Fatal recurrence of parathyroid carcinoma after seven years

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SYNOPSIS The case is reported of a woman who died at the age of 36 from parathyroid carcinoma. The removal, seven years earlier, of a large parathyroid tumour, judged at that time to be benign, was followed by a remission of symptoms for about four years after which they recurred. At necropsy, a well-differentiated parathyroid carcinoma showed local invasion and lymph-node metastases in the neck. Review of the original 'adenoma' suggested that this growth might have been a carcinoma.

The total number of recorded cases of hyperfunctioning parathyroid carcinoma is still limited but has now reached at least 37. Carcinoma is rarely to be diagnosed except at necropsy; nevertheless, it seems to be the important cause of delayed recurrence of symptoms after parathyroidectomy. The evolution of the growth is often very slow.

Individual experience of a rare condition such as carcinoma of the parathyroid must be limited and in consequence the natural history of the disease evolves from reviews of isolated case reports. Several excellent reviews have appeared in the literature since 1945, in particular by Norris (1948), by Black and Ackerman (1950), and by Black (1954). It is difficult to assess accurately the true incidence of this tumour as varying criteria are adopted by different authors in determining the malignancy of a parathyroid tumour. For example, Alexander, Pemberton, Kepler, and Broders (1944) reported 13 'carcinomata' out of 14 cases of parathyroid tumour but these are rejected by Albright and Reifstein (1948) as being questionable.

The assessment of Woolner, Keating, and Black (1952) that carcinoma of the parathyroid gland accounts for approximately 0.5% of all cases of primary hyperparathyroidism appears to be realistic. The present case, which has particularly unusual features, is thus considered worthy of report.

CASE REPORT

Mrs. O.N. was aged 25 in 1948 when she first complained of epigastric pain coming on several hours after food, with relief after taking alkalis. A barium meal at another hospital was reported as showing a chronic duodenal ulcer. In June 1950 she attended the Surgical Out-patient

Department at the Royal Infirmary on account of haematuria, together with frequency and scalding micturition, and in addition it was noted that she complained of some weakness in her arms and legs, together with rheumatic type pains. Physical examination revealed no outstanding clinical abnormalities and the cause of the haematuria was not demonstrated. In August 1951 her symptoms of muscle weakness and general malaise became more marked; she now had persistent and severe stabbing pain in both legs and walked with a limp in the right leg. Skeletal type pains were also complained of in the chest and upper limbs. She had lost some weight and had developed thirst, polyuria, and nocturia. There was amenorrhoea.

In 1952, now aged 29, she was admitted, and investigations showed a raised serum calcium level (14.8 and 15.1 mg./100 ml.), normal serum phosphorus (3.7 and 3.5 mg./100 ml.), raised serum alkaline phosphatase (78 King-Armstrong units), and an iron-deficiency anaemia (Hb 10.2 g./100 ml.). Radiographs showed considerable osteoporosis of the ribs with several fractures, some of which were healing, and extreme rarefaction of the dorsal and lumbar vertebrae and skull with some denser shadows in the skull. Bilateral nephrocalcinosis was shown.

A diagnosis of hyperparathyroidism was made, and the patient was sent home pending admission to a surgical ward. However, in October 1952 she tripped and fell at home, and was thereupon admitted to the orthopaedic ward, where she was found to have bilateral fractures in the mid-shaft of both femora. A palpable nodule was noted in the lower and anterior part of the left side of the neck, and on 13 October 1952 a large parathyroid adenoma was removed by Mr. W. J. Lytle from behind

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the lower pole of the left lobe of the thyroid. The histological appearances of this tumour were reported by Dr. L. C. D. Hermitte as showing the classical structure of a benign parathyroid adenoma which is mainly of the clear-celled type.

After operation, pain in the bones abated immediately, the serum calcium level fell precipitously from 15.4 mg./100 ml. to 7.0 on the fifth and to 6.3 on the eighth day, and she developed tetany which responded to intramuscular injections of calcium gluconate. Serum alkaline phosphatase fell progressively from 78 units to 20 units in the first 13 weeks. There was clinical and radiological evidence of healing of the bone fractures and she rapidly gained weight, the polyuria and thirst subsiding. In November 1953 she was reported as fit and well, and had gained over 35 lb. (16 kg.) in weight. At this point, her case was reported upon as one of benign parathyroid adenoma in a series published by Baird, Grainger, and Rowlands (1954).

In April 1955 now aged 32, the patient experienced an attack of renal colic and haematuria which rapidly subsided, although it was radiologically demonstrated that renal calcinosis persisted. In November 1956 when next reviewed, she complained of a recurrence of ulcer-type pain, together with attacks of profuse vomiting and episodes of watery diarrhoea. She was thought to have a dilated stomach, and a loud succussion splash was demonstrated. The clinical diagnosis of pyloric stenosis from chronic duodenal ulcer was advanced. A barium meal, however, showed no delay in gastric emptying and no evidence of duodenal ulceration. Her symptoms had by now subsided and no further observation was undertaken. By June 1957 vomiting had completely ceased and she complained only of intermittent ulcer pain and diarrhoea. In January 1959, some four months before her ultimate admission, the epigastric pain became continuous and unrelieved by alkali. Vomiting began again and was sometimes copious, containing undigested food. Anorexia developed and weight loss (14 lb. in four weeks), and she again noticed thirst, polyuria, and nocturia, with a return of general malaise and muscle weakness. Now, in addition, she developed cramp-like pains in both legs and in the lower part of the back, sufficient to prevent her sleeping at night. Menstruation became irregular and scanty.

On her final admission in April 1959, now aged 36, examination revealed a thin, pale woman, weighing 6 st. 10 lb. (43 kg.). She seemed to be gravely ill but was able to account for herself. Her skin was dry and her tongue was thickly furred and she appeared grossly dehydrated. Mucous membranes were of good colour and the finger nails were normal. A hard nodule, some $\frac{3}{4}$ in. (2 cm.) in diameter was palpable on the right side of the neck medial to the lower end of the sternomastoid muscle. Blood pressure was 95/70 mm. Hg and the pulse was regular at 90 per minute. The heart was not enlarged and the heart sounds were faint but normal. There was no sacral or ankle oedema, and the lung fields were clear. In the abdomen a succussion splash could be elicited; the stomach appeared dilated and showed visible peristalsis. The liver was felt two fingerbreadths below the right costal margin. Rectal examination was normal. Examination

of the central nervous system showed no gross abnormality. Considerable tenderness of the bone was noted over the spine and long bones of the leg.

Chemical analyses showed raised serum calcium (15.2 mg./100 ml.), raised serum phosphorus (7.0 mg./100 ml.), and raised blood urea (141 mg./100 ml.) levels. The 24-hour excretion of calcium was 330 mg. in a urine volume of 510 ml. The electrophoretic pattern of serum proteins was normal. Radiographs showed general rarefaction of the skeleton, subperiosteal bone resorption in the phalanges of the hands, mottled rarefaction of the skull, and an ill-defined cystic lesion of the upper part of the right tibia. Bilateral nephrocalcinosis was again demonstrated, but the radiographs failed to reveal the diffuse pulmonary calcification which was found after death.

The patient was treated with gastric suction and intravenous fluid replacement therapy. At first there was some improvement, the blood urea then rose to 323 mg./100 ml. and the urine volume fell. Her general condition rapidly deteriorated and she died in coma three weeks after admission.

POST-MORTEM EXAMINATION AND HISTOLOGY

The post-mortem examination was conducted within 24 hours of death.

Externally, the body was that of a middle-aged woman of slim build with very little subcutaneous fat. There was a faint scar across the front of the lower part of the neck and an old paramedial abdominal scar through which the appendix had at some time been removed. Both femurs and both forearms appeared to be slightly bowed.

The internal examination revealed important changes in the region of the parathyroid glands, in the bones, in the kidneys, and in the lungs.

As for the other organs, the heart was firm and small and weighed 230 g.; the aorta, coronary and other arteries were almost free from atheroma; the brain weighed 1,230 g. and its substance, together with the meninges and blood vessels, appeared normal; the whole alimentary tract was examined and there was found a small posterior wall pouch distal to the pylorus representing a healed duodenal ulcer, a healthy appendicectomy site, but no tumours or other abnormality; the pancreas was normal; the liver weighed 1,650 g. and showed slight fatty change but no necroses or metastases; the pelvic organs were all normal; the pituitary gland and both adrenals were normal; there was no general enlargement of lymph glands and no evidence of metastatic new growth outside the region of the neck. Histological sections were prepared of all the structures mentioned and no pathological changes were observed.

PARATHYROID GLANDS AND NECK The left inferior parathyroid gland, which was the seat of the

adenoma removed seven years previously, was not identified, but just below the lower pole of the left lateral lobe of the thyroid gland there was a nodule of partially calcified tissue, resembling a tuberculous lymph gland since soft creamy material exuded from the sliced surface. It proved later to be parathyroid tissue.

On the right side of the neck a small firm tumour presented in the substance of the lower pole of the lateral lobe of the thyroid gland. It was 22 mm. across and showed radial nodules grossly resembling a carcinomatous metastasis in the thyroid but, on being proved to be of parathyroid tissue, it was interpreted as a tumourous development of the right inferior gland. On the same side there were some firm and enlarged lymph glands, one immediately below the tumour within the thyroid capsule and others in a small group opposite the hyoid. The superior parathyroid glands were not found.

Histological examination showed parathyroid tumour in the lymph gland on the left side, in the nodule within the right lower pole of the thyroid, in the lymph gland just below this, and in one of a small group of lymph glands at the level of the hyoid.

In all situations the parathyroid growth has the same histological pattern. It consists of finely lobulated masses of uniform box-like cells with slightly granular but feebly staining cytoplasm and regular rounded nuclei, but mitotic figures and binucleated cells are not infrequent (Fig. 1). Central necrosis with calcification occurs in the centre of some of the large cell masses (Fig. 2) and there is patchy calcification of some of the fibrous septa. At the edge of the tumour in the right lobe of the thyroid there is distinct infiltration by the tumour cells of the fibrous capsule and attached striped muscle (Fig. 3). In the group of lymph glands to the right of the hyoid, parathyroid tumour metastasis appears in one of the glands (Fig. 4).

BONES Osteitis fibrosa was seen in diffuse or focal form in several bones. The vault of the skull was thickened up to 1 cm. with loss of diploë, and the histological sections (Fig. 5) show a diffuse form of osteitis fibrosa with many areas of osteoclasts but also much new apposition of coarse-fibred bone upon previously eroded trabeculae. A more osteolytic form is seen in sections of one iliac crest. Several bone specimens were radiographed after death, and diffuse osteitis fibrosa demonstrated in the seventh and eighth right ribs and a more cystic lesion in the upper end of the right tibia (Fig. 6).

KIDNEYS Each kidney weighed 120 g. and the appearances of each were similar. The capsule was adherent over a very granular cortex which, on

slicing, was indistinctly separated from the medulla. There were a few small cysts in the cortex and small leiomyoma in the left pole of the kidney just below the capsule. In the medulla, dilated tubules could be observed and their walls seemed to be calcified. There was a general sensation of grittiness on the cut surface of each kidney.

A post-mortem radiograph of the kidneys showed very heavy calcinosis, mainly picking out the pyramids of the medulla (Fig. 7).

Sections show these larger masses to be surrounded by cellular fibrous tissue in areas where the normal structure of the kidney has been much destroyed. But there are also large deposits of calcium within the collecting tubules and within the lumen and in the cells of scattered convoluted tubules in the cortex. There is also chronic pyelonephritis.

LUNGS The lungs were heavy and firm and greatly distended as though in the position of inspiration but samples of all parts of the lungs floated in water. On slicing a fine honeycombing of the surface could be seen and the interlobular septa stood out very clearly as a mosaic in both the cut and the subpleural surfaces.

Histologically there is most extensive pulmonary calcinosis. This takes the form of thin plates of calcium in the alveolar walls (Fig. 8). The majority of the alveoli in all parts of both lungs are so affected though the collar of calcium is not complete around every alveolus. In favourable fields in the section it seems that the calcium has been deposited between the capillary endothelium and the alveolar epithelium. There is also calcinosis of the media of many blood vessels, both arteries and veins, ranging in diameter from approximately 50 to 300 μ . There are no large focal calcified masses. In many alveoli there is epithelial proliferation with mucinous exudate and a light polymorph emigration, though the distension of the lungs, which were not airless, seems to be due to the rigidity of the alveolar structure rather than to pneumonic exudate.

REVIEW OF THE PARATHYROID TUMOUR REMOVED SEVEN YEARS BEFORE DEATH

It is doubtful if any pathological diagnosis could have been made at the time other than that of adenoma, but, in the light of the subsequent history, indications of carcinoma have now been carefully sought. Certain features are worth particular comment because they raise the possibility that this original parathyroid tumour had malignant potentialities. First, the tumour, though of smooth outline, was large, measuring 30 $\times$ 22 mm. in section after

FIG. 1. Nodule from thyroid on right side. Regular box-like cells, but note mitosis near the centre and double nuclei at lower left. Haematoxylin and eosin $\times 500$.

FIG. 2. Nodule from thyroid on right side. Lobulated pattern of tumour with coarse fibrous septa and central necrosis with calcification in some of the cell masses. Haematoxylin and eosin $\times 125$.

FIG. 3. Parathyroid carcinoma infiltrating the fibrous capsule of the right lower pole of the thyroid and attached muscle. Haematoxylin and eosin $\times 125$.

FIG. 4. Metastasis of parathyroid carcinoma in one of a group of lymph glands in the right side of the neck. Haematoxylin and eosin $\times 125$.

FIG. 5. *Osteitis fibrosa in skull vault. Haematoxylin and eosin $\times 50$.*

FIG. 6. *Radiograph of post-mortem specimen of right tibia, showing cystic lesion of osteitis fibrosa.*

FIG. 7. *Calcinosis of kidney: the radiograph of the post-mortem specimen shows the main concentration of calcium in the pyramids.*

FIG. 8

FIG. 8. *Calcinosis of lung: the section shows calcification in alveolar and blood vessel walls. Van Kossa's method $\times 50$.*

FIG. 9

FIG. 9. *Tumour cells in mitosis in the original 'adenoma' of the parathyroid removed seven years before death. Haematoxylin and eosin $\times 500$.*

fixation. Secondly, the fibrous capsule is seen in section to be split by small islands of tumour tissue. Thirdly, here and there throughout the tumour are cells in mitosis (Fig. 9).

DISCUSSION

The patient whose case we report had a hyperfunctioning parathyroid tumour removed which at the time was thought on reasonable grounds to be benign. Seven years later she died after recurrence of manifest hyperparathyroidism, and necropsy showed a locally invasive parathyroid tumour on the opposite side and lymph-node metastases on both sides of the neck, together with osteitis fibrosa of several bones and calcinosis of lungs and kidneys.

Adenoma of the parathyroid gland accounts for about nine out of 10 cases of primary hyperparathyroidism, the other causes being primary hyperplasia and hypertrophy (Castleman, 1952). The diagnosis of carcinoma is not easily made unless the

growth is seen to be freely invasive or metastasis can be proved. That the histological appearances of the tumour as a guide to malignancy are unreliable is agreed by nearly all authorities, and Woolner *et al.* (1952) report a case in which the histological appearances of a proven carcinoma were indistinguishable from a benign parathyroid adenoma, apart from the invasion of surrounding structures by the tumour. Castleman (1952) stresses that nuclear hyperchromatism and the presence of giant nuclei in an adenoma do not necessarily denote cancer but states, perhaps too dogmatically, that mitotic figures which are always present in carcinoma are not seen in an adenoma. The usual histological indications of malignancy may thus be lacking in a parathyroid tumour, and we agree with the views of Black and Ackerman (1950) and of Rapoport, Sepp, and Brown (1960) that a tumour should only be considered as a parathyroid carcinoma if it shows evidence of local invasion or metastases together with endocrine hyperfunction. Visceral metastases occur

in about a third of the cases (Rapoport *et al.*, 1960). Black and Ackerman were loath to accept even local invasion of the tumour as one of the criteria if this was not present at the time of the initial operation, believing that spread from a previously resected tumour might be due to a local recurrence caused by the implantation of spilt cells from the adenoma at the time of operation. This view appears extreme and is rejected by Castleman (1952) who believes that local recurrence occurring after the removal of a tumour is proof that the original lesion was a carcinoma. Although non-functioning parathyroid carcinoma may occur, it would be virtually impossible to distinguish from carcinoma of the thyroid gland and it is best excluded from consideration. The series of 46 cases collected by Jordan, Curd, Gyorkey, and DeBakey (1958), for example, contains many which showed no proof of parathyroid function.

The recorded cases of parathyroid carcinoma meeting the more rigid requirements of proven hyperfunction with local invasion or metastasis reach only a limited total, but their number is gradually increasing and Tange (1958) is right to point out that the possibility of carcinoma in a case of hyperparathyroidism is becoming a consideration of importance to the practising surgeon.

Tange, writing from Melbourne, analyses 24 reported cases, seven with lymph-node metastases, seven with local recurrence, and four with local invasion but no recurrence, and he adds a case of his own. When Tange's series is collated with that of Rapoport *et al.* (1960), who start from the earlier series of Black (1954), there seem to be 31 reported cases of parathyroid carcinoma to which may be added the cases of Cook (1958), of Wright and Mathieson (1958), of Kleinfeld (1959, two cases), and of Summers, Hawe, and Davis (1959). These with our present case make a total of 37 cases on record, which is a minimum since the literature has not been exhaustively searched.

Our case was undoubtedly one of parathyroid carcinoma though not recognized as such until necropsy. The main tumour mass lay on the opposite side of the neck from which the original tumour was removed and the presence of parathyroid tissue in the lymph glands on both sides of the neck confirms that this was indeed a malignant invasive tumour and not an implantation recurrence. As to the nature of the original tumour removed seven years before death, there are two possibilities: either this tumour was an adenoma and the patient subsequently developed a carcinoma of another parathyroid gland, or the tumour removed was in fact a carcinoma and had already metastasized. We favour the second of these alternatives since review of the

original growth does reveal some mitotic figures and invasion of the fibrous capsule by the cells of this very large tumour. Castleman (1952) notes that many cases of carcinomas have long histories and suggests that all carcinomas of the parathyroid gland might originate in adenomas, although conceding that this hypothesis would be difficult to prove. Recurrence of symptoms is by no means unusual and the progress of the disease is not rapid. Black (1954) refers to 16 cases that relapsed after operation; 15 of these were dead after the disease had run its course for periods ranging from eight months to 20 years (average duration 69.5 months). In a few of these cases a second operation was performed.

A remarkable example of a relapsing course due to the growth of successive tumour nodules has recently been reported by Summers *et al.* (1959) a man aged 46 with a long history of duodenal ulcer and of hyperparathyroidism. Five years before death, a parathyroid tumour, with no obvious features of carcinoma, apart from occasional mitotic figures, was removed from behind the left lobe of the thyroid. Symptoms and signs of hyperparathyroidism recurred and the right lobe of the thyroid containing a normal parathyroid gland was excised without ameliorating the condition; a few months later a large parathyroid tumour was removed from behind the left clavicle but symptoms persisted. The patient died a little later and necropsy showed extensive infiltration of the left lobe of the thyroid gland by invasive parathyroid tumour. There was renal but no pulmonary calcinosis.

The difficulties facing the surgeon operating on a parathyroid tumour in deciding whether a given tumour is malignant have been stressed by both Norris (1948) and by Cope, Nardi, and Castleman (1953). They point out that the adherence of the tumour to the surrounding structures and difficulty in dissecting it out should suggest the possibility of malignancy. It has also been noted that carcinomas are usually larger tumours than adenomas and the presence of a palpable mass in the neck before operation should put the surgeon on his guard. Black (1954) observed that carcinomas have approximately three times the volume of an adenoma and it is of interest that the tumour was large and was palpable in the neck of our patient at her first operation.

The recurrence of symptoms of hyperparathyroidism after the successful removal of an apparent parathyroid adenoma should also raise the possibility of the malignancy of the original tumour. Multiple adenomas which account for some 6 to 8% of all cases of hyperparathyroidism (Castleman 1952) must be thought of, but they usually declare themselves by the persistence of the symptoms of

hyperparathyroidism immediately after the removal of one adenoma; they are less likely to cause recurrence of symptoms after a considerable lapse of time. True recurrence of a benign parathyroid adenoma appears to be extremely rare and Greenfield, Verner, and Engel (1959), reporting one case, could find only one other in the literature.

Our patient showed very extensive metastatic calcification involving the kidneys and lungs. This finding is common with carcinoma of the parathyroid, and Black (1954) found nephrocalcinosis to be present in eight out of 10 patients coming to necropsy. This high incidence of nephrocalcinosis presumably reflects the length of time to which the tissues of these patients are exposed to high concentrations of calcium salts. Metastatic calcification is a well recognized complication of hyperparathyroidism, from whatever cause; its localization in the kidneys, lungs, and stomach is ascribed to the fact that these organs secrete acid and thus leave the tissues relatively alkaline, a condition that favours the precipitation of calcium salts from the blood (Anderson, 1957).

The clinical history of this patient in the four years before death is the final point of interest. The recurrence of symptoms of nausea, vomiting, and epigastric pain following some time after operation was attributed to a recurrence of the chronic duodenal ulcer from which she had previously suffered, especially as there were signs suggesting pyloric obstruction. The absence of radiological confirmation of this diagnosis should, in retrospect, have stimulated a search for biochemical evidence of recurrent hyperparathyroidism, as gastro-intestinal symptoms such as anorexia, nausea and vomiting, and abdominal pain are not infrequently the dominant symptoms in this condition. At the time of her last admission to hospital it was obvious that the gastro-intestinal symptoms were indeed due to acute parathyroid poisoning as described by Albright and Reifstein (1948). Atsmon, Frank, Nathan, and de Vries (1960) have stressed the serious prognosis in this condition. Duodenal scarring was found at

necropsy but there was no evidence of an active ulcer or of organic pyloric obstruction, and it is unlikely that her latest abdominal symptoms were related to this finding. An association between hyperparathyroidism and peptic ulcer was first noted by Rogers (1946) and Rogers, Keating, Morlock and Barker (1947), and Lee, McElhinney, and Gall (1955) found that 24% of cases of hyperparathyroidism at the Mayo Clinic had an associated peptic ulcer.

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REFERENCES

- Albright, F., and Reifstein, E. C. (1948). *The Parathyroid Glands and Metabolic Bone Disease*. William and Wilkins, Baltimore.
- Alexander, H. B., Pemberton, J. deJ., Kepler, E. J., and Broders, A. C. (1944). *Amer. J. Surg.*, 65, 157.
- Anderson, W. A. D. (1957). *Pathology*, 3rd ed., p. 1010. Mosby, St. Louis.
- Atsmon, A., Frank, M., Nathan, P., and de Vries, A. (1960). *Gastroenterology*, 39, 83.
- Baird, I. McLean, Grainger, R., and Rowlands, B. C. (1954). *Brit. J. Surg.*, 42, 140.
- Black, B. K. (1954). *Ann. Surg.*, 139, 355.
- , and Ackerman, L. V. (1950). *Cancer (Philad.)*, 3, 415.
- Castleman, B. (1952). *Atlas of Tumor Pathology. Tumors of the Parathyroid Glands*. Fasc. 15: Armed Forces Institute of Pathology, Washington, D.C.
- Cook, P. B. (1958). *J. Bone Jt. Surg.*, 40B, 546.
- Cope, O., Nardi, G. L., and Castleman, B. (1953). *Ann. Surg.*, 138, 661.
- Greenfield, J. C., Verner, J. V., and Engel, F. L. (1959). *J. Amer. med. Ass.*, 171, 164.
- Jordan, G. L., Curd, G. W., Gyorkey, F., and DeBaakey, M. E. (1958). *Arch. Surg.*, 76, 87.
- Kleinfeld, G. (1959). *Cancer (Philad.)*, 12, 902.
- Lee, C. M., McElhinney, W. T., and Gall, E. A. (1955). *Arch. Surg.*, 71, 475.
- Norris, E. H. (1948). *Int. Abstr. Surg.*, 86, 1.
- Rapoport, A., Sepp, A. H., and Brown, W. H. (1960). *Amer. J. Med.*, 28, 443.
- Rogers, H. M. (1946). *J. Amer. med. Ass.*, 130, 22.
- , Keating, F. R., Morlock, C. G., and Barker, N. W. (1947). *Arch. intern. Med.*, 79, 307.
- Summers, V. K., Hawe, P. R., and Davis, J. C. (1959). *Brit. J. Surg.*, 47, 274.
- Tange, J. D. (1958). *Ibid.*, 46, 254.
- Woolner, L. B., Keating, F. R., and Black, B. M. (1952). *Cancer (Philad.)*, 5, 1069.
- Wright, R. B., and Mathieson, R. (1958). *Scot. med. J.*, 3, 176.