoma. After a stormy post-bronchoscopy period she was referred to The Churchill Hospital for radiotherapy.

A course of cobalt gamma-ray therapy was given between 26 February and 17 April 1969, divided between 8 sessions. It is estimated that the tumour received 4000 rads and the spinal cord 2800 rads. Later in the year she developed signs of mediastinal obstruction and was given a second course of irradiation between 17 July and 14 August 1969. 2500 rads to the mediastinum and 2800 rads to the cord were given in 5 sessions.

In December 1969 she was readmitted to Tindal Hospital because of swelling of the neck, dysphagia, dyspnoea, and haemoptysis. She was treated by one dose of

parenteral nitrogen mustard via the inferior vena cava and later by oral endoxana. In January 1970 she began to have urinary retention with overflow, and also complained of pain in her right leg. Loss of sensation and of motor power gradually developed in the right and then, to a lesser extent, the left leg. She is said to have become completely paraplegic but because of her very poor state a full neurological examination was not performed. The dysphagia became increasingly distressing. She died on 2 March 1970.

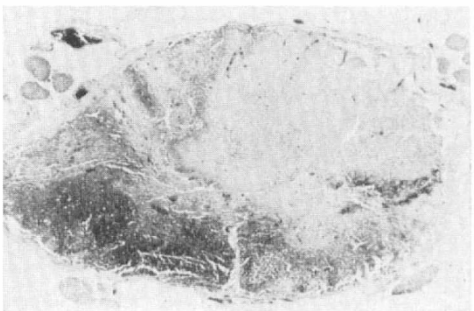

FIG. 3

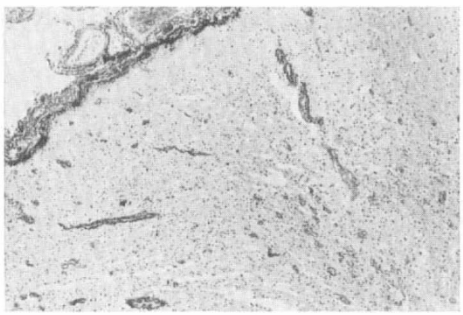

FIG. 4

Case 1

Fig. 3.—Very low power photomicrograph of section of segment T9 to show loss of normal pattern. Normal myelin is stained black.

Fig. 4.—Photomicrograph of section of segment T9 stained with Van Gieson to show the numerous small arteries with thickened walls.

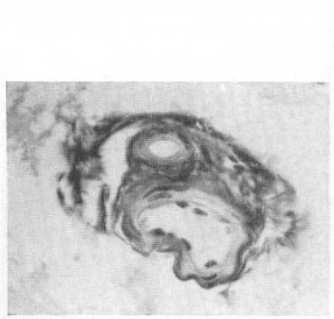

FIG. 5

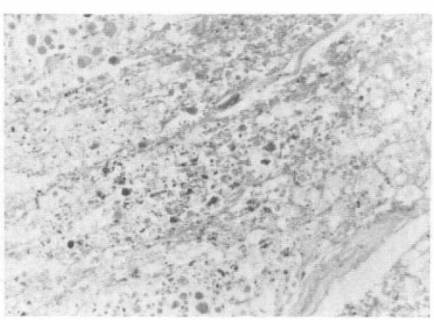

FIG. 6

Fig. 5.—Higher magnification of same section as in Figure 4.

Fig. 6.—Photomicrograph showing details of one thickened artery with internal proliferation.

Autopsy Findings. Autopsy was carried out on 3 March. The body was that of a small woman. Internal examination showed extensive induration of the structures of the lower neck and mediastinum. The oesophagus was tethered posteriorly by what appeared to be fibrosis and showed extensive ulceration and necrosis in the anterior wall at the level of the upper trachea. The latter also showed necrotic ulceration and rings of cartilage projected from the slough into the lumen. These oesophageal and tracheal lesions were at the same level and were closely related to each other. The epithelial linings of both bronchi were reddened. There was some grey indurated tissue resembling fibrosis, surrounding the right main and right lower lobe bronchi, but there was no macroscopically apparent tumour. The lower lobes of the lungs were congested,

indurated, and oedematous. The hilar and carinal nodes were enlarged but not infiltrated. Microscopy of sections from the right main bronchus show one focus of slightly atypical epithelium lining a duct to an acinar gland but no definite evidence of recurrent carcinoma. The lymph nodes also were free from tumour.

The heart was normal. The colon showed a marked degree of diverticular disease with inflammation in the sigmoid region. The uterus contained several fibroids. There was no evidence of any metastases.

The brain was of normal appearance externally, and serial coronal slicing showed no hint of metastasis or of any focal lesion.

The spinal cord was exposed by a posterior laminectomy. There was no evidence of extradural tumour or of disc protrusion. The bodies of the cervical and thoracic vertebrae appeared diffusely pale and sclerotic. After fixation in formal saline the dura was opened. The meninges and vessels appeared normal. The cord showed no evidence of tumour or focal lesion externally. Serial transverse cuts through the cord showed Wallerian degeneration of the posterior columns above the level of cord segment T6 and of the pyramidal tracts below this level.

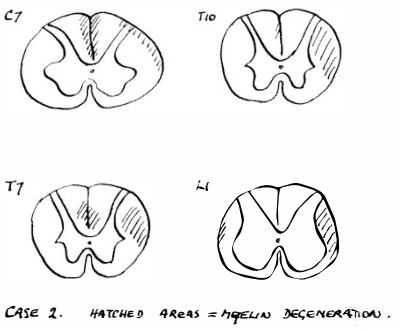

FIG. 7

Case 2.—Diagram to show the extent of myelin degeneration in the spinal cord at various levels.

Microscopic examination of sections taken from the cord confirm the presence of bilateral Wallerian degeneration of ascending tracts above segment T6. Pyramidal degeneration is present below this level but it is only slight on the left. Figure 7 shows diagrammatically the areas of myelin degeneration at various levels in the cord. Sections at levels T5 and T6 show extensive necrosis of

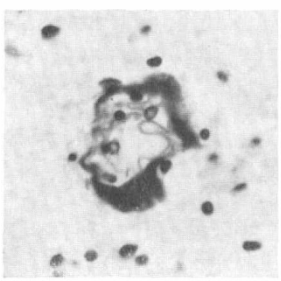

FIG. 8

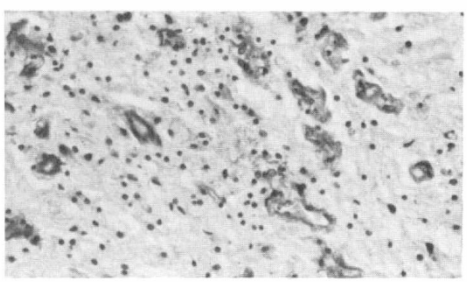

FIG. 9

Case 2

Fig. 8.—Photomicrograph of section from T6 showing necrosis and calcium deposition in the lateral columns.

Fig. 9.—Photomicrograph of small artery in section of segment T6.

the right lateral white matter and posterior columns and some loss of neurones in the grey matter. There is no gliosis and only slight cellular reaction. Figure 8 is a photomicrograph from the necrotic area of the lateral column in T6. Besides necrosis it shows some haemotoxyphilic granular material which on special staining proves to be calcium salts. The extent of the necrosis is less than in the previous case but the apparent proliferation and thickening of blood vessels is similar. Figure 9 is a photomicrograph of a typically thickened vessel with some intimal hyperplasia.

DISCUSSION

The clinical aspects and differential diagnosis of radiation myelopathy have been well reviewed by Reagan *et al.* (1968). They describe 4 major syndromes, *viz.* (1) a transient myelopathy, (2) lower motor neurone disease following abdominal irradiation, (3) acute paraplegia or tetraplegia, and (4) chronic progressive radiation myelopathy. The clinical features of the two cases here presented correspond with Reagan's fourth category. The latent period of 13 and 10 months which elapsed between commencement of radiotherapy and the onset of neurological symptoms in the present cases are characteristic. The clinical picture is one of a progressive myelitis. Patients present with weakness, spasticity, or a Brown-Sequard lesion and later progress to paraplegia or quadriplegia. Lumbar puncture shows normal pressure and fluid which is usually of normal composition, but occasionally the protein content of the fluid has been reported to be raised. Radiography of the vertebral column shows no evidence of tumour deposits and myelography is normal. As Reagan *et al.* point out the differential diagnosis includes intramedullary tumour metastasis and a 'remote' carcinomatous myelopathy.

The mechanism whereby irradiation brings about myelopathy is not entirely clear. It is certain that the blood vessels in the brain and spinal cord react to irradiation in much the same way as do vessels in other tissues. As early as 1921 Bagg concluded from experimental work on animals that X-ray injury to the brain was secondary to vascular changes. Pennybacker and Russell (1948) drew the same conclusions from the appearances they saw in human material. A variety of vascular changes have been described in experimental animals but these have usually been associated with acute radiation injury. What part such changes play in delayed radiation necrosis is uncertain. Some authors argue that the latent period before the onset of symptoms points to an indirect effect via vascular changes. O. Bailey (1962), in a review of the subject, drew the conclusion that irradiation had a direct effect on the cord. In monkeys myelin degeneration and axonal degeneration have been shown in the irradiated part of the cord apparently unrelated to any vascular change. O. Bailey has also confirmed the work of Arnold and P. Bailey (1954) which showed that the glial cells are injured by radiation. Oligodendroglia swell and disintegrate at an early stage, a process which may be related to the myelin degeneration. Astrocytes also degenerate and for a pro longed period no glial response can be elicited and compound granular corpuscles are not seen; an abnormal degree of collagen proliferation occurring during this period. In the adult animal the nerve cell itself appears resistant to irradiation and degeneration is found only in areas of total necrosis. However, Brownson *et al.* (1964) have described histochemical changes in the neurones of irradiated brain.

Thus the mechanisms of radiation induced myelopathy is certainly more complex than once thought. Glia, myelin, blood vessels, and possibly neurones, are all affected, probably by the direct effect of irradiation on intracellular structures. An alternative hypothesis postulating the presence of an immune process similar to that seen in experimental allergic encephalitis has, as yet, little to support it.

The true incidence of post-irradiation myelopathy is difficult to assess. It

would seem highly likely that cases go unrecognised, being assumed, as was the first case reported here, to be the result of metastases and an almost terminal event. Clearly, also, many patients must die of their cancers before the necessary latent period has elapsed. Several authors have made retrospective assessments of the incidence of myelopathy and figures ranging from 2 per cent. to 10 per cent. are quoted. Maier *et al.* (1969), in an analysis of the cases of testicular tumours treated at the Walter Reed General Hospital, found 15 cases of irradiation myelitis occurring in the 343 patients who survived a minimum period of 3 years following radiotherapy.

The possibility of increased individual sensitivity to irradiation playing a significant role is raised by Locksmith and Powers (1968). They found that in three out of six cases of permanent myelopathy, which occurred after treatment of carcinoma of the lung with a betatron machine, a severe oesophagitis had occurred during treatment and that in two of these dilatation had been required subsequently. In their experience severe oesophagitis is very unusual in the treatment of lung cancer, and the incidence in the group with myelopathy was greatly increased. It is of interest that the second of the present cases had a severe oesophagitis.

The clinical diagnosis and recognition of radiation myelopathy is most important. Clinicians who are concerned with the care of patients who have received irradiation in the region of the cord, and neurologists, must bear the condition in mind. Reagen *et al.* stress that the initial symptoms may suggest a cord lesion lower in level than the segment of cord irradiated and thus obscure the diagnosis. Clearly, failure to demonstrate a metastasis as the cause of the neurological symptoms should lead the clinician to institute active measures to prevent the urinary tract and pressure area complications of paraplegia, just as he would in traumatic paraplegia.

Summary

The clinical details of autopsy findings from two cases of paraplegia following the treatment of carcinoma of the bronchus by radiotherapy are given and the pathogenesis of radiation myelitis is discussed. Histopathological examination of the spinal cords revealed necrosis without gliosis, and hyaline thickening of small arteries with some endothelial proliferation.

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Résumé

Les détails de l'autopsie des deux cas de paraplégie consécutive à une carcinome des bronches par radiothérapie sont donnés, et la pathogénèse de la myélite par irradiation est discutée.

L'examen hysto-pathologique des moelles épinières a révélé une nécrose sans gliose et un épaississement hyalin des petites artères avec une certaine prolifération endothéliale.

REFERENCES

AHLBOHM, H. E. (1941). *Acta Radiol.*, **22,** 155.
ARNOLD, A. & BAILEY, P. (1954). *A.M.A. Arch. Pathol.*, **57,** 383.
BAGG, H. J. (1921). *Amer. J. Roentgenol.*, **8,** 536.
BAILEY, O. (1962). In *Response of the Nervous System to Ionizing Radiation.* Ed. T. J. Haley, and R. S. Snider, Acad. Press.
BODEN, G. (1948). *Brit. J. Radiol.*, **21,** 464.
BODEN, G. (1950). *J. Facul. Radiol. (Lond.)*, **2,** 79.
BROWNSON, R. H., SUTER, D. B., OLIVER, J. L., INGERSOLL, E. H. & BURT, D. H. (1964). In *Response of the Nervous System to Ionizing Radiation.* Ed. T. J. Haley, and R. S. Snider, Acad. Press.
DYNES, J. B. & SMEDAL, M. I. (1960). *Amer. J. Roentgenol.*, **83,** 78.
FISCHER, A. W. & HOLFELDER, H. (1930). *Dtsch. Z. Chir.*, **227,** 475.
FRIEDMAN, M. (1954). *Proc. 2nd Natl. Canc. Conf.*, **1,** 390.
GREENFIELD, M. M. & STARK, F. M. (1948). *Amer. J. Roentgenol.*, **60,** 617.
INNES, J. R. M. & CARSTEIN, A. (1962). In *Response of the Nervous System to Ionizing Radiation.* Ed. T. J. Haley and R. S. Snider. Acad. Press.
ITABASHI, H. H., BEBIN, J. & DE JONG, R. N. (1957). *Neurology* (Minneapolis), **7,** 844.
KOZUKA, KAWAMINA & TERASHITA (1964). *Brain and Nerve*, Japan, **16, 11,** 965.
LAMPERT, P. W. & DAVIS, R. L. (1964). *Neurology* (Minneapolis), **14,** 912.
LOCKSMITH, J. P. & POWERS, W. E. (1968). *Amer. J. Roentgenol.*, **102,** 916.
MAIER, J. G., PERRY, R. H., SAYLOR, W. & SULAK, M. H. (1969). *Radiology*, **93,** 153.
MALAMUD, N., BOLDREY, E., WELCH, W. K. & FODELL, E. J. (1954). *J. Neurosurg.*, **11,** 353.
MARRA, A., & GIUFFRÈ, R. (1968). *European Neurology*, **1,** 234.
PALLIS, C. A., LOUIS, S. & MORGAN, R. L. (1961). *Brain*, **84,** 460.
PECK, F. C. JR., & MCGOVERN, E. R. (1966). *J. Neurosurg.*, **25,** 536.
PENNYBACKER, J. & RUSSELL, D. S. (1948). *J. Neurol. Neurosurg. and Psychiat.*, **11,** 183.
PHILLIPS, T. L. & BUSCHKE, F. (1969). *Amer. J. Roentgenol.*, **105,** 659.
RASKIND, R. & BAGSHAW, M. A. (1966). *Radiobiol. Radiotherap.* (Berlin), **7,** 31.
RASKIND, R. (1967). *Int. Surg.*, **48,** 430.
REAGAN, T. J., THOMAS, J. E. & COLBY, M. Y. Jr. (1968). *J.A.M.A.*, **203,** 106.
STEVENSON, L. D. & ECKHARDT, R. E. (1945). *Arch. Path.*, **39,** 109.
TAN, B. C. & KHOR, T. H. (1969). *Clin. Radiol.*, **20,** 329.
VERJAAL, A. (1964). *Nied. T. Geneesk.*, **108,** 1123.
WACHOWSKI, T. J. & CHENAULT, H. (1945). *Radiology*, **45,** 227.