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Idiopathic Pulmonary Haemosiderosis and the Goodpasture Syndrome

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Idiopathic pulmonary haemosiderosis (I.P.H.) is a distinct clinical and pathological syndrome characterized by haemoptysis, iron-deficiency anaemia, diffuse pulmonary shadowing, haemosiderin-laden macrophages in the sputum, and brown induration of the lungs. Until recently this condition was regarded as an uncommon disease, practically confined to childhood; it is now being recognized with increasing frequency in adults, and Soergel and Sommers (1962), in a comprehensive study of the literature, reviewed 112 cases, including four new patients of their own. Twenty-one of these patients were 16 years or older when the disease was first diagnosed. Sprecace (1963) reported six patients, and Canfield *et al.* (1963) three patients, all of whom were 18 years of age or older; two of Sprecace's patients and all of Canfield's had, in addition, glomerular lesions in the kidneys, and hence represented a clinical variant of I.P.H. known as the Goodpasture (1919) syndrome. This syndrome, rare in children, is found predominantly in young adult males.

We now report a further three adult patients, two of whom are examples of the Goodpasture syndrome; the third patient has uncomplicated I.P.H.

Case 1

A 30-year-old man, with a past history of four to five years' underground gold-mining at Kalgoorlie and one to two months in the asbestos mine, Wittenoom Gorge, was admitted to Sir Charles Gairdner Hospital (formerly Perth Chest Hospital), Western Australia, in June 1962 with haemoptysis, anaemia, and a chest radiograph which showed diffuse bilateral "ground-glass" mottling, most pronounced in the right mid-zone. His only relevant past history was a previous admission to Kalgoorlie District Hospital in 1957 with a diagnosis of pneumonia. At that time he was found to be very anaemic and was transfused with 4 pints (2.3 litres) of blood. Thereafter he returned to work and was well until mid-May 1962 apart from a harsh smoker's cough and occasional blood-streaked mucoid sputum.

On examination he appeared fit but pale, with a chest expansion of 2½ in. (6.3 cm.). There were no other abnormal physical signs, such as heart murmurs, finger-clubbing, splenomegaly, petechiae, or purpura. The Hess test was negative. A chest radiograph on 5 July (Fig. 1) showed that there had already been some clearing of the "ground-glass" mottling seen on the pre-admission chest radiograph. Mantoux was negative to 1/1,000. Sputum was negative for acid-fast bacilli, but showed many haemosiderin-laden macrophages. E.C.G. was normal. Bronchoscopy was normal apart from a small quantity of blood clot in the right main bronchus. Vital capacity, forced expiratory volume, and ventilation equivalent were all normal. Blood examination showed an iron-deficiency anaemia with a haemoglobin of 8.8 g./100 ml., M.C.H.C. 29%, white-cell count 7,400/c.mm. (polymorphs 52%, eosinophils 6%), and an E.S.R. of 1 mm. in one hour (Westergren). Bone-marrow was normal. There was no evidence of loss of blood from any system other than the lung. Rectal examination and proctoscopy, barium-meal examination, and stool tests for occult blood were all negative. Urine microscopy showed no red cells or haemosiderin; there was no evidence of intestinal malabsorption. Serum iron was 29 μg./100 ml. (normal males, 80–170 μg./100 ml.), total iron-binding capacity 180 μg./100 ml. (normal males, 240–390 μg./100 ml.), and saturation 11% (normal males, 25–65%).

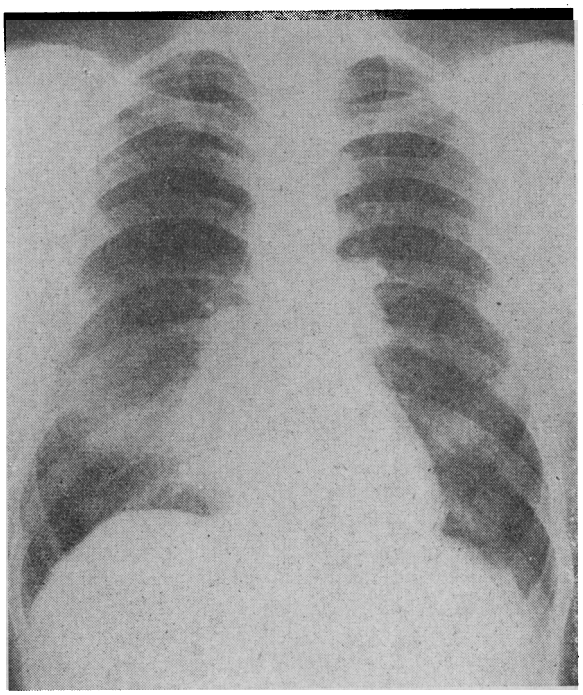

FIG. 1.—Case 1. Radiograph taken on 5 July 1962.

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On the basis of the above findings a diagnosis of idiopathic pulmonary haemosiderosis was made, being confirmed by needle biopsy of the lung, using the Jack needle (Smith, 1964). Biopsy material was taken first from the right lower lobe and later, after complete radiological clearing had occurred, from the left lower lobe. Both showed identical pictures—namely, a collection of brownish-pigment-containing cells in the alveoli and to a lesser extent in the interstitial connective tissue. The brownish pigment gave a strongly positive reaction to iron. There was no evidence of arteritis or necrotizing alveolitis in the biopsy material. There were some macrophages which contained doubly refractile needle-like crystals of silica. Liver biopsy was normal. Skin biopsy showed no evidence of iron storage. Detailed studies of radioactive iron were carried out. 11 μc ^{59}Fe combined with 1 mg. of ferrous sulphate as a carrier, was administered orally without fasting the patient, with a view to determining whether the radioactive iron was absorbed normally, and whether there was any significant increase in the deposition of radioactive iron over the lung fields. Faeces were collected daily until the daily faecal iron was less than 1% of the dose on two successive days. Surface counting with a scintillation counter over the heart, liver, spleen, kidneys, sacrum, and lungs was performed for 17 days. Total excretion of iron in the faeces was 51%, suggesting iron deficiency with excessive adsorption of iron. There was a 25% increase in activity over the lungs as compared with counts in normal patients. This suggested deposition of radioactive iron in the lungs.

While in hospital his haemoptysis gradually diminished, haemoglobin rose on ward diet plus oral iron, the chest radiograph cleared, and he was discharged. When seen again six months later, he was fit and well, with a clear radiograph. He was working in the north-west of Western Australia, and it has been impossible to obtain a recent chest radiograph.

Case 2

A female clerk aged 17 was admitted to Sully Hospital, South Wales, United Kingdom, on 4 August 1960 with a four-month history of recurrent small haemoptyses varying from blood-streaked sputum to 30 ml. of bright blood daily. She had also noted increasing fatigue and exertional dyspnoea. There was no relevant past history apart from a presumed tuberculous submandibular adenitis in 1953 treated with calciferol.

On examination she was afebrile, but pale. There was no finger-clubbing or clinical abnormality in her chest, heart, abdomen, or central nervous system. Blood-pressure was 120/90 mm. Hg. Her chest radiograph showed fine nodular shadows through both lower lobes with a calcified node in the left hilum. Sputum contained haemosiderin-laden macrophages on several occasions and were negative for acid-fast bacilli. Blood examination showed: haemoglobin 8 g./100 ml., M.C.H.C. 31% ; white count 6,000/c.mm., with a normal differential count ; E.S.R. 5 mm. in one hour (Westergren). There was no evidence of haemolysis. Coombs test, osmotic fragility, and bleeding, clotting, and prothrombin times were normal. Urine showed 1 g. of protein per litre of urine, and microscopy revealed many red blood cells and a few cellular casts ; there were no white cells. Blood urea was 30 mg./100 ml. Bronchoscopy and bronchography were normal. A lung biopsy specimen from both upper and lower lobes was obtained by right thoracotomy on 18 October 1960. Sections showed marked haemosiderosis with haemosiderin-laden macrophages packing the alveoli and dotted throughout the interstitial tissue with some increase in alveolar, reticular, and collagen fibres (Fig. 2).

The serum iron was 61 μg./100 ml. (normal female, 60–160 μg./100 ml.). After a loading dose of 600 mg. of ferrous sulphate the level rose to 146 μg./100 ml. six hours later. Skin biopsy showed no evidence of iron storage. Studies with radioactive iron showed a normal surface pattern but a very pronounced movement of iron into the bone-marrow. The clearance of radioactive iron from the plasma was entirely normal ; a red-cell survival study done with radioactive chromium revealed a normal chromium loss of 2.4%/day.

Ventilatory function tests revealed an indirect maximum breathing capacity of 69 litres per minute, with a forced vital capacity of 2.1 litres and a normal residual volume. There was marked hyperventilation on exercise while breathing air ; this was less marked on breathing oxygen. Although the mixed venous P_{CO_2} measured by the rebreathing method was normal at rest and the single-breath pulmonary diffusing capacity, using carbon monoxide, was at the lower limit of normal, it was felt that the marked exercise hyperventilation, together with the reduction in lung volume, was strongly suggestive of alveolar-capillary block.

Treatment with prednisone, 40 mg. daily, was begun on 1 November 1960 and later reduced to a maintenance dose of 10 mg. daily. Despite prednisone, haemoptyses continued and became more frequent. Review five months later showed that the diffusing capacity measured by the single-breath carbon monoxide technique had deteriorated from the previous level of 19.5 ml./min./mm. of mercury to 13 ml./min./mm.

In July 1961 urine still contained red blood cells and granular and cellular casts, and concentrated to only 1,018 after 12 hours' fluid deprivation. There was 1 g. of albumin per litre of urine. Blood urea varied from 30 to 50 mg./100 ml. Urea clearance was 73% of average normal, and creatinine clearance 85 ml./min. (normal 95–105 ml./min). An intravenous pyelogram showed good bilateral renal function.

Oxyphenbutazone was added to prednisone, but haemoptysis continued. By February 1962 oral iron could no longer maintain her haemoglobin, and over the next few months blood transfusions were given with increasing frequency. In June 1962, 22 months after her initial admission, splenectomy was performed because of rapidly increasing loss of weight, weakness, dyspnoea, and haemoptysis. Fig. 3 shows the chest picture on 6 July. There was a marked reduction in haemoptysis over the next two months. Subsequently, however, daily bleeding recurred and she died of a massive haemoptysis on 19 October 1962. Permission for necropsy was not obtained.

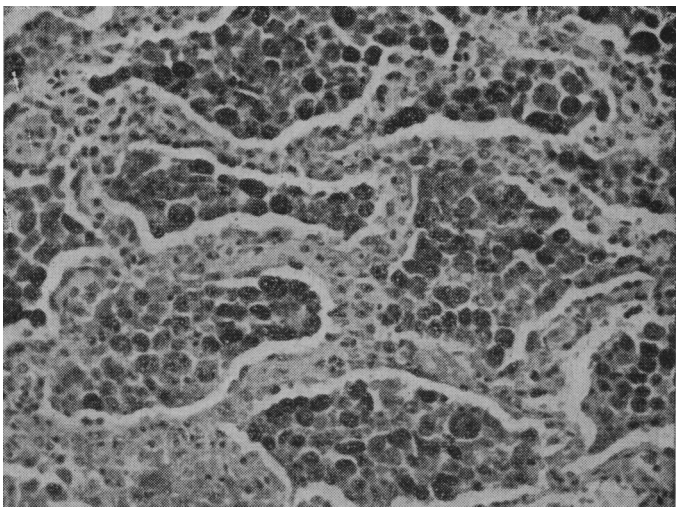

FIG. 2.—Case 2. Lung biopsy. High-power view showing alveoli packed with haemosiderin-laden macrophages and thickening of alveolar walls.

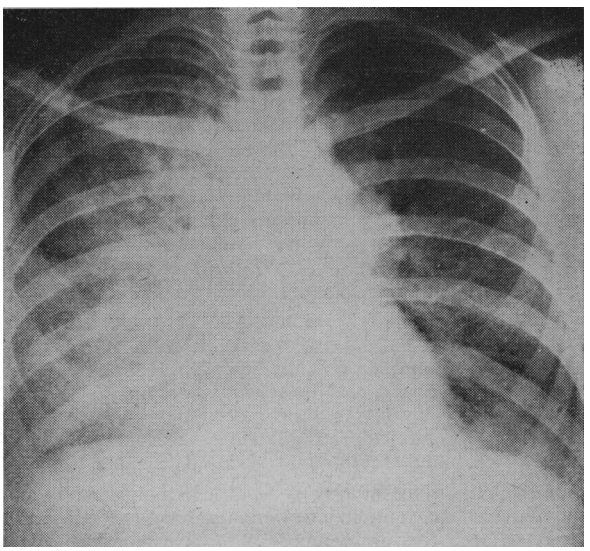

FIG. 3.—Case 2. Radiograph taken on 6 July 1962, three months before death.

Case 3

A 20-year-old apprentice baker was admitted to Sir Charles Gairdner Hospital, Western Australia, on 26 January 1963 after a fairly profuse haemoptysis of 24 hours' duration. He gave a three-month history of chronic cough and frothy sputum occasionally mixed with small quantities of fresh blood. He also complained of pallor, fatigue, weakness, and slight effort dyspnoea of three weeks' duration.

On admission he looked fit and seemed to be in good general condition. There were generalized rhonchi and scanty crepitations throughout the left upper lobe. There was no evidence of mitral-valve disease and no other findings of note.

A chest radiograph (Fig. 4) showed diffuse mottling throughout the right lung and upper and mid-zones of the left lung. Mantoux

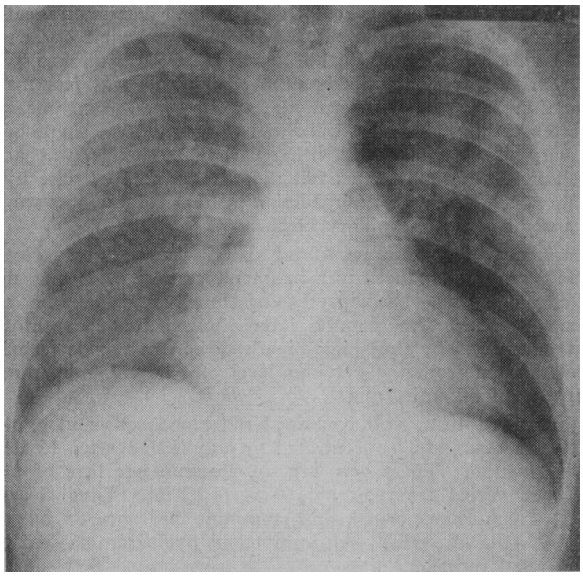

FIG. 4.—Case 3. Radiograph taken on admission, 26 January 1963.

test was negative to 1/100. The sputum showed no acid-fast bacilli or significant secondary pathogens, but there were large numbers of iron-containing macrophages. The haemoglobin was 7.7 g./100 ml.; P.C.V. 22%, M.C.H.C. 32%, platelets 120,000/c.mm. Prothrombin, bleeding, clotting, and thromboplastin generation times were all normal. The osmotic fragility test was normal, and there were no cold agglutinins. Total plasma protein 5.3 g./100 ml. Electrophoresis showed slightly raised alpha-2, beta-, and gamma-globulin. Serum iron was very low at 8 μg./100 ml. (normal males, 80–170 μg.), iron-binding capacity 190 μg./100 ml. (normal males, 240–390 μg.), saturation 4% (normal males, 25–65%). Vital capacity, forced expiratory volume, and ventilation equivalent were all normal. At least six specimens of urine showed a small amount of albumin with fairly large numbers of red cells, a few white cells, and granular and hyaline casts. Blood urea was normal. Needle biopsy of the right lower lobe, using the Jack needle, showed many iron-containing macrophages in the alveoli with a distinctly frayed appearance of the basement membrane but no necrotizing alveolitis and no arteritis. There were no siderocytes in the interstitial tissue.

Radioactive-iron studies were again made. In this case there was no conclusive evidence of a build-up of activity in the chest as in Case 1. Also, in contrast to Case 1, the result suggested a steady residual amount of iron in the kidneys. He was given 2 pints (1,140 ml.) of blood and oral iron. Haemoptysis diminished and chest radiography showed rapid clearance, suggesting that most of the shadowing was due to intrapulmonary bleeding. Subsequent radiographs were almost normal.

The patient has since been seen on several occasions as an outpatient. At his last visit, in mid-January 1964, he felt extremely well and had been free of haemoptysis for five months. His urine and blood count were entirely normal, and the chest radiograph could be classed as normal.

Discussion

The cause of both idiopathic pulmonary haemosiderosis and the Goodpasture syndrome is unknown. Possibilities considered in the past have been a virus, some irritating or allergenic substance which could possibly be related to environmental or occupational hazards, or perhaps an autoimmune mechanism. Sprecace (1963) reported that five out of six of his adult patients with I.P.H. were exposed to gasoline or its combustion products in concentration greater than the average for either military or civilian life, and suggested that more work could be done in recording details of such possible toxic factors in future cases. As regards an autoimmune mechanism, no definite proof has been obtained, although Chikamitsu (1940) induced a form of nephritis in rabbits by using an anti-rabbit-lung serum, and Eisen *et al.* (1950) have shown in experiments on rats that anti-lung serum contains components which specifically localize in the lungs and kidneys. Soergel and Sommers (1962), however, report that the serum of six patients failed to reveal any antibodies to human lung or kidney tissue.

It is still uncertain whether the Goodpasture syndrome is simply a variant of I.P.H., as believed by Rusby and Wilson (1960) and MacGregor *et al.* (1960), or represents a distinct disease entity, as suggested by Soergel and Sommers (1962). Another possibility is that it may be an early stage of polyarteritis nodosa, as suggested by Miles Walker and Joekes (1963). In one case of the Goodpasture syndrome Soergel and Sommers found a "degenerative splitting and partial dissolution of the alveolar capillary basement membrane which was not shown on the routine haematoxylin-eosin stain, together with swelling of the alveolar epithelium." They postulate that this basement-membrane change is not found in I.P.H., where the main defect appears to be an alveolar epithelium which is not only swollen but degenerated with shedding and hyperplasia of the alveolar epithelial cells associated with localized alveolar capillary dilatation. Soergel and Sommers (1962) seem to base this histological differentiation on their one case of the Goodpasture syndrome. A review of other necropsy findings and biopsy reports in the literature is not helpful; there is often a failure to mention the basement membrane as distinct from the alveolar epithelium and the type of stain used in each particular case. It appears, therefore, that more careful attention to detail in future biopsy and necropsy studies, and perhaps the use of electron microscopy, may clarify the situation. In the present state of knowledge we agree with MacGregor *et al.* (1960), who feel that young adults with I.P.H. seem liable to develop a rapidly progressive diffuse glomerulonephritis, characterized histologically by unusually numerous necroses in the glomerular tufts and an absence of arteritis.

With regard to the clinical features it must be remembered that not all patients with I.P.H. have overt haemoptysis, as it is now recognized that the amount of blood lost into the lung is out of all proportion to the actual amount expectorated. In some patients haemoptysis occurred only as a terminal event, and yet the iron content of washed and dried lung tissue was anything from 5 to 2,000 times greater than normal. Similarly, radiographic changes are not essential for diagnosis (Bronson, 1960). In an acute exacerbation the radiograph will almost always show some change, but the lung fields may clear rapidly and be classed as normal within a few days or weeks. Some patients may present with severe dyspnoea, fever, radiograph changes, and anaemia, and may be diagnosed as cases of "pneumonia," as was our first patient in 1957. The usual spontaneous clearing on the radiograph is then attributed to antibiotics and other therapy.

The prognosis of I.P.H. has until recently been regarded as grave, most patients dying after an average of three years from the date of diagnosis. It is reasonable to postulate that with increasing awareness of this disease entity many milder

cases may be recognized, with a better prognosis: this particularly applies to patients who present with small haemoptyses and iron-deficiency anaemia, with or without radiographic change. Our first patient is still alive and well six years after his first episode of haemoptysis and anaemia, and over this period he has remained well apart from one further episode in 1962. It has been suggested that steroids may alter the prognosis in some cases, although Soergel and Sommers (1962), after reviewing the literature, felt that long-term steroids, while possibly improving the patient's immediate prognosis, did not alter the ultimate progress of the disease. Most clinicians would agree that steroids should be tried in the seriously ill patient.

In the Goodpasture syndrome, where the prognosis is even more grave, steroids are thought by many to influence the course of the disease favourably. Fairley and Kincaid-Smith (1961) advised the use of steroids at an early stage before deterioration in renal function occurs. They state (personal communication, 1964) that three of their patients, all proved by renal biopsy, who were treated early while renal function was good, are still alive 30 to 36 months after diagnosis, whereas seven other cases, treated when renal function was poor, had died. Miles Walker and Joekes (1963) also report the case of a patient with a positive renal biopsy, who was given steroids, and is alive and symptom-free six years after diagnosis. Cases 2 and 3 are almost certainly examples of the Goodpasture syndrome, although, unfortunately, histological proof of the renal lesion was not obtained in either case. The second patient died despite the use of steroids, while the third seemed to have obtained a complete remission 18 months after diagnosis, without the use of steroids.

Summary

Three adult cases are reported; one had idiopathic pulmonary haemosiderosis alone, and two had an associated renal lesion (the Goodpasture syndrome). The patient with idiopathic pulmonary haemosiderosis is still alive and working six years after his initial haemoptysis. The second patient died of a massive haemoptysis two years after her initial symptoms despite the use of steroids. The third patient is still alive and well without steroids, and is in remission 18 months after diagnosis.

Idiopathic pulmonary haemosiderosis is probably more common in adults than hitherto believed, and should be considered in patients who present with radiographic shadowing and anaemia, with or without haemoptysis and with or without signs of renal involvement. Haemoptysis may be scanty or absent, and the chest radiograph may be clear except during an acute exacerbation. Lung biopsy, performed during a clinical remission, may be necessary to obtain histological proof of the disease, although the clinical picture is usually fairly characteristic.

Prognosis may be less grave than hitherto believed. There is no definite evidence that steroids appreciably alter the prognosis in idiopathic pulmonary haemosiderosis or the Goodpasture syndrome, although they are worthy of trial in severe cases.

The aetiology and pathogenesis is still unknown; autoimmunity may play some part. Further detailed histochemical and experimental studies are necessary to decide whether the Goodpasture syndrome is a variant of idiopathic pulmonary haemosiderosis or a separate disease entity.

Addendum

Since the paper was completed another patient with the Goodpasture syndrome has been seen at Sir Charles Gairdner Hospital. The patient, a woman aged 64, was admitted in May 1964 with a three-month history of progressive dyspnoea, weakness, and haemoptysis, and had noted haematuria for one week before admission. She was anaemic (haemoglobin 8 g./100 ml.) and the urine contained numerous red and white cells. Blood urea was 70 mg./100 ml. A chest radiograph showed diffuse nodular opacities. Needle biopsy of the lung revealed appearances compatible with pulmonary haemosiderosis. The patient's condition rapidly deteriorated, and she died in July 1964, four months after the onset of symptoms. Necropsy confirmed the clinical diagnosis of Goodpasture syndrome. We are grateful to Professor E. G. Saint for permission to mention this case. A detailed report will be published elsewhere.

Recently we have seen another case of idiopathic pulmonary haemosiderosis proved by lung biopsy in a female aborigine aged 20.

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