BILHARZIAL PULMONARY HYPERTENSION IN NATAL*

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In 1939 Shaw and Ghareeb[1] published their necropsy findings on 282 cases of bilharzia in Egypt. They reported bilharzial involvement of the lungs in 33% of their series, but in 2% massive embolization of bilharzia ova had resulted in obliterative pulmonary arteriolitis, pulmonary hypertension and death from right ventricular failure.

Numerous further reports of bilharzial cor pulmonale have emanated from Egypt,[2-4] Brazil[5,6] and Puerto Rico,[7] all areas where *Schistosoma mansoni* is endemic. More recently reports have come from Iraq[8] where *Schistosoma haematobium* alone is endemic.

Reports of this fatal complication of bilharzia from Africa south of the Sahara have been very few. Gelfand[9] has described one case in Southern Rhodesia and a few cases have been reported from West Africa.[10-12] From East Africa Williams[13] published one case in 1958 and more recently Turner[14] reported 5 cases from Uganda and Kenya. We know of no previous published reports of this complication of bilharzia from the Republic of South Africa, although the diagnosis has been made twice before in Durban, once by Houghton,[15] whose patient was a Bantu male aged 31 years in whom the diagnosis was confirmed at necropsy, and once by Bhagwandeen,[16] a necropsy diagnosis in an Indian boy aged 14 years. Yet *S. haematobium* is endemic over a large part of the country and *S. mansoni* and *S. haematobium* coexist in Natal.

Within a period of 18 months 5 cases of cor pulmonale attributable to bilharzial obliterative pulmonary arteriolitis have been seen at our cardiac clinic, suggesting that this complication of bilharzia probably occurs more frequently in Natal than has hitherto been suspected.

CASE REPORTS

Case 1

A Bantu male aged 10 years was first seen on 29 September 1965, with a history of increasing exertional disability for 2 years with a sudden increase in severity during the preceding 2 weeks. He had had untreated haematuria 'for several years'.

On initial examination he appeared to be a well-nourished boy with no pitting oedema, cyanosis or pallor. The peripheral pulses were equal and of poor volume. The jugular venous pressure was elevated 1 cm. water with a pronounced 'a' wave. A visible and palpable heave was found over the entire left precordium.

The first heart sound at the apex was loud. The second heart sound was narrowly split, with accentuation of the pulmonary component, followed by an early diastolic murmur. A third heart sound was present at the 4th left intercostal space.

There was a tender hepatomegaly 4 cm. below the costal margin but no splenomegaly. Hyperpnoea without other signs of respiratory disease was striking.

Special investigations gave the following results: Haemoglobin concentration was 15·4 G/100 ml. and white cell count was 6,000/cu.mm. (eosinophils 840/cu.mm.). Viable ova of *S. haematobium* were present in the urine and ova of *S. mansoni* were present in the stool. The chest radiograph (Fig. 1) showed moderate enlargement of the

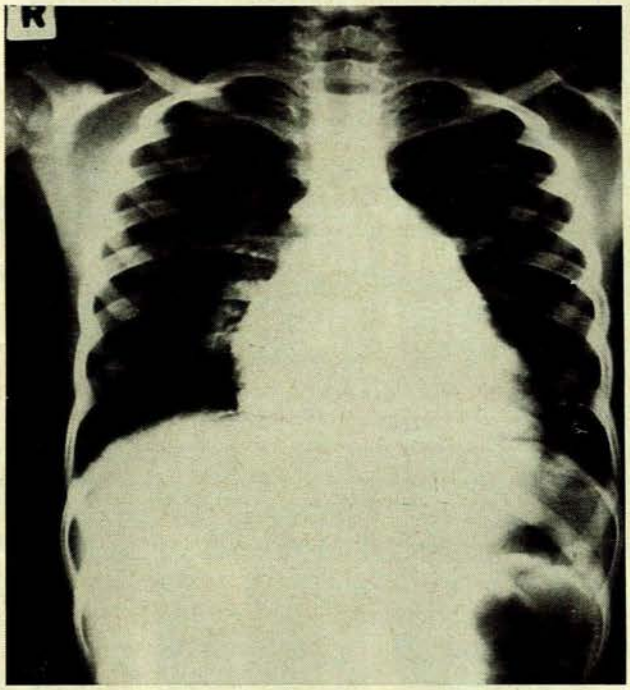

Fig. 1. Anteroposterior chest radiograph of case 1.

*Date received: 1 July 1968.

TABLE I. CARDIAC CATHETERIZATION RESULTS

Case No.	*RA mean*	*RV*	*MPA mean*	*Wedge mean*	*LV*	*Aorta*	*Arterial O_2 sat.*	*CI/litre min./sq.m.*	*PVR / SVR* %
1	**10**	110/6-12	80	4	125/0-5	125/90	96%	1·85	80
2	19	80/5-22	45	4	100/-2-5	100/85	92%	1·63	62
3	**14**	110/2-20	70	5·5	100/2·5-7·5	110/85	95%	1·58	97
4	16	125/0-25	87	7	115/0-10	115/85	97%	1·68	89

All pressures recorded in mm. of mercury.
RA = right atrium; RV = right ventricle; MPA = main pulmonary artery; Wedge = pulmonary artery wedge (indirect left atrial pressure); LV = left ventricle; O_2 sat. = oxygen saturation; CI = cardiac index in litres per minute per square metre of body surface area; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance.

heart, particularly of the right atrium and the main pulmonary artery. The peripheral pulmonary vascularity was within normal limits. Right axis deviation and severe right ventricular pressure overload were detected on the ECG (Fig. 2). Cardiac catheterization (Table I) showed pulmonary hypertension with no evidence of primary cardiac disease. Low vital capacity with no evidence of obstructive airways disease was recorded by spirometry (Table II).

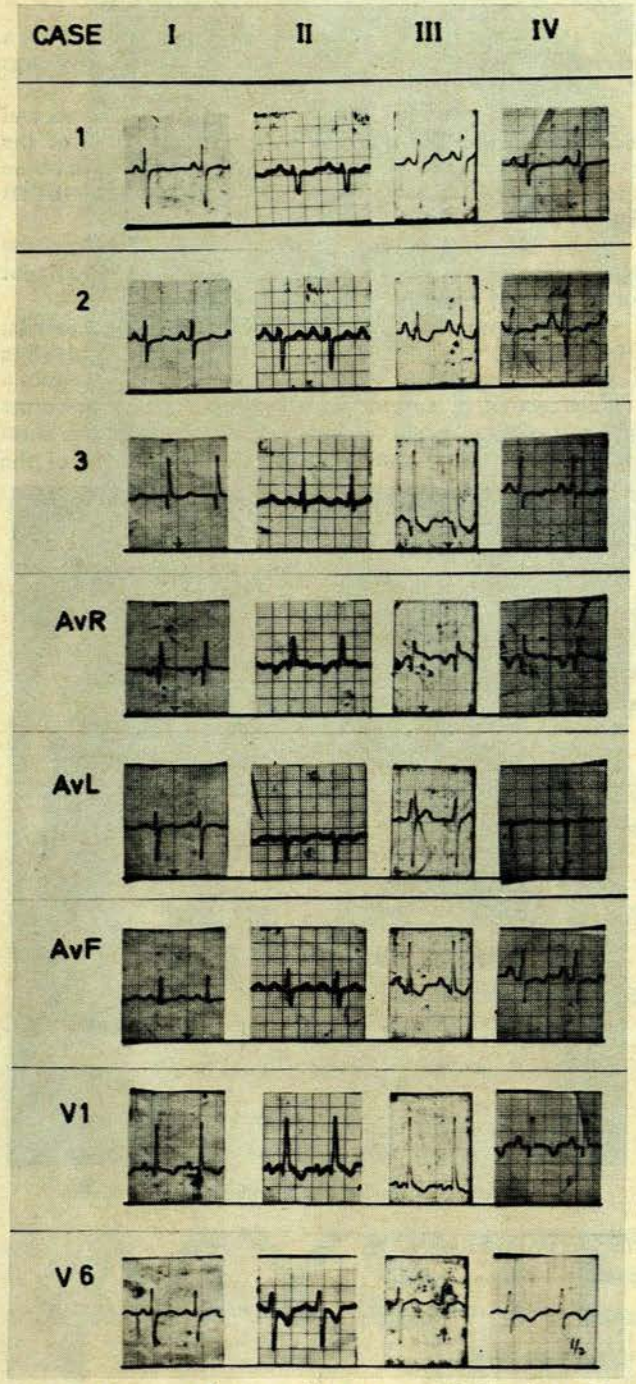

Fig. 2. Electrocardiograms in 4 cases of bilharzial pulmonary hypertension, showing right axis deviation, prominent P waves in lead II, a qR pattern followed by T inversion in lead V_1, and deep S waves in lead V_6. Right bundle-branch block is present only in case 2.

TABLE II. SPIROMETRY RESULTS

Case No.	*Vital capacity (VC)*	*Predicted VC*	*FEV_1 % of VC*	*FEV_2 % of VC*	*FEV_3 % of VC*
1	1·125	2·5	97	100	100
2	1·23	2·6	91	97	100
3	1·36	2·6	97	100	100
4	2·35	3·3	85	94	100

$FEV_{1,\ 2}$ and $_3$ = forced expiratory volume in the first 1, 2 and 3 seconds, respectively.

On lung biopsy extensive obliterative arteriolitis in association with bilharzial ova was found.

Right heart failure was controlled in hospital by treatment with digoxin and diuretics. Removed from hospital by his parents, he was readmitted 2 weeks later in gross right heart failure and died shortly after admission.

At necropsy bilharzial obliterative pulmonary arteriolitis was found with involvement of the bladder by *S. haematobium* and of the bowel by *S. mansoni*.

Case 2

A Bantu male aged 70 years was admitted on 10 May 1966 with a history of increasing effort disability for more than 2 years, with onset of dragging abdominal pain and swelling of his legs for 1 week. He had had untreated haematuria 'for several years'.

He was a well-nourished boy with gross dependent oedema. The jugular venous pressure was elevated 4 cm. water with a pronounced 'a' wave. The peripheral pulses were all of poor volume and the apex of the heart could not be defined. A marked heave was present over the left precordium. Auscultation revealed fine splitting of the second heart sound with accentuation of the pulmonary component and an early diastolic murmur of pulmonary valve incompetence. A third heart sound was heard at the left sternal border. There was a tender hepatomegaly 8 cm. below the costal margin but no splenomegaly. Hyperpnoea with no other signs of respiratory disease was striking.

Special investigations revealed the following: Haemoglobin concentration was 13·8 G/100 ml. and white cell count was 10,000/cu mm. (eosinophils 3,600/cu.mm.). Viable ova of *S. haematobium* were present in the urine and no parasites were found in the stool. The chest radiograph (Fig. 3) showed a massive generalized increase in the heart shadow obscuring the hilar shadows. The peripheral pulmonary vascular markings were poor. On ECG examination (Fig. 2) right axis deviation and right ventricular pressure overload with right bundle-branch block were evident. Cardiac catheterization confirmed the diagnosis of pulmonary hypertension without primary cardiac disease (Table I). Spirometry showed low vital capacity with no evidence of obstructive airways disease (Table II). On lung biopsy pulmonary bilharziasis with obliterative arteriolitis was found.

Treatment with digoxin and diuretics produced initial improvement but recurrent acute episodes of right heart

failure occurred and the patient eventually died in intractable right heart failure one month after his admission to hospital.

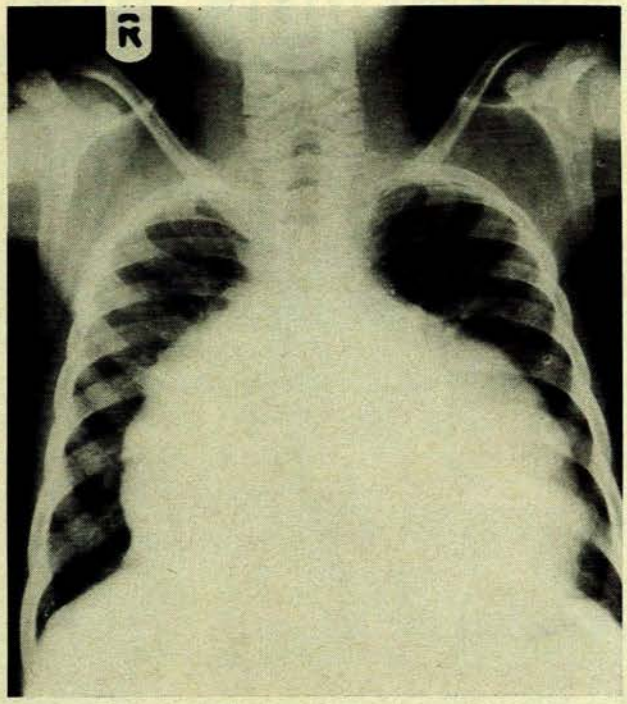

Fig. 3. Chest radiograph of case 2.

At necropsy bilharzial obliterative pulmonary arteriolitis and involvement of the bladder by *S. haematobium* and of the bowel by *S. mansoni* were found.

Case 3

A Bantu male aged 10 years was admitted on 21 September 1966 with a history of increasing exertional disability for more than 2 years. A dragging pain in the abdomen and swelling of limbs and abdomen had been present for 2 weeks. Untreated haematuria had been present for a long time.

Initial examination showed a well-nourished boy with massive dependent oedema. The jugular venous pressure was elevated 8 cm. water with a pronounced 'v' wave. There was marked left precordial pulsation, but the apex of the heart could not be defined. A pansystolic murmur of tricuspid valve incompetence was heard maximally at the 4th left intercostal space. The second heart sound was narrowly split with accentuation of the pulmonary component, followed by a short early diastolic murmur. A third heart sound was heard at the left sternal border. The liver was enlarged 7 cm. below the costal margin; it was pulsatile and tender to palpation but there was no splenomegaly. Hyperpnoea without other signs of respiratory disease was present.

Special investigations showed: Haemoglobin concentration was 12·5 G/100 ml. and white cell count was 12,000/cu.mm. (eosinophils 1,200/cu.mm.). Viable ova of *S. haematobium* were present in the urine but no abnormality was found in the stool. The chest radiograph showed marked enlargement of the heart, in particular the right ventricle and right atrium, and enlargement of the main pulmonary artery with normal peripheral vascular markings. On ECG examination (Fig. 2) right axis deviation and right ventricular pressure overload were detected. Cardiac catheterization (Table I) showed the presence of pulmonary hypertension without evidence of primary cardiac disease. Low vital capacity without evidence of obstructive airways disease was found on spirometry (Table II). On liver biopsy pigment in the Kupffer cells was in keeping with bilharzial involvement. Lung biopsy was not undertaken.

Right heart failure was controlled by treatment with digoxin and diuretics. A course of niridazole, 750 mg. daily, was given for 7 days. No toxic effects were observed clinically or electrocardiographically during treatment and for a period of 30 days thereafter; repeated examination of the urine revealed no viable ova of *S. haematobium* 30 days after treatment was completed.

After 3 months in hospital he was discharged home on maintenance digoxin and diuretic therapy.

Case 4

A Bantu male aged 14 years was admitted on 24 February 1967 from Edendale Hospital, Pietermaritzburg, where he had been treated for congestive cardiac failure since August 1966. There was no history of haematuria.

He was a well-nourished boy with no pitting oedema. The jugular venous pressure was elevated 2 cm. water with a pronounced 'v' wave. The apex of the heart was felt in the 5th left intercostal space in the anterior axillary line. A marked heave was palpable over the left precordium. A pansystolic murmur of tricuspid valve incompetence was heard at the lower end of the sternum. The

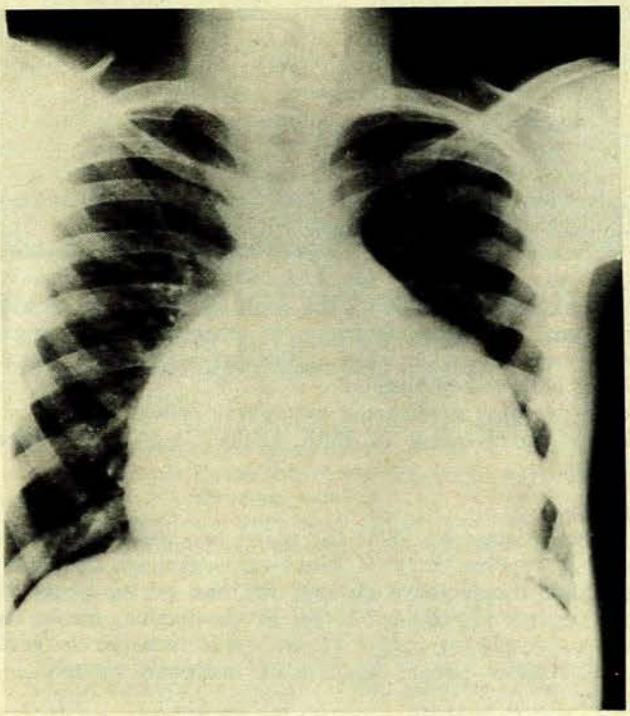

Fig. 4. Chest radiograph of case 4.

second heart sound was narrowly split with accentuation of the pulmonary component, followed by an early diastolic murmur of pulmonary valve incompetence.

The liver was enlarged 3 cm. below the costal margin and was pulsatile. The spleen was not felt. Hyperpnoea with no other evidence of respiratory disease was present.

Special investigations showed: Haemoglobin concentration was 13·5 G/100 ml. and white cell count was 7,000/cu.mm. (eosinophils 2,170/cu.mm.). No abnormality was discovered in the urine but ova of *S. mansoni* were present on rectal biopsy. The chest radiograph (Fig. 4) showed massive enlargement of the heart obscuring the hilar shadows. The peripheral pulmonary vascular markings were poor. On ECG examination (Fig. 2) right axis deviation and right ventricular pressure overload were evident. Cardiac catheterization (Table I) showed pulmonary hypertension with no evidence of primary cardiac disease. Low vital capacity with no evidence of obstructive airways disease was registered on spirometry (Table II). Lung biopsy was not undertaken.

Right heart failure was controlled by treatment with digoxin and diuretics. A course of niridazole, 750 mg. daily, was given for 7 days without any deleterious clinical or electrocardiographic effect during the period of treatment or thereafter for 30 days. After 8 months in hospital he was discharged on maintenance therapy of digoxin and a diuretic.

Case 5

A Bantu female aged 10 years was admitted on 13 February 1967 with a history of swelling of the feet, severe effort dyspnoea, cough and occasional vomiting for one week only. Terminal haematuria had been present for 1 year. Initial examination showed a well-nourished girl, in extremis with marked hyperpnoea, barely palpable peripheral pulses, dependent oedema and distension of the jugular veins where a 'v' wave was present. The first heart sound was loud at the apex; a pansystolic murmur of tricuspid valve incompetence was heard at the lower left sternal edge and the second heart sound was narrowly split with accentuation of the pulmonary component, followed by an early diastolic murmur of pulmonary valve incompetence. There was a tender hepatomegaly 3 cm. below the costal margin, but no splenomegaly.

Special investigations showed: Haemoglobin concentration was 16·2 G/100 ml. The chest radiograph showed moderate enlargement of the heart with large main and proximal pulmonary arteries. No other clinical investigations could be undertaken as this patient died soon after being admitted to hospital.

At necropsy a bilharzial pulmonary arteriolitis and bilharzial involvement of both bladder and bowel were found.

Pathology

Lung biopsy was done for us on two patients (cases 1 and 2) by Prof. B. T. le Roux via a standard but modified left thoracotomy through the bed of the sixth rib without rib resection. The tip of the lingula, measuring approximately $1\frac{1}{2}$ cm. × $\frac{1}{2}$ cm., was removed in each case. Neither patient was unduly distressed by thoracotomy.

Histology revealed parenchymatous pseudotubercles lying in close proximity to small pulmonary arteries (Fig. 5). Bilharzial ova were seen in some of these lesions, being either calcified or ingested by foreign-body giant cells (Fig. 6). Identification of the ova as regards species

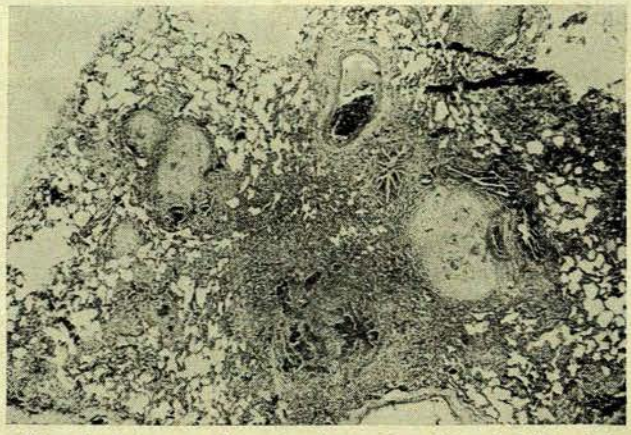

Fig. 5. Lung section showing parenchymal bilharzial pseudotubercles (H & E × 60).

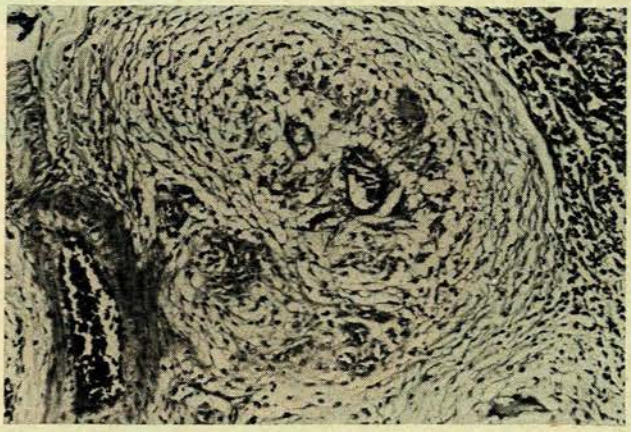

Fig. 6. Lung section showing a bilharzial pseudotubercle, a central giant cell containing a distorted schistosomal ovum (H & E × 500).

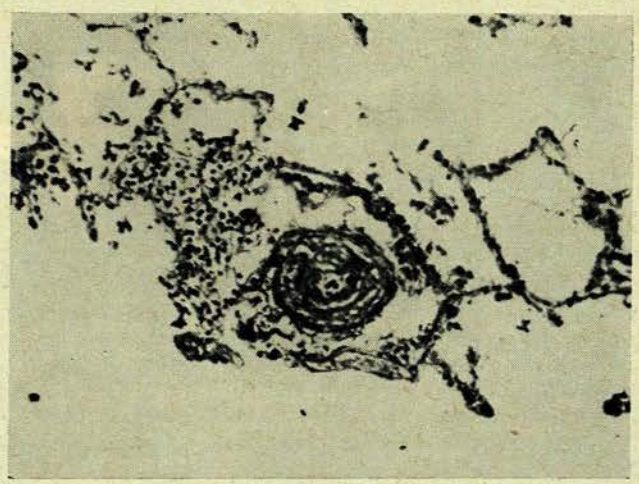

Fig. 7. A pulmonary arteriole not related to ova, but showing intimal thickening (H & E × 500).

was not possible on account of their distortion. Some of the tubercles were completely necrotic.

In addition to the granulomatous lesions, marked vascular alterations of arterioles and muscular arteries were observed. Such changes consisted of diffuse intimal hyperplasia, medial thickening and thrombosis with organization. Diffuse intimal thickening of arterioles not directly related to ova was also noted (Fig. 7). Larger arteries showed medial and adventitial thickening.

A postmortem examination was undertaken in the 3 fatal cases (cases 1, 2 and 5). All were found to have gross generalized oedema and small peritoneal, pleural and pericardial effusions. Cardiac enlargement consisting of marked right ventricular hypertrophy and right atrial enlargement was common to all. The left atria and ventricles appeared normal in size. No abnormality of the heart valves was noted and there was no evidence of intracardiac thrombi. Apart from infarction of the entire left lower lobe and a small basal area of the right lower lobe in case 1 the lungs showed no striking macroscopic abnormality. It was only after a careful search that multiple small nodules were palpable in the lungs in case 1. Cases 2 and 5 revealed no such feature.

Pulmonary arteriography performed on both lungs in case 1 revealed obstructions at the level of the segmental arteries with filling defects peripheral to these. That such large obstructions were in fact thrombotic in origin was later confirmed on dissection. Peripheral venous thrombosis was sought, but not found in any of the 3 cases. Cases 2 and 5 showed no evidence of significant pulmonary artery occlusion by thrombus.

Bilharzial involvement of the bladder and rectum was found in all 3 cases, and in case 1 bilharzial granulations were found over the peritoneum in the rectovesical pouch. The livers were severely congested in every case and early pipestem fibrosis was present in cases 1 and 5. In all cases the spleen was of normal size and showed no abnormality beyond congestion.

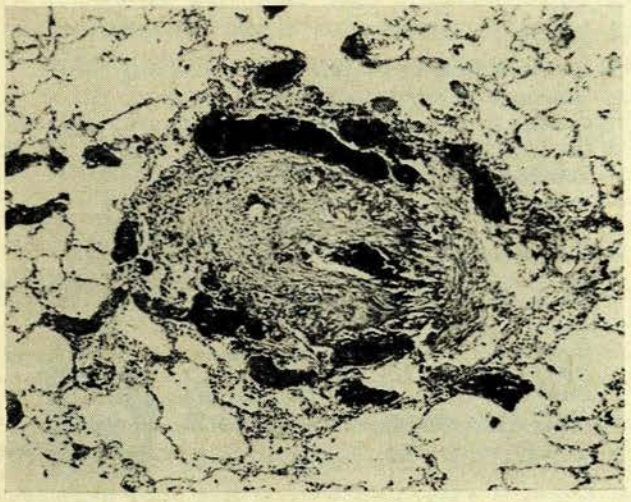

Fig. 8. Lung section showing intravascular pseudotubercles surrounded by dilated, thin-walled vessels giving rise to an 'angiomatoid' lesion (H & E × 150).

Microscopic examination confirmed the presence of vesical and colonic bilharziasis in all cases.

Liver sections, in addition to severe centrilobular congestion, revealed early bilharzial cirrhosis and bilharzial pseudotubercles in cases 1 and 5. Unfortunately a section of liver was not available for histological examination in case 2. The myocardium and spleen showed no evidence of bilharzial involvement.

Histological sections from lungs in all necropsy cases revealed bilharzial lesions as described in the lung biopsy sections. It is of importance to mention that although bilharzial pseudotubercles with or without ova were found in all cases these were not numerous. Marked obliterative changes involving arterioles not directly related to the pseudotubercles were, however, particularly striking. In addition, numerous angiomatoid lesions (Fig. 8) were present, indicating chronic pulmonary hypertension.

DISCUSSION

All 5 patients presented with the typical features of pulmonary hypertension and varying degrees of right heart failure. Severe effort intolerance, probably as a result of a fixed low cardiac output[14] and hyperventilation, a constant finding in severe pulmonary hypertension,[17] were striking features. Eosinophilia was present in the peripheral blood of the 4 patients investigated and bilharzial ova were found in the bladder and/or bowel in every case.

The pathological changes occurring in bilharzial pulmonary hypertension were comprehensively described by Shaw and Ghareeb[1] and Cavalcanti *et al.*[6] analysed the clinical presentation and haemodynamic changes in this condition. A more recent review of the subject was made by Turner.[14] Chaves[18] suggests that once the ova have impacted in the pulmonary arterioles the enclosed miracidiae secrete a lytic substance by means of which they digest their way through the vessel walls, lodging finally in the adjoining parenchyma. In a small number of susceptible individuals an acute vasculitis produced by this migration promotes obliterative alterations in the vessel as healing takes place.

Granulomatous lesions (Figs. 5 and 6) may be localized or diffuse, and may be found in the lumen, in the vessel wall, in the lung parenchyma adjoining the vessel and in the alveolar septa or the bronchial adventitia. Ova may or may not be seen within these granulomata.

Obstruction of the pulmonary arteries produces the right ventricular hypertrophy and failure, and is considered to be due not only directly to impaction of ova in the same way that multiple small emboli from venous thrombosis can produce it,[19] but also to an allergic response which promotes vasoconstriction and endarteritis.[6]

Bilharzia is extremely common in Natal; approximately 1,000 patients seek treatment at King Edward VIII Hospital, Durban, annually and many others do not seek treatment because haematuria is so common as to be acceptable in a primitive society. Isolated ova or adult worms are often seen in the lungs at necropsy in patients without vascular changes, and indeed without any inflammatory response whatsoever. Thus, the presence of inflammatory response in certain cases suggests an individual hypersensitivity to the presence of ova or their products in the lungs. Girgis *et al.*,[4] while commenting on

the comparative rarity of bilharzial pulmonary hypertension in Egypt, noted that some patients with this condition were either free from or had only mild infestation of the bladder and bowel. This lends further support to the theory of individual hypersensitivity. However, all the present cases had active bilharziasis and the bladders and bowels of those examined at necropsy were heavily infested. Filho[20] has shown experimentally that the lungs of previously infested mice produce an initial diffuse infiltrative, probably allergic, reaction when re-embolized by schistosomal cercariae. The arteriolitis so produced progressed to fibrous occlusion of the vascular lumen between 30 and 40 days after reinfestation.

The angiomatoid lesions (Fig. 8) once thought to be a distinctive feature in bilharzial arteriolitis[1,2] result from recanalization of obliterated vessels and are a non-specific result of severe pulmonary hypertension from any cause.[21]

Zaky *et al.*,[22] as a result of catheter studies on patients with pulmonary bilharziasis, demonstrated bronchopulmonary as well as splenic shunts and postulated that such shunts, plus repeated showers of ova in the lungs, contributed towards cor pulmonale in bilharziasis. Authors from countries where bowel infestation with *S. mansoni* is predominant[1,2,5,15] emphasize the presence of bilharzial hepatic cirrhosis with splenomegaly and imply that this is a prerequisite for the pulmonary involvement. Jawahiry and Karpas,[8] however, reported 15 cases, all complicating bladder infestation by *S. haematobium*, in whom 3 had what was considered to be only coincidental hepatic cirrhosis, and Turner[14] emphasizes that it is not necessary for hepatic cirrhosis to be present for *S. mansoni* ova to reach the lungs. Gelfand[23] found *S. mansoni* in the vesical veins of cases with ova in the lungs. The 3 children who have died in this series were all found to have had infestation of both bladder and bowel by *S. haematobium* and *S. mansoni* respectively. Two cases had insignificant hepatic cirrhosis and in none was there evidence of portal hypertension. The emphasis given by some authors to hepatic cirrhosis therefore seems unwarranted when considering bilharzia as the cause of pulmonary hypertension.

Our 2 surviving patients (cases 3 and 5) have each received a course of treatment with niridazole (Ambilhar) which has been shown not only to be an effective schistosomicide[24] but also to have little or no cardio-toxic effect.[25] In the past the toxicity of effective antimonial preparations precluded their use in such cases. Neither patient, despite severe cardiac abnormality, showed any signs of intolerance to niridazole, the object of such treatment being to eradicate the adult parasites from the bladder and bowel and by so doing prevent further embolization of ova to the lungs. Both patients, however, still require continuous treatment with digoxin and diuretics to prevent right heart failure and it is doubtful whether in such advanced cases any resolution of the established pulmonary hypertension can take place.

We feel certain that the paucity of previous reports of this condition from Southern Africa reflects a failure to recognize bilharzia as a cause of pulmonary hypertension, and in reporting these 5 cases of bilharzial pulmonary hypertension seen within a period of 18 months in one centre in the Republic of South Africa, it is our purpose to emphasize that this fatal complication of bilharzia occurs in this area more commonly than has been suspected. Experience from these cases leads one to stress the lack of obvious naked-eye lesions and apparent normality of the lung at necropsy. Furthermore, there may be areas of the lung microscopically devoid of typical bilharzial lesions, so that random sections might result in bilharzia as a cause of pulmonary hypertension being missed. A bilharzial aetiology should be considered in any case of pulmonary hypertension in a young person resident in a bilharzial area, even if a history of haematuria is not volunteered.

SUMMARY

Five cases of bilharzial pulmonary hypertension in Bantu children in Natal are reported. The presenting clinical features and the haemodynamic and pathological findings are presented, and a review of the literature is included.

It is emphasized that a bilharzial aetiology should be considered whenever pulmonary hypertension and eosinophilia are found in a young individual who has been resident in a bilharzial area.

The 2 surviving patients have been treated with niridazole (Ambilhar). It is hoped that this drug, by disposing of the adult schistosomes, will prevent further embolization of ova to the lungs.

We wish to thank Dr H. R. J. Wannenburg, Medical Superintendent of King Edward VIII Hospital, and Dr S. Disler, Medical Superintendent of Wentworth Hospital, for facilities and permission to publish. We should also like to thank Mr R. Stuart for the photomicrographs and Mrs E. I. Walsh for technical assistance.

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