Idiopathic pulmonary haemosiderosis with myocarditis
Radio-isotope studies in a patient treated with prednisone

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This disease of children and young adults is characterized by recurrent intrapulmonary haemorrhage with deposition of haemosiderin in the lungs and the development of interstitial pulmonary fibrosis. Detailed reviews of the condition have been published by such authors as Rudnick and Takamura (1961), Soergel and Sommers (1962), and Ognibene and Johnson (1963).

A further case is here reported of a young adult in whom detailed studies of iron absorption and turnover were undertaken.

METHODS

In the fasting state an oral dose of 10 µc. $^{59}$Fe was given in 25 mg. of ferrous sulphate accompanied by 42.5 mg. of ascorbic acid.

Iron utilization by the red cells was measured by counting the radioactivity in samples of 5 ml. of haemolysed whole blood. Measurements were made in a well-type sodium iodide scintillation counter.

Absorption of radioactive iron was determined by means of a simple whole-body counter. At first a 7.5 cm. diameter x 7.5 cm. thick sodium iodide crystal was used, but this was later replaced by a 12.5 cm. diameter x 7.5 cm. thick crystal. Counts were made over the subject both prone and supine with the counter in three reproducible positions, the distance from crystal to bed being 49 cm. This procedure was found to be relatively independent of radioactive redistribution within the body. Whole-body counting was carried out in a normal unshielded room, and to obtain some reduction in background there was a 2.5 cm. thick lead shield at the sides of and above the crystal. Allowance was made for radioactive decay and electronic drift by counting a standard quantity of $^{59}$Fe in a reproducible position at the time of each whole-body measurement.

To study the selective uptake of radioactive iron in the lungs, measurements were made using a shielded 7.5 cm. diameter x 7.5 cm. thick sodium iodide crystal with a straight-sided 7.5 cm. diameter collimator. Rough counts were made while tracking the crystal by hand over the chest area as close to the chest as possible. When the position of maximum counting rate was found, an accurate measurement was taken and compared with a count made over the thigh, which was assumed to represent the level of activity in the blood.

Two series of observations were made, one during a phase of remission and one during a period of treatment with corticosteroids (tests 1 and 2).

CASE REPORT

This young man, the only child of healthy parents, enjoyed normal health until the age of 16 years. There was no history of rheumatic fever or its equivalents, nor of any urinary symptoms. At 16 he developed a febrile illness with left-sided pleuritic pain, cough without haemoptysis, and consolidation of the lower lobe of the left lung. This illness responded to penicillin. Two months later he had two episodes of slight haemoptysis and became breathless on exertion. The chest radiograph showed patchy opacities mainly in the middle and lower zones of the right lung field (Fig. 1). These subsequently cleared completely (Fig. 2). A further six months later he was found to be grossly anaemic, with bilateral retinal haemorrhages and a haemoglobin of 37% (5.4 g./100 ml.). The chest radiograph showed a symmetrical diffuse fine shadowing in the lower zones of both lung fields. After the administration of oral iron for six weeks the haemoglobin had risen to 82% (12.1 g./100 ml.). He remained well for another nine months, when iron-deficiency anaemia with dyspnoea on exertion recurred. Again the haemoglobin was only 37% (5.4 g./100 ml.) and rose to 87% (12.7 g./100 ml.) on oral iron therapy.
FIG. 1. Chest radiograph at time of first haemoptysis showing patchy opacities consistent with recent intra-pulmonary haemorrhage.

FIG. 2. Chest radiograph two months later showing clearing.
stippling of the lower zones was still present on the chest radiograph (Figs 3a and 3b). Treatment with iron was continued, and he remained well until the age of 19½, when symptoms recurred after a period of 36 months from the initial minor haemoptysis. He developed a cough productive of white sputum and became dyspnoeic on moderate exertion, such as walking uphill or running. There was a single minor recurrence of haemoptysis. He had no wheeze or chest pain. It was at this stage in his illness that he first came under our observation.

He was a pleasant and alert young man of slight build. There was no mucosal pallor, no cyanosis, and no clubbing of the fingers. He was not dyspnoeic at rest, and physical signs in the chest were all normal. The radial pulse was 80 per minute, regular with occasional extrasystoles, and of normal volume. The right radial artery was aberrant. The arterial pressure was 115/80 mm. Hg. The jugular venous pressure was not raised, but a venous ‘a’ wave was visible in the supraclavicular fossa. The apex beat was normal in character and position, but there was a slight right ventricular impulse to the left of the sternum. The second heart sound in the pulmonary area was increased; the first sound was normal. A grade 2/6 systolic murmur at the aortic area was
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conducted into the right carotid artery. There were no diastolic murmurs.

The liver edge was not palpable, although there was an area of resistance below the right costal margin. The spleen was enlarged, with a firm smooth edge palpable about 4 cm. below the left costal margin. The external genitalia were normal. No abnormalities were found on examination of the central nervous system, and the optic fundi and retinal vessels were normal in all respects.

The chest radiograph showed extensive diffuse stippled shadowing symmetrically involving the middle and lower zones of both lung fields (Fig. 4). The heart shadow was normal with a cardiothoracic ratio of 140:290. The electrocardiogram (E.C.G.) (Fig. 5) showed left axis deviation of -30°. This was associated with intraventricular conduction delay of left-sided type, the QRS complex slightly exceeding 0.1 second and its main deflection in lead I being positive. The conduction defect, together with depression of the ST segment and inversion of T in leads V₆ and V₇, suggested a left ventricular abnormality which was unexpected in the context of chronic pulmonary disease. There was also clockwise rotation, but no evidence of any right or left ventricular abnormality. The flattening and inversion of T in the standard and unipolar limb leads was interpreted as a non-specific indication of myocardial disease. At this time the anaemia was slight and liver function was normal (Table I). The Coombs' test was negative. The serum contained a weak cold agglutinin active at 40°C, but inactive at room temperature.

The progressive radiographic changes in both lungs were consistent with interstitial lung disease, and the associated remitting iron-deficiency anaemia, out of all proportion to the degree of haemoptysis, suggested a diagnosis of idiopathic pulmonary haemosiderosis. Gastric washings were therefore examined for haemosiderin-laden macrophages (siderophages). Smears stained by the Prussian blue method contained numerous small groups of strongly positive granules thought to represent intracellular haemosiderin. The possibility that iron given by mouth had been deposited in the gastric mucosa was considered, and gastric lavage was repeated after a period of six weeks, during which no iron was administered. The resulting smears showed many haemosiderin granules in cells from fasting juice and from the washings. With

FIG. 4. Chest radiograph three years after onset showing extension of the diffuse shadowing.
The patient was now feeling well, with no dyspnoea on exertion, but the low serum iron with an unsaturated iron-binding capacity suggested that depletion of his iron stores was continuing. An investigation of his iron metabolism was undertaken with the object of determining the site of any abnormal loss and the effect of treatment.

Radio-iron was administered by mouth and retention of activity was measured on a whole-body counter (see Methods). Surface counting allowed areas of concentration of activity to be mapped out. Red cell activity was measured in whole blood samples. Eventually he was allowed to leave hospital and attended as an out-patient for the measurements to be continued.

Ten weeks after his original admission to the Respiratory Diseases Unit he was readmitted to the ward. For two days he had experienced lethargy, fatigue, and dyspnoea on exertion, and there had been a slight increase in his cough. No haemoptysis had occurred, but his parents noticed that the colour had left his face. On admission he was pale but not orthopnoeic or sweating. There was a tachycardia of 100 per minute. The supine blood pressure was 90/60 mm Hg. There was no oedema and the internal jugular veins were not distended, although 'a' and 'v' waves were visible to a height of about 5 cm above the sternal angle. The right ventricular impulse was markedly increased, but again there was no left ventricular heave. The pulmonary second sound was increased, and there was an aortic systolic murmur

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<td><strong>Hb (%)</strong></td>
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<td><strong>Reticulocytes (%)</strong></td>
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FIG. 5. E.C.G. at time of first admission (see text).

this evidence supporting the diagnosis of idiopathic pulmonary haemosiderosis it was felt that to proceed to lung biopsy at this stage was not justifiable. Despite radiographic shadowing suggestive of diffuse interstitial pulmonary fibrosis it was established that the patient had no abnormality of ventilatory function nor any significant degree of hypoxaemia at rest or immediately after exercise (Table II).
as before. Triple rhythm was not present. Fine end-inspiratory crepitations were audible over the mid and lower regions of both lungs posteriorly. The degree of splenic enlargement was unchanged.

The chest radiograph showed a further intensification of the fine mottling over the mid and lower zones of both lung fields. The E.C.G. had not altered. The haemoglobin was 42% (61 g./100 ml.) and packed cell volume 20%. There was slight arterial oxygen desaturation to 90%. Non-specific cold agglutinin was still present in the serum. There was no antinuclear factor.

On the assumption that he was suffering from an acute haemorrhage into the lung tissues he was given a transfusion of the packed red cells from two pints of whole blood. Oxygen (100%) was given by face mask, and digoxin and bendrofluazide were prescribed over the period of the transfusion and for the next few days. Corticosteroid therapy was begun with prednisone by mouth in a dose of 60 mg. daily. After two days this was reduced by decrements of 10 mg. daily to a maintenance level of 20 mg. daily.

While in the ward he remained cheerful, although often feeling tired and easily fatigued, and was up and about. Studies of iron metabolism were repeated in the hope that corticosteroid therapy might have slowed the rate of iron loss.

Thirty-one days after readmission he suffered a sudden massive haemorrhage from the lungs and died almost immediately.

**PATHOLOGICAL FINDINGS** A necropsy was carried out eight hours after death: permission was obtained for examination of the thoracic and upper abdominal organs only. No external abnormalities were seen. The trachea and main bronchi contained blood. A few fibrous pleural adhesions were present bilaterally. The lungs were bulky, did not collapse on removal from the chest, and were firm and rubbery in consistency. The cut surface was reddish-brown in colour except for the apices of both upper lobes. Hilar, paratracheal, and mediastinal lymph nodes were moderately enlarged and showed brown pigmentation. No thymic tissue was found. The heart (395 g.) showed slight dilatation of all chambers. The pericardium was healthy, but variable degrees of myocardial fibrosis were seen in all parts of the left ventricular wall with moderate endocardial fibrosis. The right ventricle and pulmonary artery were normal and no valvular lesions were present. No atheroma was seen in the aorta or coronary arteries. An intra-pericardial lymph node was found at the origin of the pulmonary artery. The spleen (360 g.) was slightly enlarged and on section showed evidence of lymphoid hyperplasia. Several enlarged lymph nodes were present in the mesentery. The liver (2,185 g.) was slightly enlarged but appeared normal on section. Other organs were normal.

**HISTOLOGICAL EXAMINATION** The lungs showed the usual appearance of idiopathic pulmonary haemosiderosis (Fig. 6). The changes were most severe in the lower lobes. The alveolar walls were thickened as a result of capillary congestion, oedema, and slight fibrosis. Some ruptured capillaries were found, and most alveoli were filled with red cells and siderophages in varying proportions. There was also swelling and desquamation of alveolar lining cells. Elastic fibres in alveolar walls and blood vessels showed widespread fragmentation and encrustation with granules of haemosiderin (Fig. 7). There was no evidence of a vasculitis and no specific inflammatory features were seen.

In the hilar, paratracheal, and mediastinal nodes there were dilated sinuses filled with siderophages together with plasma cells and lymphocytes. Free haemosiderin encrusting connective tissue and blood vessels was also seen. No haemosiderin was found in any other tissue. The mesenteric and intrapericardial nodes showed non-specific lymphoid hyperplasia. The spleen contained fewer red cells than usual, consistent with a terminal haemorrhage; it was thus evident that its enlargement was also due to lymphoid hyperplasia. No thymic tissue was found histologically. The sternal bone marrow showed active normal haemopoiesis.
FiguRE 7. Lung, showing haemosiderin deposited on elastic fibres in alveolar walls and vessels. H. and E., ×130.

FiguRE 8. Heart, showing diffuse interstitial fibrosis and patchy round cell infiltration. H. and E., ×50.

FiguRE 9. Heart, showing a focus of recent myocardial change, with a predominantly polymorphonuclear infiltrate. H. and E., ×275.

FiguRE 10. Liver, showing fine bands of fibrosis radiating from portal tracts. H. and E., ×50.
The right ventricle showed no pathological changes. In the left ventricle there was extensive fibrosis of variable severity affecting the inner half of the myocardium in general, but involving the whole thickness in places. Most of the fibrous tissue was mature and associated with a patchy, moderate infiltration with lymphocytes, histiocytes, plasma cells, and also a few polymorphs and eosinophils (Fig. 8). Active fibroblastic proliferation was present in places and there were scattered foci of recent myocardial necrosis accompanied by a polymorph reaction (Fig. 9). No micro-organisms were seen and there was no evidence of any primary vascular lesion.

In the liver there was centrilobular congestion. A few portal tracts showed fine outward-radiating strands of fibrosis which occasionally linked with contiguous tracts (Fig. 10). No cause for these changes was evident. The kidneys showed no evidence of any glomerulonephritis, such as that described in some cases of idiopathic pulmonary haemosiderosis and reviewed by Soergel and Sommers (1962) and by Sprecace (1963). Other organs examined showed no significant pathological changes.

**IRON ABSORPTION AND TURNOVER STUDIES** The serum iron was persistently low during the first admission, remaining in the region of 60 µg./100 ml. (normal 80 to 180 µg./100 ml.) on repeated examinations, and falling to 30 µg./100 ml. in the stage of clinical relapse (Table I). The rate of iron clearance from the plasma was considerably increased, the half-time being only 36 minutes (normal 70 to 140 minutes). In Fig. 11 surface radioactivity over the thigh and lungs is plotted against time in the two successive experiments. In Fig. 12 the red cell activity and the ratio of the chest count to the thigh count, where thigh represents a control muscle mass, are plotted against time. It is clear that the amount of radio-

**FIG. 11.** Comparison of radioactivity in chest and in thigh during clinical remission (test 1, solid symbols) and during relapse treated with steroids (test 2, open symbols).

**FIG. 12.** Radioactivity in chest expressed as a ratio to a control muscle mass compared with radioactivity in whole blood during clinical remission (test 1, solid symbols) and during relapse treated with steroids (test 2, open symbols).
activity in the lungs rose steadily and continued to do so as the red cell activity subsided. This observation is taken to indicate loss of blood into the lung tissue. If this interpretation is correct, it should be expected that a reciprocal relationship would exist between the two curves. The rate of fall-off of red cell activity being proportional to the rate of accumulation of radioactivity in the lungs. A comparison of the curves in the two experiments confirms this relationship (tests 1 and 2). The observation that activity in red cells declines more rapidly as the rate of accumulation in the lungs increases is a function of the constant relationship between these parameters, and can only be due to a continuing loss of red cells into the lungs.

The absorption of the oral dose of iron was of the order of 72% in the first test and 90% in the second.

DISCUSSION

Idiopathic pulmonary haemosiderosis is a clinical entity that is becoming increasingly well recognized, and yet the aetiology remains unexplained. Haemorrhage into pulmonary tissue, deposition of haemosiderin within the lungs, and the development of anaemia and pulmonary hypertension are all factors in the production of the clinical syndrome. There is, however, no general agreement as to the basic pathogenesis. A capillary or other structural defect may underlie the intrapulmonary haemorrhage which leads to deposition of haemosiderin with pulmonary fibrosis. The theory of a developmental weakness of the pulmonary elastic fibres has been widely held in various forms since Ceelen (1931) first described the disease in two children whom he had demonstrated to the Berlin Pathology Society 10 years earlier. Soergel and Sommers (1962) suggest a primary abnormality of alveolar epithelial cells. Steiner (1954) postulates an immuno-allergic basis with the pulmonary alveoli as the shock organ and rather begs the question by designating the disease 'immuno-allergic lung purpura'. Loss of iron into the pulmonary tissue and haemosiderin deposition are conceivably active metabolic processes, producing changes in capillary and alveolar walls that predispose to haemorrhage.

No new pathological observations have been made in the present case. The lung changes are typical and the appearances in the heart are similar to those described by Campbell and Macafee (1959). The relationship between the heart and lung changes is uncertain. That the combination is fortuitous is unlikely, since the association of idiopathic pulmonary haemosiderosis with a myocarditis or myocardial abnormality other than cor pulmonale has been reported in at least nine other subjects in the past (Gellerstedt, 1939; Glanzmann and Walthard, 1941; Scheidegger and Dreyfus, 1945; Wigod, 1955; Soergel, 1957; Campbell and Macafee, 1959; Saltzman, West, and Chomet, 1962; Murphy, 1965). Nor is it likely that the pulmonary changes are secondary to cardiac damage, as pulmonary haemosiderosis similar to that found with severe mitral stenosis or prolonged left ventricular failure has not, so far as the authors are aware, been reported with other cardiac abnormalities. That the cardiac lesion is secondary to recurrent haemorrhage in the lung is a possibility worth considering. The release in the lungs of 5-hydroxytryptamine or related substances could conceivably produce myocardial fibrosis similar to that seen in the right ventricle in carcinoid syndrome, but if this were the case cardiac abnormalities might be expected to occur more frequently in idiopathic pulmonary haemosiderosis. Myocardial ischaemia is a possible additional factor if the haemoglobin falls to low levels.

It remains more likely that the cardiac and pulmonary lesions are manifestations of the same process. A vasculitis was not found in either the lungs or the myocardium in the present case. A virus infection has not been excluded as a possible aetiological factor. The disease, however initiated, may be perpetuated by an auto-immune disorder. The lymphoid hyperplasia found in this case and in others is consistent with this theory although unsupported by immunological evidence (Soergel and Sommers, 1962).

The changes in the liver in this patient are slight and their relationship to the heart and lung changes is uncertain. While not amounting to a cirrhosis, these features may represent an early stage of its histogenesis.

The clinical course, with exacerbations and remissions and fatal termination in the case under consideration, is characteristic of the disease. The patient showed the typical radiological features of patchy pulmonic opacities in the acute phase and increasing diffuse stippling of the lung fields during the chronic phase. There was also a characteristic hypochromic anaemia with a low serum iron and unsaturated iron-binding capacity.

A previous study of iron metabolism in idiopathic pulmonary haemosiderosis suggested that during remission the plasma iron turnover was normal and radio-iron accumulated solely in the bone marrow (Apt, Pollycove, and Ross, 1957). The present findings indicate that loss of blood into the lungs continued even when the patient was symptom-free. This blood loss was reflected by a persistently low serum iron, a high iron-binding capacity, and a rapid plasma clearance of
Iron, and by the absence of stainable iron in the marrow, spleen, and liver despite transfusion. High values for iron absorption from the gut were obtained. It is not possible at present to say whether the increased absorption was related to the disease itself or was due to the state of iron depletion of the patient. Although the body is apparently severely iron-deficient it must be emphasized that there are large deposits of inaccessible iron in the lung tissue.

Prednisone, in a dose of 20 mg. daily, failed to induce remission in this patient. Indeed, the rate of blood loss into the lungs increased while this treatment was being given (Fig. 12). To draw general conclusions from a single observation would be unwise, and all that can be stated is that this patient failed to respond to this particular dose of corticosteroid. Larger doses might possibly have produced a better result, or the same dose might have been more effective if given during a less acute phase of the illness. The vast majority of cases, whether given corticosteroids or not, proceed to a fatal termination, and it is clear that this form of treatment seldom influences the outcome of the disease. Even in those cases in which a therapeutic response to corticosteroids has been claimed the improvement may be explicable on the basis of a spontaneous remission (Browning and Houghton, 1956; Halvorsen, 1956; Irvin and Snowden, 1957; Cooper, 1960; Sprecace, 1963). The same could be said of any treatment other than urgent supportive measures, including immunosuppressive therapy, for which Steiner and Nabradi (1965) have recently claimed success.

The use of radio-isotopes in demonstrating loss of blood into the lungs in this condition was originally described by Apt et al. (1957) and by Doering and Gothe (1957). One of two patients studied with radio-iron by Frick, Brunner, Gasser, and Hitzig (1962) had been treated with prednisone, but the effect of treatment was not directly investigated.

So far as the authors of the present report are aware this is the first time radioactive techniques have been used to assess the effects of treatment. It is now apparent that clinical impressions of the progress of the disease may be misleading, and only by the application of such techniques is an accurate evaluation of any therapeutic regimen possible.

**SUMMARY**

The progress to a fatal termination of idiopathic pulmonary haemosiderosis presenting in a boy of 16 is described in detail. An unusual feature was the association with a left ventricular abnormality, distinguished by electrocardiographic changes and the presence of a myocarditis. The relationship of heart and lung changes is discussed.

Detailed studies of iron metabolism using radioactive iron and surface-counting techniques indicated that loss of blood into the lungs continued during clinical remission and throughout a relapse treated with a corticosteroid. Such techniques provide an accurate method of assessing alterations in the rate of blood loss into the lungs. A plea is made for the use of these techniques to assess the effect of therapy in this condition.

We should like to thank Mrs. J. D. Leask for the iron-clearance measurements and Mr. T. C. Dodds and Mr. J. Paul, of the Department of Medical Photography, University of Edinburgh, for the illustrations.

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