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SUMMARY
A brief history, together with the clinical features, possible aetiology and incidence of Stevens-Johnson syndrome, is given. An ultra-long-acting sulphonamide, sulphorthodimethoxine (Ro 4/4393), was given weekly to 480 healthy, newly recruited Bantu mineworkers in a clinical prophylactic trial against pneumonia. Three cases of severe bullous erythema multiforme (Stevens-Johnson syndrome) are presented following the use of this drug. All responded well to oral betamethasone. The suggestion is put forward that, as the reported incidence of the syndrome following ordinary long-acting sulphonamides is one or 2 cases per 10,000,000 doses, the ultra-long-acting sulphonamides possibly carry with them a greater risk, although the present series is too small for proof of this.

IDIOPATHIC PULMONARY HAEMOSIDEROSIS: A REVIEW AND REPORT ON TWO CASES*

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Although more than 100 cases of idiopathic pulmonary haemosiderosis (IPH) have been described, I do not think it superfluous to report new observations and to present a review of this baffling condition. Occurring in the absence of known causes of pulmonary haemosiderosis, this is a distinct clinical and pathological disorder resulting from repeated intra-alveolar haemorrhages, characterized by attacks of respiratory disturbances associated with anaemia. In the past, the diagnosis was most often made only at autopsy but, in recent years, as the rather typical manifestations of IPH have become more familiar to clinicians, an increasing number of cases have been diagnosed during life.

This paper, which is believed to be the second documented report in the South African medical literature, records 2 cases of IPH and draws attention to the varied clinical aspects of this disorder.

CASE REPORTS
Case 1
D.J., an 8-year-old Coloured male, had been ill for about a week before admission. He started coughing, becoming easily tired and short of breath, and had a small haemoptysis. A mild occasional cough had been his only symptom in the past.

He was found to be an acutely-ill child, very pale and dyspnoic. His temperature was 95°F, pulse rate 160/min, respiratory rate 80/minute and blood pressure 90/50 mm.Hg. He was not in cardiac failure; a grade 1/6 systolic murmur was heard over the mitral area and scattered, fine crepitations were present throughout both lung fields. The haemoglobin was too low to be recorded accurately on a Spencer haemoglobinometer. The leucocyte count was 15,000/cu.mm. with 80% neutrophils. The red blood cells were moderately hypochromic and the platelets were normal. An X-ray of the chest showed a diffuse, fine mottling of both lungs, with the apical regions somewhat spared, no detectable glandular enlargement and a normal cardiac shadow. The patient received penicillin and oxygen therapy, but died suddenly very soon after admission and before a blood transfusion could be commenced.

Fig. 1. Case 1. Section of the lung, showing alveolar wall thickening, intra-alveolar haemorrhages and haemosiderin-laden macrophages (Perl's stain).

At postmortem examination the lungs were found to be reddish-brown, firm and heavy, histologically showing (Fig. 1) some alveolar-wall thickening, extensive intra-alveolar haemorrhages and numerous iron-filled macrophages filling the alveoli in solid sheets. The rest of the organs showed no abnormalities.

Case 2
M.R., a Coloured female child, first presented at the age of 1 year with progressive pallor and listlessness of 1 week’s duration. Her birthweight was normal and her diet adequate. She had suffered from occasional respiratory infections in the past and there were no familial illnesses.

She was a little underweight, pyrexial and extremely pale but not distressed. Her chest was clear on auscultation, and apart from tachycardia and a soft apical systolic

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REFERENCES

I wish to thank Dr. C. M. Ross, dermatologist, who saw and advised on cases 1 and 2, and Dr. W. J. Bam of Roche Products (Pty) Ltd., whose cooperation was much appreciated. I should also like to thank Dr. A. M. Coetzee, Director of Medical Services, Rand Mines Limited, for his encouragement to publish this paper.
murmur, physical examination was not helpful.

The haemoglobin was 2 G/l 100 ml., the leucocyte count 12,000/cu.mm. with 70% neutrophils. The red cells were hypochromic, anisocytic and polychromatophilic, showing a reticulocytosis of 7% and 8 normoblasts per 100 nucleated cells. The platelet count was 350,000/cu.mm. and they were of normal appearance. The erythrocyte sedimentation rate was 5 mm. in the first hour. Urinalysis was normal. Bone-marrow examination showed a very reactive erythroid series and mild iron deficiency, but was otherwise normal. A chest X-ray showed mild, blotchy shadowing of both upper lobes and a normal cardiac outline. The electrocardiogram was within normal limits for the patient's age. Blood chemistry, including bilirubin and urea, was not disturbed. The serum-iron level was 30 μg./100 ml., serum-folate and vitamin B12 levels being normal. The stools, which were of normal appearance, showed no occult blood, parasites or pathogens. Blood culture, Wassermann, agglutination, and histoplasmosis complement-fixation tests, cold agglutinins and tuberculin skin-test all proved to be negative. Extensive hematological studies failed to produce any evidence of intravascular haemolysis.

As the anaemia seemed to be of an iron-deficiency type, although its cause was far from clear, the patient was treated with iron and folic acid and received a blood transfusion. A reticulocytosis of up to 15% occurred and thereafter she maintained her haemoglobin at around 10 G/l 100 ml.

The other aspect of the problem was evidence of persistent pulmonary pathology on X-ray. This took the appearance of bilateral, ill-defined, patchy infiltrations which soon after admission became rapidly progressive and diffuse for 2 weeks (Fig. 2). Then at one stage they disappeared completely, only to be present again shortly afterwards with marked fluctuation in extent. Repeated tuberculin skin-tests were negative, the electrophoretic pattern of the serum proteins and the sweat electrolytes were normal. Swabs taken from the nasopharynx revealed a klebsiella organism on a few occasions. Gastric washings repeatedly showed no haemosiderin-laden macrophages, and were negative on Kirschner culture and guinea-pig inoculation.

Numerous courses of a variety of antibiotics, including a 3-month trial of antituberculous therapy, did not seem to result in any improvement. However, despite the X-ray appearances, the child remained well, apyrexial and asymptomatic, maintaining her haemoglobin on haematinics, although weight gain was slow. She was eventually discharged on iron supplements.

She reappeared 2 months later, having remained well and asymptomatic until 1 week before admission when she became short of breath, vomited a little blood on one occasion and was noticed to have become progressively paler. She was again extremely pale, mildly dyspnoeic with a tachycardia and only a few scattered fine crepitations were heard over the chest. Her haemoglobin was 2 G/l 100 ml. with a 5% reticulocytosis, and most of the tests previously performed were repeated and again were not helpful. X-ray of the chest still showed diffuse, poorly-defined pulmonary infiltrates with very little clearing being evident. She was treated with antibiotics, haematinics and a blood transfusion, and improved rapidly. Her parents were traced and any common or rare cause of haemolytic anaemia was excluded. The child was then transferred to a convalescent home on iron therapy, and was followed-up at 2-weekly intervals.

She was readmitted a few months later when she developed a 'cold' with persistent coughing, some dyspnoea and moderate pyrexia. Scattered evanescent crepitations were present over both lungs and an X-ray of the chest showed, as before, an extensive, patchy infiltration with now obvious paratracheal adenopathy.

No treatment was instituted and she became totally asymptomatic after a few days.

She was then kept in hospital for a further attempt at elucidating the diagnosis. Seven months after the onset

Fig. 2. Case 2. Chest X-ray showing bilateral diffuse blotchy shadows.

Fig. 3. Smear from bronchial aspirate showing haemosiderin-laden macrophages (Perl's stain).
of symptoms, this was still obscure. The features that dominated were a diffuse alveolar process of fluctuant severity associated with repeated episodes of acute anaemia. The laboratory studies obtained so far, had not offered much help in positively establishing a diagnosis. Before deciding on a long-considered lung biopsy, a bronchial lavage was performed under general anaesthesia, and smears from the aspirate showed numerous macrophages which, when stained specifically for iron, were seen to be heavily loaded with haemosiderin (Fig. 3), thus demonstrating loss of blood into the lungs. Evidence of milk sensitization was absent, as cow's milk gave a negative intradermal reaction and serum precipitins were not found.

As the clinical course in this case pointed to IPH and siderophages were found in the bronchial aspirate, a lung biopsy was not needed to confirm the diagnosis. The child thrived and on maintenance iron therapy has been free of symptoms for the last 6 months.

**DISCUSSION**

**Incidence and Onset**

Until recently considered a rare disease occurring almost exclusively in children, IPH was seldom recognized during life. The first anatomical description was made by Virchow in 1864 who reported 'brown lung induration' in young girls with no evidence of cardiac disease. This was followed in 1931 by the histopathological study of 2 cases diagnosed at autopsy by Ceelee. A better knowledge of the disorder thereafter led to an increasing number of well-documented reports (over 100 have been published to date) from many parts of the world, including South Africa. Similarly, the number of cases diagnosed during life also increased.

The disease can occur at any age, the onset of symptoms ranging from an age of 4 months to 47 years. It is commoner in childhood, but in 1 out of 5 reported cases it has appeared for the first time in adult life. There is no heredo-familial tendency or sex predilection and a particular regional or seasonal incidence has not been observed.

**Clinical Course**

The essential feature of IPH is intrapulmonary haemorrhage, and the intensity and duration of the haemorrhages usually determine the clinical course. The classical picture associates an iron-deficiency anaemia, dyspnoea with blood-stained sputum or frank haemoptysis often occurring in bouts, and X-ray evidence of patchy bilateral lung infiltrations of variable intensity.

Although no typical pattern is followed, in general the disease evolves in the following manner: The onset is often insidious and fatigability, pallor, abdominal pain and failure to gain weight are symptoms which easily lead to an incorrect diagnosis. However, mild continuous intrapulmonary bleeding will eventually cause a chronic cough and occasionally the sputum may be blood-stained. Pulmonary changes may already be present on X-ray but not uncommonly are totally absent for a while. After a period of time varying from a few weeks to several years, an acute attack occurs, precipitated by a sudden and severe intra-alveolar haemorrhage. It is often the first indication of the disorder, in many instances terminating fatally, as illustrated by the first case reported in this article. These episodes are characterized by the coexistence of acute respiratory distress and anaemia. The patients appear very pale with a persistent cough; some of them complain of pain in the chest or abdomen, and may have polyarthralgia. Young children are often extremely irritable and restless. A mild pyrexia and occasionally slight jaundice may be noted. External bleeding varies from slight streaking of the sputum to frank haemoptysis; in young children the blood is frequently swallowed, and haematemesis and melaena occur. On auscultation, the lung fields may reveal a few scattered rhonchi or fine crepitations, but are often strikingly clear. A haemorrhage, systolic murmur is heard over the precordium, and hepatosplenomegaly and generalized lymphadenopathy have occasionally been observed. The acute anaemia which develops is usually out of proportion to the intensity of the haemoptyses, and often severe enough to necessitate an emergency blood transfusion. Chest X-rays show ill-defined blotchy infiltrations, occasionally sparing the apices and costophrenic angles; mild cardiomegaly has also been noted. The electrocardiogram rarely shows abnormalities. After a few weeks, the symptoms disappear, the anaemia gradually improves, even without therapy, and the X-ray appearances may return to normal.

The disease then follows a course of exacerbations and remissions over some months or even years. During periods of apparent remission the patient may remain relatively asymptomatic, or become increasingly anaemic without any lung symptoms. Less dramatic episodes may recur at intervals due to moderately severe intra-alveolar haemorrhages causing mild respiratory symptoms, while sometimes the anaemia worsens and the chest X-ray shows patchy infiltration. These subacute episodes are usually very transient and are mostly misdiagnosed.

The frequency and severity of the acute attacks vary. Most patients who survive eventually develop pulmonary haemosiderosis and fibrosis. They are underweight, anaemic, easily tired, complain of chronic cough or exertional dyspnoea and occasionally have clubbing of the fingers. The radiological changes become permanent, showing perihilar reticulation, miliary stippling and mediastinal lymphadenopathy. In a few patients a spontaneous, permanent remission seems to have taken place. Many others survive for very long periods, although the pulmonary haemorrhages still occur. Death from pulmonary insufficiency and right heart failure is rare, massive haemorrhage being the usual cause. This may occur at any time, even in cases where a long remission of many years had appeared to be permanent.

**Laboratory Findings**

A hypochromic, microcytic anaemia is regularly present, with a tendency to partial correction during periods of remission. After acute bleeding episodes, the serum unconjugated bilirubin and urinary urobilinogen may be transiently elevated, and signs of active blood regeneration may be present, such as increased reticulocyte count with numerous peripheral normoblasts and marked erythroid hyperplasia in the bone marrow. Leucocytosis is common during exacerbations and an unexplained eosinophilia may be present. Serum-iron levels are low, with an elevated iron-binding capacity. No clotting defects, evidence of intravascular haemolysis or abnormalities of the
platelets, serum proteins and sedimentation rate have been observed. Using $^{59}$Fe and red cells tagged with $^{51}$Cr it has been shown that the anaemia of IPH is simply due to blood loss into the lungs, where excessive iron gets stored and is not available for haemoglobin synthesis.\(^6\) Continuous intra-alveolar bleeding occurs even in asymptomatic patients.\(^2\) The Coombs test was weakly positive in one patient and a few cases had slightly elevated titres of cold agglutinins. No bacteria or viruses have been isolated as aetiological agents. The LE phenomenon has never been demonstrated. There are few reports of detailed pulmonary function and right heart catheterization. The Coombs test is rarely shown a significant elevation of pulmonary artery pressure.

**Diagnosis**

When the illness presents in its typical form and is characterized by recurrent episodes of respiratory symptoms, mainly dyspnoea, cough and haemoptyses, with an associated anaemia, correct diagnosis presents no problems and rests on:

1. The observation of specific X-ray changes consisting of fluctuant diffuse blotchy shadowings which represent the acute lesions, and a slowly developing permanent reticular pattern due to haemosiderin deposition and early interstitial fibrosis.\(^5\)

2. The existence of a posthaemorrhagic type of anaemia.

3. The demonstration of siderophages of pulmonary origin. An outstanding clinical feature in the history is the occurrence of ‘acute attacks’ in critically ill patients.\(^1\)

Diagnostic difficulties occur when the symptoms are few and atypical. An awareness of the clinical entity together with systematic, specific investigations will be necessary to recognize these forms of the disease. IPH may show itself as an obscure iron-deficiency anaemia or may often mimic severe haemolytic crises, many cases being severely anaemic without respiratory symptoms or X-ray changes. Subacute attacks are often misdiagnosed as severe upper respiratory infections or virus pneumonia. Small children often vomit swallowed blood and present with haematemesis and occasionally with melaena. Many cases have been diagnosed as chronic granulomatous bronchopneumonia and have often been treated for tuberculosis, as extensive X-ray changes, including a miliary pattern and mediastinal lymph nodes, may be present with relatively few symptoms. In numerous instances, haemoptysis never occurs.

The demonstration of continuous blood loss into the lungs by the finding of haemosiderin-laden macrophages of pulmonary origin has been considered diagnostic of IPH,\(^1\) provided passive constriction due to other causes can be ruled out. These cells, when stained for iron, may be found in smears of sputum or gastric washings. In their absence, lung biopsy by needle-aspiration\(^9,10\) or open thoracotomy\(^11\) will be necessary to confirm the diagnosis. In many instances, particularly in children, no sputum is present, siderophages are not found in the gastric contents and is there any evidence of blood in the faeces. For many months this was the case in the second child reported in this article, despite repeated tests. Before resorting to lung biopsy, it was decided to make use of diagnostic bronchial lavage which, in recent years, has provided much valuable information in chronic pulmonary disease.

This simple procedure, in the hands of a paediatric anaesthetist, carries no risk and, had it been done earlier, would have saved this child unnecessary investigations and protracted hospitalization.

**PATHOLOGICAL FINDINGS**

At postmortem examination the lungs are heavy, firm, reddish-brown in colour and their iron content is greatly increased.\(^12,13\) Haemosiderin is only found in the lungs and mediastinal lymph nodes which are often enlarged. Degeneration, excessive shedding, hyperplasia of the alveolar epithelium and marked local alveolar capillary dilatation have recently been considered specific of IPH.\(^13\) Intra-alveolar haemorrhages with haemosiderin-laden macrophages are diffusely present throughout the lungs, together with fragmentation of the elastic fibres and interstitial fibrosis. Mild right-ventricular dilatation and hypertrophy have often been noted.

**PATHOGENESIS**

The cause of the intra-alveolar haemorrhages responsible for the varying symptomatology of IPH remains obscure and the physiopathological mechanism is still at the hypothetical stage. The condition was originally thought to be due to primary degeneration of the elastic tissue of the lung but these morphological alterations are now regarded as secondary to the haemorrhages. Episodes of intermittent pulmonary hypertension due to a defective vasomotor control were suggested by some authors,\(^10,15\) but have not been substantiated by catheterization studies. Steiner,\(^15\) among other workers, considers IPH to have an immunological basis with the lung alveoli as the shock tissue, and as evidence of this he points out the eosinophilia and reticulo-endothelial hyperplasia, the presence of cold agglutinins in some cases, the occasional positive Coombs test and the satisfactory results sometimes obtained with steroids, splenectomy and immunosuppressive therapy. From extensive histological studies, Soergel and Sommers\(^16,17\) suggest, on the other hand, that a congenital abnormality of alveolar growth and function leads to extensive degeneration and hyperplasia of alveolar epithelial cells, thus critically affecting the mechanical stability of the capillaries. Heiner et al.\(^17\) reported 6 infants with illnesses similar to IPH who had positive intradermal tests and serum precipitins to cow's milk, with disappearance of symptoms when milk was removed from the diet. In 7 patients with proved IPH, however, as in the child reported here, evidence of milk sensitization was not found.

To add to these differing views, IPH has been recorded in association with other disorders: myocarditis,\(^10\) glomerulonephritis,\(^18\) and rheumatoid arthritis.\(^18\) The association of glomerulonephritis with pulmonary haemosiderosis has been reported in more than 50 adult cases and is regarded as a definite clinical entity under the name of Goodpasture's syndrome. It almost exclusively affects young adult males and progresses rapidly from haemoptysis and anaemia to severe, usually fatal, glomerular disease. There have been 9 cases in children, but the prognosis is better than in adults. Soergel and Sommers\(^10\) think it necessary to regard IPH as a separate entity from Goodpasture's syndrome as they failed to demonstrate an antigenic identity between the alveolar and glomerular
Until pathologic and causative uncertainties are clarified and more prolonged therapeutic trials provide a better knowledge of the disease, withdrawal of milk from the diet and the use of steroids and immunosuppressive agents, in addition to essential supportive care, are worthy of trial in severe or rapidly deteriorating cases.

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DIE DOKTER EN DIE DUIKER*

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Gedurende die afgelope twee jaar gaan mense al hoe meer onder de water rondloer, hetsy vir ontspanning of om te werk. Veral oor naweke is daar 'n magdom van swembeweging, wat naby vergelykbaar is met die aanspansende beweging van duikers of kunslongduikers.

Fysika
Die lugdruk by seeppiele is ongeveer 15 lb./sq.dm en 33 voet onder seeppiele vermeerder die druk met 'n atmosfeer (d.i. ± 1 lb./sq.dm./voet). So by sal die druk by 66 voet 3 atmosfore absoluut wees. Volgens die wet van Boyle is die uitsetting of inkrimping van gasse vir dieselfde vertikale beweging, baie groter nader aan die oppervlakte.

*Referaat gelever tydens die 46ste Suid-Afrikaanse Mediese Kongres (M.V.S.A.), Durban, Julie 1967.