21 or 22 in the Denver classification), but no direct evidence has been put forward to show the mechanism responsible for the loss. It could be either a deletion or a translocation, with the distinction uncertain because the Ph¹ is only slightly smaller than the normal small acrocentrics, so that collateral evidence of translocation would be difficult to collect. It has been suggested (Ohno *et al.*, 1961) that the involvement of the acrocentric chromosomes in nucleolar organization may expose them to risk of damage. A fundamental and so far unsolved question concerns the relation of the Ph¹ chromosome to the leukaemic process; does its presence precede and possibly stimulate the onset of the disease, or is it a result of the leukaemic transformation? It is unlikely to result from treatment, since it has been found in untreated patients.

In our material there were two abnormal small acrocentric chromosomes, the Ph¹ and the "minute." These were present in a high proportion of cells in all three marrow specimens, during both the acute exacerbation and the subsequent remission of the disease. There were also a good many apparently normal mitoses, which was to be expected in a tissue with a mixed cell population like the marrow. Both abnormalities appeared to characterize fundamentally altered—that is, leukaemic—cells; and, since the composition of the marrow specimens was very different in the first specimen compared with the second and third specimens, it appears that the Ph¹ and the "minute" acrocentrics were contained in leukaemic blasts as well as myelocytes which could not otherwise be distinguished from their normal counterparts.

The new abnormality was interesting because of the extremely small size of the chromosome. If this had arisen from a translocation, one would have expected to find a reciprocal abnormality in another chromosome. In over 50 completely analysed figures we have not seen any suggestion of this. At the same time, the "minute" was itself capable of further division; many of the tetraploid figures contained two "minutes" (Fig. 3). We suggest that this chromosome abnormality arose from a deletion of chromatin material either before or after the onset of leukaemia. The same may well be true of the Ph¹ chromosome, and both might be the consequence of damage during nucleolar organization, as suggested by Ohno *et al.* (1961).

The rather constant translocation between the No. 2 and one of the 6–12 chromosomes was probably the result of treatment, either radiotherapy or chemotherapy. It occurred only in cells carrying the Ph¹, and its high frequency suggests that it must have conferred some selective advantage on the cells carrying it. The increasing proportion of tetraploid mitoses was of interest in view of the fact that polyploidy has been found associated with radio-resistance in some other pathological materials (De, 1961).

The three blood cultures showed, in strong contrast to the direct (non-cultured) marrow preparations, a notable paucity of all types of chromosomal abnormality. This suggests that the dividing cells in the blood were mostly non-leukaemic. The blood picture was practically normal on all occasions, and it is probable that most of the mitoses arose from large lymphocytes or monocytes which, in normal blood, are the only cells capable of division (Bond *et al.*, 1958). In the type of case here described the direct marrow preparations had thus a notable advantage over those derived from blood cultures, in that they yielded a far higher proportion

of the characteristic abnormal mitoses. This finding is in line with the arguments put forward by Sandberg *et al.* (1960, 1961). It also disposes of the contention that the Ph¹ chromosome may be an artifact produced in culture (Trujillo *et al.*, 1961).

SUMMARY

Repeated examination of the bone-marrow of a patient with chronic granulocytic leukaemia showed the presence of the Ph¹ chromosome as well as that of a hitherto undescribed minute chromosome replacing a second small acrocentric and probably originating from a deletion of chromatin material. These abnormalities were more easily found in direct marrow preparations than in cultures of the peripheral blood. They were present during remission as well as during an acute exacerbation of the disease.

ANGELA ADAMS,* B.Sc.

P. H. FITZGERALD, M.Sc.

F. W. GUNZ, M.D., Ph.D., M.R.C.P.

Department of Pathology, Christchurch Hospital,
and B.E.C.C. Radiation Biology Group, Wakari
Hospital, Dunedin, New Zealand.

REFERENCES

- Baikie, A. G., Court Brown, W. M., Buckton, K. E., Harnden, D. G., Jacobs, P. A., and Tough, I. M. (1960). *Nature (Lond.)*, **188**, 1165.
Bond, V. P., Cronkite, E. P., Flidner, T. M., and Schork, P. (1958). *Science*, **128**, 202.
Bottura, C., and Ferrari, I. (1960). *Nature (Lond.)*, **186**, 904.
De, N. (1961). *Brit. J. Cancer*, **15**, 54.
Kinlough, M. A., Robson, H. N., and Hayman, D. L. (1961). *Nature (Lond.)*, **189**, 420.
Moorhead, P. S., Nowell, P. C., Mellman, W. J., Battips, D. M., and Hungerford, D. A. (1960). *Exp. Cell Res.*, **20**, 613.
Nowell, P. C., and Hungerford, D. A. (1960a). *Science*, **132**, 1497.
— (1960b). *J. nat. Cancer Inst.*, **25**, 85.
Ohno, S., Trujillo, J. M., Kaplan, W. D., and Kinoshita, R. (1961). *Lancet*, **2**, 123.
Sandberg, A. A., Koepf, G. F., Crosswhite, L. H., and Hauschka, T. S. (1960). *Amer. J. hum. Genet.*, **12**, 231.
— Ishihara, T., Miwa, T., and Hauschka, T. S. (1961). *Cancer Res.*, **21**, 678.
Tough, I. M., Court Brown, W. M., Baikie, A. G., Buckton, K. E., Harnden, D. G., Jacobs, P. A., King, M. J., and McBride, J. A. (1961). *Lancet*, **1**, 411.
Trujillo, J., Stenius, C., Weiler, C., Kaplan, W. D., Ohno, S., and Kinoshita, R. (1961). *Proc. Amer. Ass. Cancer Res.*, **3**, 274.

Medical Memoranda

Intra-atrial Sarcoma

When Prichard (1951) reviewed tumours of the heart he found that secondary tumours were 20 to 40 times more common than primary tumours, the most frequent primary sites being breast, lung, and the lymphatic system. Myxomas constituted nearly 50% of the primary cardiac tumours, with sarcomas second. Whorton (1949) reviewed the primary malignant tumours of the heart, and collected and classified 100 sarcomas. Among these were 18 round-cell sarcomas, 18 spindle-cell sarcomas, 11 pleomorphic sarcomas, and 5 were classified as leiomyosarcomas. Isolated case reports have been published since then, so that the total number of reported cases of primary malignant tumours of the heart is now probably about 160.

Primary tumours of the major blood-vessels are of even greater rarity—Giaccai (1949), reviewing reported cases, found 26 (9 benign and 17 malignant). Some are similar to the present case.

*Working for the Canterbury Division, British Empire Cancer Campaign Society.

Baldwin (1910) described a pedunculated sarcoma arising from the region of the mouth of the pulmonary veins and almost filling the left auricle. Ausbüttel (1939) described a pleomorphic-celled sarcoma arising in the right pulmonary vein, proliferating as far as the left atrium. Ravid and Sachs (1943) reported a primary myxosarcoma of the left auricle and pulmonary vein, and Cumming and Shillito (1957) described a tumour with the features of an osteogenic sarcoma, which arose from the right superior pulmonary vein, and grew into the left atrium, obstructing the mitral opening by a ball-valve mechanism.

The following case report describes a somewhat similar tumour in a woman of 35.

CLINICAL HISTORY

A 35-year-old housewife was first seen at the Royal Victoria Hospital, Belfast, on November 30, 1959. She gave a two-months history of exertional dyspnoea and of three episodes of haemoptysis. On clinical examination there were no abnormal physical signs. A chest x-ray film showed a prominent pulmonary conus but no evidence of a lung lesion, the Mantoux 1:10,000 was positive, and the E.S.R. was 65 mm. in the first hour (Westergren). Over the next four weeks she was examined several times and was admitted on December 26. There had been no change in the history of her complaint and no history of rheumatic fever could be elicited. On examination an early diastolic murmur had appeared at the lower end of the sternum, and a mid-diastolic murmur at the apex after exercise. The blood-pressure was 125/80 mm. Hg and the pulse was in sinus rhythm. The chest x-ray film was as before. E.S.R. was repeatedly elevated (85 mm., 38 mm., 39 mm.), but there was no fever and no clinical or laboratory evidence of rheumatic or bacterial endocarditis. E.C.G. was non-contributory.

Some days after her admission there was a marked change in her mental state—formerly one of slight withdrawal and apprehension. She began to shout, talked in a disconnected manner, refused treatment, expressed delusions that she was being poisoned, and demanded to be allowed home. She was seen by a psychiatrist, who advised admission to Purdysburn Mental Hospital, where, on chlorpromazine 50 mg. t.d.s., she settled down quite rapidly. While there her E.S.R. was persistently elevated (40–50 mm. in the first hour), and after further mild haemoptyses she was readmitted to the Royal Victoria Hospital on February 12, 1960. The physical signs were very much as before, with a heaving right ventricular outflow tract, an early diastolic murmur, and an inconstant apical mid-diastolic murmur. Three days after her second admission she became tense and hallucinated, and expressed delusions of persecution. This state was followed by a period in which she was virtually catatonic. X-ray screening at this time suggested left atrial enlargement, and the causes of mitral-valve obstruction, either by valve disease or tumour, were being considered when her mental state necessitated her readmission to the mental hospital, where she again settled down.

Three weeks later she was readmitted to the general hospital with massive haemoptysis, requiring blood transfusion, and at this time poor air entry at the left apex was noted. She was transfused, and, while she recovered physically, she became agitated and the demonstration of definite suicidal tendencies expedited her further transfer to the mental hospital, whence she returned on March 26, after another massive haemoptysis. At this time there was a tricuspid systolic murmur and a markedly heaving right ventricular outflow tract, and a tentative diagnosis of pulmonary embolism was made. However, no peripheral source of emboli could be found and all murmurs quickly disappeared. She remained dull and withdrawn and complained of unpleasant "voices" in her head, but it was felt that investigation should proceed.

Cardiac catheterization was carried out on March 31. The catheter passed easily into the right pulmonary artery and the "wedge" pressure was 11 mm. Hg at rest, rising to 17 mm. Hg on exercise. The mean pulmonary artery pressure was 20 mm. Hg. It was felt that this ruled out mitral-valve disease as a cause of the haemoptysis, and causes of intermittent pulmonary hypertension, such as left atrial myxoma, were being considered, when, the following morning, she had a further massive haemoptysis and died.

NECROPSY FINDINGS

The state of nutrition was poor. No peripheral oedema was present, nor were there effusions in any of the serous cavities.

The heart was not enlarged generally, though the left atrium was held in a dilated position by a firm mass within. On opening the atrium this was seen to be a tumour, measuring 6 by 5 by 5 cm., almost completely filling the atrium, and extending as a rounded plug into the mitral opening (Fig. 1). The mitral-valve cusps were quite

FIG. 1.—Heart viewed from behind. The tumour can be seen arising from the left pulmonary vein (see arrow), spreading into the left atrium, and extending down as far as the mitral-valve ring.

normal. The surface of the tumour was smooth, though slightly lobulated, and on section it was greyish white in colour, of very firm consistency, and showed a few small areas of haemorrhage. Although loosely adherent to the thickened atrial endocardium it could be easily stripped as far as the ostium of the left superior pulmonary vein. Here the tumour was intimately attached to the vein wall and had expanded therein to a diameter of 2.5 cm. Prolongations of tumour extended distally along the tributaries of the vein for 2–3 cm. The left inferior pulmonary vein was partially occluded by tumour, and the lower branch of this vein contained a recent thrombus. At no point had the tumour penetrated the walls of the veins or atrium.

The trachea and bronchi contained large quantities of recent blood and blood clot. Both lungs showed a reddish mottling, visible from the pleural surface and on section, due to recently inhaled blood. The tumour had not invaded neighbouring bronchi or vessels. The lungs also contained some oedema. Otherwise the texture of the right lung appeared quite normal. The upper lobe of the left lung, however, felt firm and was grey in colour, suggesting fibrosis.

No tumour metastases were located in spite of a complete and careful examination. There were no signs of disease in the remaining organs.

HISTOLOGY

The tumour was a spindle-cell sarcoma. It was composed of interlacing bundles of elongated cells with wide variation in the size and shape of their nuclei, some being very large and of bizarre shape and showing occasional mitotic figures (Fig. 2). The cell cytoplasm was faintly eosinophilic with

FIG. 2.—Photomicrograph of tumour. (H. and E. $\times 300$.) Note elongated spindle-shaped cells with large hyperchromatic nuclei.

haematoxylin and eosin. Special staining, employing Lendrum's picro-Mallory and Mallory's phosphotungstic acid haematoxylin, revealed the presence of muscle fibres. No cross-striations could be demonstrated with Heidenhain's haematoxylin.

At its point of origin from the left superior pulmonary vein the tumour was intimately associated with the vein wall, so that the two could not be separated. No extension was present outside the wall. The central areas of the tumour showed slight haemorrhage and much necrosis. Organized thrombus had been incorporated on the surface of the tumour.

Sections from the upper lobe of the left lung were of interest in that they showed an extensive interstitial fibrosis. The alveolar walls were greatly thickened by fibroblastic proliferation, with relatively few blood vessels. There was considerable variation in the size of the alveoli, and many were lined by a low cuboidal epithelium. Some contained collections of heart-failure cells, and recently aspirated red cells were also present. The small and medium-sized pulmonary arteries in this area showed a noticeable narrowing of their lumen by medial hypertrophy and intimal proliferation, resembling an obliterative arteritis.

Sections from the left lower lobe and the right lung showed red cells in bronchi, bronchioles, and alveoli. There was some distension of the broncho-pulmonary veins. No arterial changes were present in these areas. Occasional groups of haemosiderin-containing mononuclears were present.

Sections of the other organs, including the brain, revealed no lesion.

COMMENT

This case report is of a leiomyosarcoma of the left superior pulmonary vein growing into the left atrium, causing retrograde thrombosis of the left pulmonary veins, haemorrhage from the broncho-pulmonary anastomoses, and death by asphyxiation. Among the points of interest are the rarity of the tumour in the published literature, and the changes in the lung similar to those described by Andrews (1957) subsequent to pulmonary vein thrombosis, resembling interstitial fibrosis.

The clinical picture of the findings on investigation suggested left atrial obstruction. It was felt, however, that the normal wedge pressure in the right lung field excluded mitral stenosis and made left atrial myxoma unlikely. Had the wedge pressure, in addition, been recorded in the left upper lobe, the diagnosis of localized obstruction to the pulmonary venous return—probably due to tumour—would have been suggested, and the possibility of pneumonectomy and removal of the tumour might then have been considered. The accelerated E.S.R. was probably of significance, as MacGregor and Cullen (1959) have remarked on it in cases of intra-atrial myxoma; there was, however, no fever.

The mental state delayed and prevented attempts at accurate diagnosis; her symptoms were thought to be those of an acute schizophrenic reaction, with paranoid delusions, agitation, and suicidal tendencies, progressing to withdrawal and retardation. It is not clear what factors, if any, in her clinical illness can be incriminated in the production of the mental disturbance. Her pre-morbid personality was stable and there was no previous history of mental illness in the patient or her family. It is possible that abnormal tissue metabolism as a result of malignant disease, or the recurrent psychic trauma of impending cardiological investigation and surgery, could have contributed to it.

We thank Drs. T. T. Fulton, J. F. Pantridge, and D. M. Gardner, and Professor J. H. Biggart for their help and advice.

B. S. L. KIDD, M.D., M.R.C.P.Ed.,
Senior Registrar in Medicine.

D. J. L. CARSON, M.B., B.Ch.,
Assistant Lecturer in Pathology.

E. S. LAMONT, M.B., D.C.H., D.P.M.,
Senior Registrar in Psychiatry.

Royal Victoria Hospital and Institute
of Pathology, Queen's University, Belfast.

REFERENCES

- Andrews, E. C., jun. (1957). *Bull. Johns Hopk. Hosp.*, **100**, 28.
- Ausbüttel, F. (1939). *Frankfurt. Z. Path.*, **53**, 303.
- Baldwin, H. A. (1910). *J. Amer. med. Ass.*, **55**, 646.
- Cumming, A. R. R., and Shillitoe, A. J. (1957). *Brit. Heart J.*, **19**, 289.
- Giaccai, L. (1949). *Arch. De Vecchi Anat. pat.*, **13**, 353.
- MacGregor, G. A., and Cullen, R. A. (1959). *Brit. med. J.*, **2**, 991.
- Prichard, R. W. (1951). *Arch. Path. (Chicago)*, **51**, 98.
- Ravid, J. M., and Sachs, J. (1943). *Amer. Heart J.*, **26**, 385.
- Whorton, C. M. (1949). *Cancer*, **2**, 245.