The significance of these findings is discussed in relation to current work on the nature of myasthenia gravis.

Most of the thymus glands from patients with myasthenia gravis were obtained through the courtesy of Sir Geoffrey Keynes and Mr. J. E. Piercy, of New End Hospital, London, to whom we are very grateful. We also received thymus glands from Mr. F. R. Edwards, of Broadgreen Hospital, Liverpool; Sir Russell Brock, of Guy's Hospital, London; and Mr. H. Reid and Professor C. Wells, of Liverpool Royal Infirmary, and we wish to thank them for their co-operation. Post-mortem specimens of thymus glands were kindly supplied by the following pathologists: Drs. A. H. Cruickshank, R. W. Evans, Jane Gibson, and F. Whitwell. We are also grateful to Mr. R. E. A. Mapes for his advice on the statistical analysis of the results. This research was supported by a grant from the Medical Research Council, which also provided one of us (T. N. C.) with a maintenance grant. Part of the expenses were also defrayed by grants from the Distillers Company Limited, London, and the Myasthenia Gravis Foundation Inc., New York.

REFERENCES

- Auerbach, M. E. (1943). *Industr. Engng Chem. (Anal.)*, **15**, 492.
 Bowman, W. C., and Rand, M. J. (1961a). *Lancet*, **1**, 480.
 — (1961b). *Brit. J. Pharmacol.*, **17**, 176.
 Brante, G. (1949). *Nature (Lond.)*, **163**, 651.
 Desmedt, J. E. (1958). *Ibid.*, **182**, 1673.
 — (1961). *Excerpta Med. int. Congr. Ser.*, **38**, 159.
 Friedman, S. (1958). *Arch. Biochem.*, **75**, 24.
 Keynes, G. (1946). *Brit. J. Surg.*, **33**, 201.
 — (1949). *Brit. med. J.*, **2**, 611.
 Mitchell, R., and Clark, B. B. (1952). *Proc. Soc. exp. Biol. (N.Y.)*, **81**, 105.
 Munier, R., and Machebœuf, M. (1949). *Bull. Soc. Chim. biol. (Paris)*, **31**, 1144.
 Nowell, P. T., Scott, C. A., and Wilson, A. (1962). *Brit. J. Pharmacol.*, **18**, 617.
 — and Wilson, A. (1961). In *Myasthenia Gravis*, edited by H. R. Viets, p. 238. Thomas, Springfield, Illinois.
 — (1962). Unpublished observations.
 — and Wilson, H. (1959). *Quart. J. exp. Physiol.*, **44**, 229.
 Ross, R. T. (1952). *Lancet*, **1**, 785.
 — (1961). In *Myasthenia Gravis*, edited by H. R. Viets, p. 602. Thomas, Springfield Illinois.
 Simpson, J. A. (1958). *Brain*, **81**, 112.
 Wilson, A., Obrist, A. R., and Wilson, H. (1953). *Lancet*, **2**, 368.
 — and Wilson, H. (1955). *Amer. J. Med.*, **19**, 697.

INCIDENCE OF RENAL LESIONS IN POLYCYTHAEMIA A SURVEY OF 91 PATIENTS

BY

P. W. T. BRANDT, M.B., Ch.B., M.C.R.A.

J. V. DACIE, M.D., F.R.C.P.

R. E. STEINER, M.D., M.R.C.P., F.F.R.

L. SZUR, M.B., D.M.R., F.F.R.

From the Departments of Radiodiagnosis, Radiotherapy, and Haematology, Hammersmith Hospital and Postgraduate Medical School of London

[WITH SPECIAL PLATE]

Since Bliss (1929) described the case of a patient with hypernephroma and polycythaemia, which he considered to be an incidental complication, increasing numbers of cases with this association have been reported. Forsell (1946) suggested that there was a causal relationship between the two conditions, and subsequent experience has confirmed this beyond doubt. The incidence of renal carcinoma in patients with polycythaemia has been found to be about 2–4% (Videbaek, 1950; Lawrence, 1955; Damon, Holub, Melicow, and Uson, 1958). The incidence of polycythaemia in patients with renal carcinoma is about 2–3% (Berger and Sinkoff, 1957; Conley, Kowal, and D'Antonio, 1957; Damon *et al.*, 1958; Hewlett, Hoffman, Senhauser, and Battle, 1960; Ways, Huff, Kosmaler, and Young, 1961). Most of these analyses were retrospective and the criteria for the diagnosis of polycythaemia not clearly defined. The figures may therefore not be entirely reliable.

Benign renal lesions have also been described in association with polycythaemia. These include renal adenoma (DeMarsh and Warmington, 1955) and cystic lesions—solitary cyst (Nixon, O'Rourke, Rupe, and Korst, 1960), multiple cysts (Nixon *et al.*, 1960; Jones, Payne, Hyde, and Price, 1960; Cohen, 1960; Ways *et al.*, 1961; Delamore, MacDonald, and Samuel, 1962), and polycystic disease (Kurrle, 1954; Forsell, 1958; Nixon *et al.*, 1960; Friend, Hoskins, and Kirkin, 1961). Hydronephrosis has been reported with polycythaemia; it may be unilateral (Cooper and Tuttle, 1957; Gardner and Freymann, 1958; Castleman and Kibbee, 1959; Lawrence and Donald, 1959; Jones *et al.*, 1960; Ellis, 1961; Ensor, 1961; and Martt, Sayman, and Neal, 1961), or bilateral (Jaworski and Hirte, 1961).

Other tumours as well as renal ones have been found in association with polycythaemia. These include brain

tumours, especially cerebellar haemangioblastoma (Brody and Rodriguez, 1961), fibromyomata of the uterus (Singmaster, 1957), hepatocellular carcinoma (Kan, McFadzean, Todd, and Tso, 1961), hamartoma of the liver (Josephs, Robbins, and Levine, 1962), pheochromocytoma (Bradley, Young, and Lentz, 1961), and tumours causing Cushing's syndrome (Videbaek, 1950).

That the relationship between the renal lesion and the polycythaemia has been causal and not merely coincidental has been proved on many occasions by the surgical removal of the lesion being followed by remission of the polycythaemia. For instance, prolonged remission for 11 years after removal of a renal carcinoma without any other treatment of the polycythaemia has been reported (Damon *et al.*, 1958), as well as many remissions of shorter duration (Conley *et al.*, 1957; Campbell, Pasquier, St. Martin, and Worley, 1958; Damon *et al.*, 1958; Frey, 1958; Ewert, 1960; Barnard, 1961; Ensor, 1961; Ways *et al.*, 1961). An exceptionally significant case was reported by Omland (1959). The polycythaemia remitted after nephrectomy for carcinoma. Relapse was associated with the development of metastases on two occasions in the next nine years. On each occasion remission of the polycythaemia followed irradiation of the metastases.

Benign renal lesions associated with polycythaemia have also been treated surgically. Thus remissions have been reported after nephrectomy or partial nephrectomy for renal cysts (Kurrle, 1954; Forsell, 1958; Jones *et al.*, 1960; Nixon *et al.*, 1960) and after nephrectomy for hydronephrosis (Cooper and Tuttle, 1957; Gardner and Freymann, 1958; Lawrence and Donald, 1959; Jones *et al.*, 1960; Ellis, 1961; Ensor, 1961; Martt *et al.*, 1961).

It is now generally accepted that the kidney produces a factor, "erythropoietin," which stimulates erythropoiesis. Recently, assays in patients with renal lesions and poly-

P. W. T. BRANDT *ET AL.*: INCIDENCE OF RENAL LESIONS IN POLYCYTHAEMIA

FIG. 1.—Unusual displacement of left kidney by enlarged spleen. A radiograph during intravenous pyelography shows the kidneys superimposed to the right of the spine. (Note: myelosclerosis of bones).

FIG. 2.—Tracing of Fig. 1.

FIG. 3.—Case 2. Renal carcinoma. A large partially calcified tumour occupies the upper pole of the right kidney. Intravenous pyelography shows deformity of the upper and middle calices.

FIG. 4.—Case 2. Renal carcinoma. Arteriogram shows pathological tumour circulation in the large right-upper-pole mass. A few normal arteries crowded together can be seen in the lower pole.

P. W. T. BRANDT *ET AL.*: INCIDENCE OF RENAL LESIONS IN POLYCYTHAEMIA

cythaemia have been reported (Gurney, 1960; Hewlett *et al.*, 1960; Jones *et al.*, 1960; Nixon *et al.*, 1960; Delamore *et al.*, 1962), and high values have been obtained not only from the patient's blood but also from cyst fluid and cyst wall (Nixon *et al.*, 1960) and from tumour tissue (Gurney, 1960; Hewlett *et al.*, 1960). However, the methods of assay are biological and complicated, and there is not yet unanimity of opinion regarding either the best methods of assay or their reliability. In particular, the value of plasma erythropoietin assay in deciding whether removal of a demonstrated lesion is likely to produce a remission of the polycythaemia is not yet established.

Classification of Polycythaemia

The term absolute (as distinct from relative) polycythaemia implies not only an increase in the red-cell count and haemoglobin but also an increase in the circulating red-cell mass. Cases of polycythaemia have generally been divided into two large groups: (1) *primary polycythaemia*, or polycythaemia vera or erythraemia, a disease of unknown aetiology which is considered to be a member of the myeloproliferative group of disorders (Dameshek, 1951; Wasserman, 1954); and (2) *secondary polycythaemia*, or erythrocytosis, in which the increase in red-cell mass is produced by some known stimulus or is associated with a definite disease. Secondary polycythaemia most commonly occurs as a compensatory response to anoxia caused by defective oxygen saturation of arterial blood and is therefore associated with disorders such as congenital heart disease, chronic bronchitis, and pulmonary fibrosis. It has also been found in association with a variety of other disorders in which the arterial oxygen saturation is normal, such as Cushing's syndrome, various tumours, and renal lesions (see above).

It has generally been thought that polycythaemia vera can be distinguished from secondary polycythaemia because the increase in erythrocytes is accompanied by one or more of the following: leucocytosis, neutrophilia, thrombocytosis, splenomegaly, hepatomegaly. In secondary polycythaemia the proliferation of the bone-marrow is supposed to affect only the erythrocyte precursors, and this has been generally thought to be true also of polycythaemia associated with renal lesions.

These statements require some qualification. The spleen is enlarged in only about three-quarters and the liver in about one-half of the cases of polycythaemia vera, and

approximately 20% appear to have leucocyte and platelet counts within normal limits (Szur, Lewis, and Goolden, 1959). In such cases diagnosis can be very difficult, and can be arrived at only by the exclusion of the known causes of secondary polycythaemia.

Furthermore, while it is probably true that in anoxic polycythaemia the leucocyte and platelet counts are normal, and this is found in most cases of polycythaemia associated with renal lesions, there are, as pointed out by Jaworski and Hirte (1961), a number of exceptions to this in the literature of the subject. These exceptions have either been ignored or the renal lesion has been considered to be a coincidental finding in a patient with polycythaemia vera (Ways *et al.*, 1961). In a few patients, however, who had a polycythaemia with leucocytosis, thrombocytosis, or splenomegaly, associated with a renal lesion, nephrectomy has been followed by a remission of the polycythaemia (Lawrence and Donald, 1959; Ewert, 1960; Martt *et al.*, 1961). This suggests that the renal lesion was the cause of the polycythaemia in these cases.

It seemed to us that it may not be possible to distinguish polycythaemia vera from polycythaemia due to a renal lesion by clinical and haematological criteria only, and it was decided to investigate the renal tracts of all patients at Hammersmith Hospital referred with the diagnosis of or receiving treatment for polycythaemia vera. The aim was to determine the incidence of renal lesions in these patients and to discover any cases of renal carcinoma or other conditions requiring specific treatment.

Clinical Material

A total of 91 patients were investigated. They had in the past been diagnosed as cases of polycythaemia vera on the basis of haematological studies, including blood-volume estimations and bone-marrow puncture. Where necessary, other tests such as bone biopsy, oxygen saturation of arterial blood, and radioactive iron studies had been performed.

Only 2 of the 91 patients had not received treatment with radioactive phosphorus; in these patients the disease appeared to be very mild and they were practically symptom-free. The other 89 patients had been treated with radioactive phosphorus at varying intervals over a period of up to 12 years. The clinical, haematological, and therapeutic details of a large number of these patients have been reported previously by Szur *et al.* (1959) and Szur and Goolden (1960), and the radiological appearances of the chest by Pitman, Steiner, and Szur (1961). Of the whole group, 47 patients were male and 44 were female. Their ages at the time of renal investigation varied between 27 and 86 years. Only four were under the age of 40 and only 15 under the age of 50.

The vast majority presented with symptoms caused by the increased blood volume or the complications of the disease, such as haemorrhage or thrombosis. Only two had presenting symptoms referable to the urinary tract.

Methods.—The investigation consisted of plain films of the urinary tract and an intravenous pyelogram (I.V.P.). In cases of doubt, or to determine the position of a lesion in the kidney, tomography was employed, if necessary at a second I.V.P. examination. In two cases of unilateral space-occupying lesion a renal aortogram was performed in an attempt to differentiate cyst from tumour.

Results

The renal lesions found in the 91 patients are shown in Table I. Renal abnormality was not found in 72, though

LEGENDS TO FIGS. 5-10

FIG. 5.—Case 3, renal cysts. Left kidney during intravenous pyelography. The lower pole is tilted forward and the lower calices are deformed. A soft-tissue mass can be seen projecting from the lower pole.

FIG. 6.—Case 3, renal cysts. Left kidney during nephrogram phase of arteriogram. There are sharply demarcated avascular lesions corresponding to the soft-tissue mass shown in Fig. 5. The appearance is typical of cysts.

FIG. 7.—Case 5, calcified cyst or tumour. Plain film showing calcified lesion in upper pole of left kidney.

FIG. 8.—Case 5, calcified cyst or tumour. The calcified lesion in the left upper pole causes only minimal deformity of one of the upper minor calices.

FIG. 9.—Case 7, polycystic disease. Intravenous pyelography shows deformity of all the left calices and of the right lower calices. The kidneys are enlarged and lobulated, the left more so than the right.

FIG. 10.—Tracing of Fig. 9.

a variety of incidental abdominal or pelvic lesions were noted, including prostatic enlargement, gall-stones, and Paget's disease. Five women were considered to have

TABLE I.—Renal Lesions in "Polycythaemia Vera"

	No.
Normal kidneys	72 (79%)
"Significant" lesions	8 (9%)
Renal carcinoma	2
Cyst or neoplasm (unilateral)	4
Polycystic or multiple cysts (bilateral)	2
"Incidental" lesions	11 (12%)
Pyelonephritis	4
Infarcts	2
Duplex kidneys + infarcts	1
Calculus	1
Renal artery calcification	1
Duplex kidney	1
Small kidney, ? cause	1
Total investigated	91

uterine myomata on the evidence of characteristic calcification in four cases. The fifth had a large myoma, which was removed surgically.

Renal Deformities Caused by Splenic Enlargement

Two of the normal cases showed unusual left renal deformity which was attributed to massive splenic enlargement and not to an intrinsic renal lesion. The usual types of left renal deformity caused by splenomegaly were seen in many of the cases; these deformities have been well described (Delamore *et al.*, 1962), but the deformity in the two cases was so marked that there was some difficulty in determining the cause of the appearance. One patient, who had developed myelosclerosis after three years, had a left kidney which was displaced across the midline and rotated into a semi-horizontal position so that it was partially superimposed on the right kidney (Special Plate, Figs. 1 and 2). A congenital abnormality could be excluded as plain films were available showing the left kidney near its normal position four years previously. The other case showed enlargement of the left renal outline and slight splaying of all the calices. This deformity appeared to be due to compression and flattening of the kidney in the coronal plane. An I.V.P. of six years before showed a lesser degree of the same deformity. In both these cases the spleen had increased remarkably in size between the two examinations, extending below the iliac crest.

When the left kidney was displaced by an enlarged spleen it was usually pushed downwards, often with rotation. In five cases, however, it was found to be high in position in the presence of a very large spleen which appeared to have enlarged in front of the kidney and trapped it in the upper abdomen.

Renal Lesions

Of the 91 patients investigated, 19 (21%) were found to have a renal lesion. They have been divided into two groups, 8 (9%) showing lesions which have been described as causing polycythaemia ("significant" lesions) and 11 (12%) showing lesions which have not been shown to cause polycythaemia ("incidental" lesions).

"Significant Lesions."—The eight patients with "significant" lesions were of particular interest. They included two cases of carcinoma—for example, Case 2 (Special Plate, Figs. 3 and 4)—and there were four patients with unilateral space-occupying lesions, radiologically either a cyst or a neoplasm—for example, Case 3 (Special Plate, Figs. 5 and 6) and Case 5 (Special Plate, Figs. 7 and 8). Two cases showed bilateral deformities consistent with multiple cysts or polycystic disease—for example, Case 7 (Special Plate, Figs. 9 and 10). One of these had an apparently large cyst in his right kidney; the left kidney had been excised at another hospital and had been found to contain cysts. Brief clinical details of these eight patients are summarized with their haematological findings in Table II. It can be seen that all except one (Case 2) had at least one, and usually two or three, of the features—splenomegaly, leucocytosis, or thrombocytosis—in addition to erythrocytosis. In one patient (Case 5) the increase in platelets (thrombocythaemia) dominated the clinical picture. Before admission he had suffered gastrointestinal haemorrhage and was severely anaemic when first seen.

"Incidental" Renal Lesions.—The 11 patients of the second group showed a variety of renal lesions. Abnormal calices probably due to pyelonephritis were found in four cases. There was deformity due to renal infarcts in two cases, one proved later at necropsy, the second a radiological diagnosis only. Another case, investigated by I.V.P. elsewhere, showed bilateral duplex kidneys with double pelves and ureters, and deformity most likely due to infarction or pyelonephritis in the lower half of the left kidney. One patient had a renal calculus, causing no symptoms, in one of the left minor calices. Extensive calcification of the renal arteries, among others, was noted in one patient. A case of unilateral duplex kidney with double ureter was found with no evidence of pyelonephritis or other disease. One patient had a large left kidney which was probably hypertrophied to compensate for a small right kidney. The right kidney appeared normal except for its small size, and no further investigation was done, as the patient was 66 and had only slight hypertension.

TABLE II.—Clinical and Haematological Data of 8 Patients with "Significant" Renal Lesions

Case	Sex	Age	Diagnosis	Clinical Presentation	Clinical Splenomegaly	Hb (g./100 ml.)	R.B.C. $\times 10^6$	P.C.V. %	W.B.C. $\times 10^3$	Platelets $\times 10^3$	Red-cell Volume ml./kg.	Total Blood Volume ml./kg.	Course
1	M	51	Carcinoma	Dizziness, palpitation, plethora	+	21.5	10.1	70	14	350			Died of metastases 13 months
2	M	47	"	Haematuria, plethora	0	26	8.8	74	7	176	63	95	Recent nephrectomy
3	M	57	Unilateral cysts (radiological)	Headaches, cerebral thrombosis	+	14.4	7.1	55	9.4	407			Alive and well 9 years
4	M	69	Unilateral cyst or neoplasm (radiological)	Plethora	+	19.4	9.2	66	14	410	63	104	" " " 3 "
5	M	42	Unilateral calcified cyst or neoplasm (radiological)	Weakness, lethargy, vomiting	0	10.8	6.7	36	30	2,745	33.5	92.5	Alive and well 18 months
6	M	60	Unilateral cyst or neoplasm (radiological)	Inguinal hernia, plethora	+	18.8	8.3	67	11	662	59	95	Alive and well 20 months
7	M	57	Bilateral polycystic disease (radiological)	Dyspnoea on exertion and angina	+	19.8	7.3	63.5	11	260	43.6	78.5	Alive 7½ years.
8	M	67	Bilateral cysts	Pain in toes	0	19.6	7.9	70	19	560	62	96.5	Cardiac symptoms (Previous nephrectomy—cysts.) Alive and well 3 years

Haematological figures given are the highest values obtained before treatment with radioactive phosphorus. Cases 3 and 8 had been treated by venesection before admission to Hammersmith Hospital. Normal range of red-cell volume, 28–35 ml./kg. Normal range of total blood volume, 68–85 ml./kg. Upper limit of normal platelet count, 350,000.

Discussion

The radiological demonstration of renal lesions by intravenous pyelography was the basis of this survey. Intravenous pyelography is the best screening procedure available, but is subject to technical difficulties and is unlikely to show small lesions, especially if they do not deform the caliceal system or the renal outline. Because small cysts may not be demonstrable by I.V.P., it is difficult to be sure that cysts are unilateral, even though the second kidney appears normal.

Deformities of the left kidney caused by splenic enlargement have been described recently in some detail (Delamore *et al.*, 1962). It has also been recognized that a normal spleen may influence the shape of the left kidney (Frimann-Dahl, 1961). Upward displacement of the left kidney by an enlarged spleen, seen in five of our patients, did not occur in the survey described by Delamore *et al.* (1962). They did not describe such severe deformities as occurred in two more of our patients, both of whom had splenic enlargement greater than is usually found in polycythaemia vera. It is apparent that splenic enlargement most commonly causes downward displacement of the left kidney, often with additional rotational deformities. It may also displace the kidney medially, even across the mid-line (Special Plate, Figs. 1 and 2), or compress it in the coronal plane. Occasionally it displaces the kidney upwards. These deformities caused by the spleen can usually be readily recognized, but a careful evaluation is necessary, as a renal cyst or tumour may also displace or rotate the kidney from its normal position.

The radiological differentiation of a renal tumour from a cyst may be possible by means of plain films, I.V.P., and retrograde pyelography. When differentiation cannot be made so simply, renal arteriography will usually provide the answer. Renal aortograms were obtained in two of our patients. One (Case 3) showed a sharply demarcated avascular lesion typical of cyst (Special Plate, Fig. 6). The second (Case 2) showed the pathological circulation of a tumour (Special Plate, Fig. 4). A tumour may be relatively avascular or have an avascular necrotic centre and the appearances at angiography may rarely be inconclusive. Lack of change in the pyelographic appearances over comparatively short intervals is even more unreliable, as renal tumours may grow slowly. On the other hand, cysts may increase in size. Unless the diagnosis of carcinoma can be made by simple methods, it is advisable to obtain renal arteriograms in all patients with unilateral space-occupying renal lesions. If nephrectomy is not undertaken, all the patients diagnosed as having cystic lesions by this method must be followed up with intravenous pyelography at intervals to exclude an atypical tumour.

The overall incidence of renal abnormalities revealed by our investigations is 21%. It may be of interest that a retrospective survey of the causes of death in polycythaemia vera carried out in Denmark (Chievitz and Thiede, 1962) showed the presence of disorders of the urinary tract in 30%. The majority of these patients had pyelonephritis or renal calculi. In our series the incidence of "significant" renal lesions (those of a type which has been described in association with polycythaemia) is 9%. The incidence of proved renal carcinoma (2%) in this survey is near to that previously reported (Videbaek, 1950; Lawrence, 1955; Damon *et al.*, 1958). Though a definitive diagnosis excluding tumour is not yet possible in a few of our cases, it is likely that six patients (7%) have benign cystic renal lesions. This suggests that cystic renal disease may be two to three times more common in our series of

polycythaemic patients than is renal carcinoma. No previous reports have suggested this.

Nixon *et al.* (1960), in a review of literature up to June, 1960, noted 50 cases of renal carcinoma but only 14 cases of benign renal lesions reported in association with polycythaemia. This discrepancy may have arisen because of the nature of previous investigations. Most of them have been retrospective surveys of polycythaemic patients (Videbaek, 1950; Damon *et al.*, 1958) or patients with renal carcinoma (Berger and Sinkoff, 1957; Conley *et al.*, 1957; Hewlett *et al.*, 1960) or proved renal lesions (Ways *et al.*, 1961). Retrospective investigation can be expected to provide a reasonably accurate estimate of the incidence of carcinoma, but benign lesions are unlikely to be discovered by this method. To our knowledge the only previous systematic investigation of the urinary tract in a group of living polycythaemic patients has been reported by Delamore *et al.* (1962). These authors found one case of hydro-nephrosis among 26 patients with "polycythaemia vera," and two cases of unilateral cystic renal disease out of seven patients with "erythrocytosis." The number of patients in this series was rather small, but if one considers the group as a whole the incidence of benign possibly significant renal lesions is 9%, which is near the incidence we have found in a large group.

The sex distribution of the cases is interesting. The 91 patients consisted of almost equal numbers of males and females. Most of them formed the case material of a previous survey (Szur *et al.*, 1959). Most series report a male preponderance of about 1.3:1 in polycythaemia vera (Lawrence, 1955). The fact that all our patients with a "significant" type of renal lesion were male appears to be more than coincidence. A review of 65 cases reported in the literature mentioned in the introduction to this paper shows that 56 were male and only 9 female. It appears that the male preponderance in polycythaemia associated with renal abnormality is very much greater than in polycythaemia vera.

In all our cases we do not know if the polycythaemia was caused by the associated renal lesion. Except for one (Case 2), all the patients who had a "significant" renal lesion had clinical and haematological features which are usually associated with polycythaemia vera (Table II). The incidence of these lesions in the group (9%) seems high, although we have no comparative figures for the incidence of renal lesions of this type in a similar population matched for age and sex. We could be certain that the polycythaemia was caused by the renal lesions if surgical removal of the lesion led to permanent disappearance of the polycythaemia (Jaworski and Hirte, 1961). One of our patients with renal carcinoma (Case 1) had widespread metastases when the tumour was diagnosed. The other (Case 2) has had a nephrectomy, but it is too early to assess the effect of this on his polycythaemia.

Surgical treatment of the patients with polycystic disease bilaterally is not possible. The clinical decision whether to advise surgery in the four patients we have discovered with probably benign unilateral lesions is not easy. Some have been well controlled by their treatment with radioactive phosphorus—for example, one (Case 3) is alive and well nine years after diagnosis of polycythaemia vera. The operative risk in these patients, some of whom have had pulmonary, cerebral, or cardiac infarcts also has to be considered, together with the fact that we cannot be sure that surgery would cure the polycythaemia in any particular patient. Erythropoietin assays are being obtained from the plasma and urine of all the living patients with possibly significant lesions. We do not know if the results will help

in the decision whether or not to advise surgery in the patients with unilateral lesions.

In most previously reported cases of polycythaemia associated with a renal lesion the polycythaemia has not been accompanied by splenomegaly, leucocytosis, or thrombocytosis. As mentioned in the introduction, however, a number of cases have been described in which one or more of these features were present, and in a few such cases a remission of polycythaemia has been reported after nephrectomy. Our own survey of a group of patients with apparent polycythaemia vera adds to those already described seven more examples of associated renal lesions and polycythaemia accompanied by splenomegaly, leucocytosis, or thrombocytosis. More information is required about the incidence of renal lesions, especially cysts, in patients with apparent polycythaemia vera, and the relationship of these lesions to the polycythaemia still needs to be clarified. At present we believe that the idea that polycythaemia due to a renal lesion can be clearly separated from polycythaemia vera with a coincidental renal lesion by the absence of splenomegaly, leucocytosis, and thrombocytosis may prove difficult to sustain. Such a division seems to have limited practical value in any case, as patients with apparent polycythaemia vera may occasionally have normal leucocyte and platelet counts in the absence of any demonstrable lesion known to cause an increase in the red-cell mass. Until further information is available, we suggest that intravenous pyelography should become part of the routine investigation of all patients with polycythaemia vera.

Summary and Conclusions

The incidence of renal lesions in 91 patients who had been previously diagnosed as suffering from polycythaemia vera by exacting criteria was determined by routine radiological investigation.

Some unusual deformities of the left kidney caused by splenic enlargement are described.

The total incidence of renal lesions discovered was 21% (19 cases).

The incidence of renal lesions which have been described as causing polycythaemia was 9% (8 cases).

Seven of the eight patients with this type of lesion showed one or more of the features splenomegaly, leucocytosis, thrombocytosis.

It is suggested that the idea that polycythaemia due to a renal lesion can be clearly separated from polycythaemia vera by the absence of splenomegaly, leucocytosis, and thrombocytosis may prove difficult to sustain.

Renal investigation should be included in the routine examination of all patients with apparent polycythaemia vera.

REFERENCES

- Barnard, H. F. (1961). *Brit. med. J.*, **1**, 1214.
 Berger, L., and Sinkoff, M. W. (1957). *Amer. J. Med.*, **22**, 791.
 Bliss, T. L. (1929). *Ann. intern. Med.*, **2**, 1155.
 Bradley, J. E., Young, J. D., jun., and Lentz, G. (1961). *J. Urol. (Baltimore)*, **86**, 1.
 Brody, J. I., and Rodriguez, F. (1961). *Amer. J. med. Sci.*, **242**, 579.
 Campbell, J. H., Pasquier, C. M., St. Martin, E. C., and Worley, P. C. (1958). *J. Urol. (Baltimore)*, **79**, 12.
 Castleman, B., and Kibbee, B. U. (1959). *New Engl. J. Med.*, **261**, 242.
 Chievitz, E., and Thiede, T. (1962). *Acta med. scand.*, **172**, 513.
 Cohen, N. N. (1960). *Arch. intern. Med.*, **105**, 301.
 Conley, C. L., Kowal, J., and D'Antonio, J. (1957). *Bull. Johns Hopk. Hosp.*, **101**, 63.
 Cooper, W. M., and Tuttle, W. B. (1957). *Ann. intern. Med.*, **47**, 1008.
 Dameshek, W. (1951). *Blood*, **6**, 372.
 Damon, A., Holub, D. A., Melicow, M. M., and Uson, A. C. (1958). *Amer. J. Med.*, **25**, 182.
 Delamore, I. W., MacDonald, A. F., and Samuel, E. (1962). *Brit. J. Radiol.*, **35**, 671.
 DeMarsh, Q. B., and Warmington, W. J. (1955). *Northw. Med. (Seattle)*, **54**, 976.
 Ellis, H. (1961). *Proc. roy. Soc. Med.*, **54**, 157.
 Ensor, R. W. (1961). *N.Z. med. J.*, **60**, 212.
 Ewert, E. E. (1960). *Surg. Clin. N. Amer.*, **40**, 767.
 Forssell, J. (1946). *Nord. med.*, **30**, 1415.
 — (1958). *Acta med. scand.*, **161**, 169.
 Frey, W. G. (1958). *New Engl. J. Med.*, **258**, 842.
 Friend, D. G., Hoskins, R. G., and Kirkin, M. W. (1961). *New Engl. J. Med.*, **264**, 17.
 Frimann-Dahl, J. (1961). *Acta radiol. (Stockh.)*, **55**, 207.
 Gardner, F. H., and Freymann, J. G. (1958). *New Engl. J. Med.*, **259**, 323.
 Gurney, C. W. (1960). *Trans. Ass. Amer. Physns*, **73**, 103.
 Hewlett, J. S., Hoffman, G. C., Senhauser, D. A., and Battle, J. D. (1960). *New Engl. J. Med.*, **262**, 1058.
 Jaworski, Z. F., and Hirte, W. E. (1961). *Canad. med. Ass. J.*, **84**, 1421.
 Jones, N. F., Payne, R. W., Hyde, R. D., and Price, T. M. L. (1960). *Lancet*, **1**, 299.
 Josephs, B. N., Robbins, G., and Levine, A. (1962). *J. Amer. med. Ass.*, **179**, 867.
 Kan, Y. W., McFadzean, A. J. S., Todd, D., and Tso, S. C. (1961). *Blood*, **18**, 592.
 Kurrle, G. R. (1954). *Med. J. Aust.*, **1**, 777.
 Lawrence, J. H. (1955). *Polycythaemia—Physiology, Diagnosis and Treatment*. Grune and Stratton, New York.
 — and Donald, W. G. (1959). *Ann. intern. Med.*, **50**, 959.
 Martt, J. M., Sayman, A., and Neal, M. P. (1961). *Ibid.*, **54**, 790.
 Nixon, R. K., O'Rourke, W., Rupe, C. E., and Korst, D. R. (1960). *Arch. intern. Med.*, **106**, 797.
 Omeland, G. (1959). *Acta med. scand.*, **164**, 451.
 Pitman, R. G., Steiner, R. E., and Szur, L. (1961). *Clin. Radiol.*, **12**, 276.
 Singmaster, L. (1957). *J. Amer. med. Ass.*, **163**, 36.
 Szur, L., and Goolden, A. W. G. (1960). *Cancer Progress*, edited by R. W. Raven, p. 186. Butterworth, London.
 — Lewis, S. M., and Goolden, A. W. G. (1959). *Quart. J. Med.*, **28**, 397.
 Videbaek, A. (1950). *Acta med. scand.*, **138**, 239.
 Wasserman, L. R. (1954). *Bull. N.Y. Acad. Med.*, **30**, 343.
 Ways, P., Huff, J. W., Kosmaler, C. H., and Young, L. E. (1961). *Arch. intern. Med.*, **107**, 154.

MALIGNANT MYELOSCLEROSIS

BY

S. M. LEWIS, M.D., D.C.P.

AND

L. SZUR, M.B., F.F.R.

Department of Haematology, Postgraduate Medical School,
and Department of Radiotherapy, Hammersmith Hospital,
London

[WITH SPECIAL PLATE]

The term "myeloproliferative disorders" has been used to stress the close relationship which exists between several diseases characterized by the proliferation of one component, or more, of the bone-marrow (Dameshek, 1951; Wasserman, 1954). These diseases are of unknown aetiology and include a number of more or less clearly defined syndromes, of which the best-recognized are acute and chronic granulocytic leukaemia, polycythaemia vera, erythroleukaemia (Di Guglielmo's disease), and myelosclerosis. It is, however, generally accepted that these conditions may merge into one another.

Myelosclerosis is a chronic but progressive and eventually fatal disease in which there is replacement of the bone-marrow by connective tissue and, at times, cancellous bone. The marrow is characterized by an increase in argyrophil reticulin and myeloid proliferation with an increase in reticulum cells and often numerous megakaryocytes. The haematological features vary. There is usually a leuco-erythroblastic anaemia, at times with a large number of circulating nucleated red cells and a moderate rise in the reticulocyte count; marked variation