

Cyanosis with hepatic cirrhosis

A case with pulmonary arteriovenous shunting

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A case is reported of cirrhosis of the liver associated with cyanosis and finger clubbing in a man of 31 years. The chest radiograph showed diffuse nodular shadows in both lower zones. Pulmonary function tests gave an arterial oxygen saturation of 91% at rest, falling to 68% on exercise; the single breath diffusing capacity for carbon monoxide was reduced to 55% of the predicted value and there was an estimated right-to-left shunt of 23%. Post-mortem injection of the lungs with Micropaque-gelatin suspension showed numerous pleural spider naevi, denser over the lower lobes, arteriovenous communications in the infrahilar regions, including leashes of dilated vessels in pleural adhesions on the diaphragm and diffuse arterial vasodilatation in the lungs; although the injection mass could be traced into the pulmonary veins in only a few regions of the lung, the dilated arterioles and spiders were possible additional channels through which blood might be shunted from the alveolar surfaces. The very low arterial oxygen saturation on exercise was probably caused by a shunt greater than the 23% estimated at rest, but the low diffusing capacity may have been partly responsible. The cause of the low diffusing capacity remains uncertain.

Arterial oxygen unsaturation in patients with liver cirrhosis—without any heart or lung disease—was first demonstrated by Snell (1935), but the observation that some cases of liver cirrhosis were associated with cyanosis and finger clubbing was made before the turn of the century. Flückiger (1884), an assistant in Küssmaul's clinic in Strasbourg, described a woman of 37 with liver cirrhosis who, without any evidence of cardiopulmonary disease, had finger clubbing and cyanosis; the diagnosis was confirmed at necropsy by von Recklinghausen. Gilbert and Fournier (1895) reported finger clubbing and osteoarthropathy of the lower extremities in seven children with liver cirrhosis.

Various explanations have been offered. Keys and Snell (1938) drew attention to a shift to the right in the oxygen dissociation curve, but this is not sufficient to account for the degree of oxygen unsaturation. Other authors sought evidence of venous admixture to the arterial blood, but until recently only two cases had been reported in which intrapulmonary arteriovenous channels were actually demonstrated by post-mortem injection techniques (Rydell and Hoffbauer, 1956; Hales, 1956). Anastomoses between the portal and

pulmonary veins were shown by injection studies in human cadavers by Calabresi and Abelman (1957) in two out of 10 cases of cirrhosis, but Shaldon, Caesar, Chiandussi, Williams, Sheville, and Sherlock (1961), using intrasplenic injections of radio-krypton (Kr^{85}), demonstrated such a shunt in only one of 12 patients with cirrhosis. Fritts (1963) concluded that oxygen unsaturation in cirrhosis may result from any of several factors, including a shift to the right of the oxygen dissociation curve, disturbances in ventilation-perfusion relationships (hypoventilated lung segments having the effect of functional if not anatomical shunting of blood, while ventilated but poorly perfused alveoli behave functionally like an addition of dead space), the existence of pulmonary arteriovenous fistulae, or the development of vascular connexions between the portal and pulmonary veins. Recently, Berthelot, Walker, Sherlock, and Reid (1966) studied 13 lungs obtained at necropsy from patients with liver cirrhosis and six from control subjects by injecting the pulmonary artery with a Micropaque-gelatin suspension. There was dilatation in the fine peripheral branches of the pulmonary artery in all 13

cases of cirrhosis and spider naevi on the pleura in six of the 13 cases, with obvious pulmonary arteriovenous shunts in only one of the 13 patients.

The present case correlates the clinical, physiological, and pathological features. The findings have a bearing on the problem of pulmonary arteriovenous fistulae in patients with hepatic cirrhosis.

CASE HISTORY

The patient, a man aged 31, was first seen in November 1963 because of breathlessness on exertion of 12 months' duration. He had a slight cough with yellow sputum and had had occasional nose bleeds for several years. He had never been jaundiced and had not taken excess alcohol.

PAST HISTORY At the age of 16 he underwent splenectomy following a football injury and was then told that his spleen was enlarged.

FAMILY HISTORY His father had frequent nose bleeds until the age of 30, and one of his three paternal cousins also had nose bleeds. All the available members of the family were examined and no evidence of mucosal or skin telangiectasia was found.

PHYSICAL EXAMINATION There was marked central cyanosis with gross finger clubbing. Spider naevi were present on the shoulders and hands. No telangiectases of the mouth, tongue, fingertips, or lobes of the ears were found. There were occasional wheezes and crepitations at both lung bases but no abnormality of the cardiovascular system. Blood pressure was 140/80 mm. Hg. The liver was palpable 2 cm. below the costal margin. The testes were small, rather soft, and not tender on pressure. The central nervous system was normal.

INVESTIGATIONS Liver function tests were normal except for a raised alkaline phosphatase, 36–40 King-Armstrong units. Serum proteins 7.8 g./100 ml., albumin 3.4 g./100 ml., globulin 4.4 g./100 ml. Electrophoresis showed raised gamma globulin. Prothrombin concentration 100%. Liver biopsy showed cirrhosis which appeared moderately active. An E.C.G. showed mild left ventricular hypertrophy. An E.E.G. was normal. Blood count: haemoglobin 11.9 g./100 ml., packed cell volume 39%, film normal, platelets 140,000/c.mm. Chest radiograph: the heart appeared a little enlarged and the pulmonary vascular tree was accentuated and unusually elaborate; there were nodular shadows in the lower zones (Figs 1 and 2). Cardiac catheterization showed the pulmonary artery pressure to be normal—22/13 (mean 18) mm. Hg. A dye curve from the right atrium showed no evidence of a right-to-left shunt. Pulmonary angiograms were taken but no arteriovenous shunt was demonstrated. The radiologist commented that the pulmonary arteries and veins were larger than normal,

however, and the interval separating arterial and venous filling appeared unusually short. Intravenous radio-krypton (Kr^{85}) studies failed to show any intra-pulmonary shunt (3.5% of injected counts appeared in the arterial blood during the appearance curve of indicator dye in the brachial artery; this is within normal limits for this technique (Fritts, Hardewig, Rochester, Durand, and Cournand, 1960)). Tests for porto-pulmonary shunting by means of intrasplenic krypton were not possible due to the previous splenectomy.

PULMONARY FUNCTION TESTS (Table) These showed normal lung volumes with no evidence of inequality of ventilation. The patient was over-ventilating at rest as shown by the high alveolar ventilation and the low arterial CO_2 tension. The diffusing capacity of the lungs for carbon monoxide was reduced to 55% of predicted. The arterial oxygen saturation, which was 91% at rest, fell to 68% on exercise. When the patient breathed 100% oxygen the arterial blood was fully saturated but the oxygen tension was only 270 mm. Hg (over 520 mm. Hg predicted). From these figures, and assuming an arteriovenous oxygen difference of 4 vol.%, the estimated right-to-left shunt of blood at rest was 23%. The shunt may have been underestimated since patients with hepatic disease

TABLE
PULMONARY FUNCTION TESTS

		Predicted
Functional residual capacity (ml. BTPS) ..	3,770	3,760
Vital capacity (ml. BTPS) ..	5,465	4,920
Inspiratory capacity (ml. BTPS) ..	3,705	3,320
Residual volume (ml. BTPS) (RV) ..	2,010	1,920
Total lung capacity (ml. BTPS) (TLC) ..	7,475	6,800
RV/TLC % ..	26.9	31.2
Mixing efficiency index (helium equilibration)	86	50–100
Forced expiratory volume (1 sec.)		
Forced vital capacity % ..	83	76+
Diffusing capacity for CO (ml./min./mm. Hg) single-breath method ..	16.1	28
Ventilation at rest		
Minute volume (l. BTPS) ..	12.6	
Alveolar ventilation (l./min. BTPS) ..	8.9	6–8
Tidal volume (ml.) (Vt) ..	1,095	
Physiological dead space (ml.) (Vd) ..	318	
Vd/Vt % ..	29.0	< 40
Respiratory quotient ..	0.885	
Arterial CO_2 tension (mm. Hg) ..	30.2	34–45
Plasma bicarbonate (mEq/l.) ..	22.6	22–28
Arterial O_2 tension (mm. Hg) ..	72.0	80+
Arterial O_2 saturation % ..	91	93–99
Arterial pH ..	7.49	7.35–7.45
Alveolar-arterial O_2 tension difference (mm. Hg) ..	42.3	< 9
Arterial O_2 tension breathing 100% oxygen (mm. Hg) ..	270	> 520
Right-to-left shunt of blood % (assuming an arteriovenous O_2 difference of 4 vol.%) ..	23.0	< 10
Ventilation on exercise (2 m.p.h., 8 degree slope)		
Dyspnoea ..	Slight	
Heart rate ..	128	110–130
Minute volume (l. BTPS) ..	69.0	35–45
Oxygen uptake (ml./min.) ..	1,712	
Oxygen utilization (ml./100 ml. ventilation) ..	2.73	4–7
Arterial O_2 saturation % ..	68.0	93–99

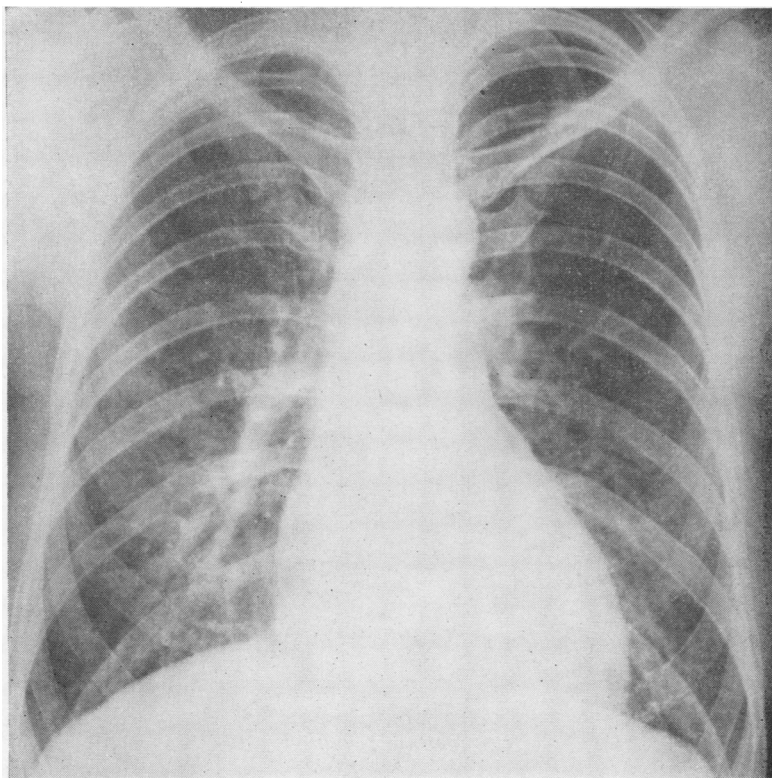


FIG. 1. *Postero-anterior radiograph (1965) showing nodular shadows at both bases.*

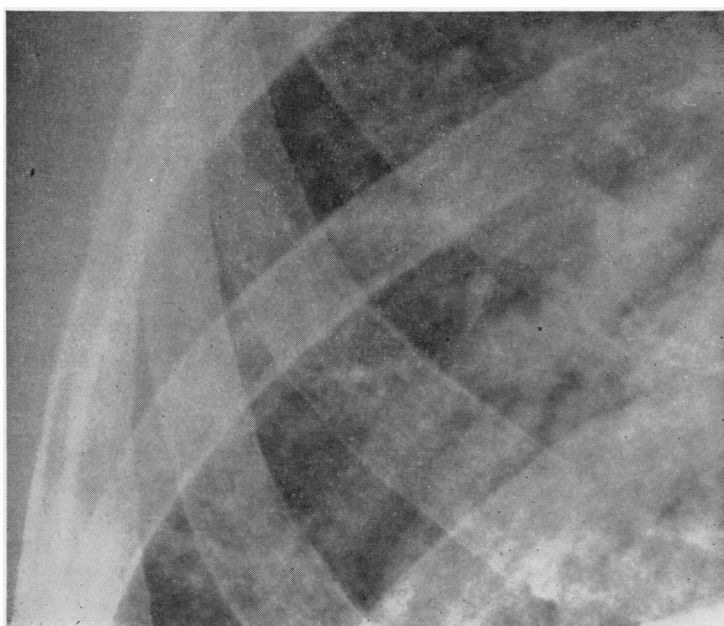


FIG. 2. *Enlargement of the right basal region shown in Fig. 1 to illustrate the nodular shadows.*

often have a high cardiac output and a low arteriovenous oxygen difference. If the arteriovenous oxygen difference was 3 vol.% the estimated shunt would have been 29%. Even a shunt of this size could not explain the gross unsaturation of the arterial blood on exercise and one must assume either an increase in the shunt on exercise or incomplete saturation of the pulmonary venous blood due to the low diffusing capacity. It is not known why radio-krypton failed to demonstrate the shunt.

At this stage it seemed likely that the patient had active chronic hepatitis with cirrhosis. Following discharge from hospital he remained fairly well except for some dyspnoea on exertion, but after three months he was readmitted following a large melaena.

SECOND ADMISSION On readmission his memory was poor, speech was slurred, and behaviour odd. He had a flapping tremor. He was transfused three pints of blood and given glucose fluids, low protein diet, and iron, and rapidly improved. Haemorrhage did not recur.

FURTHER INVESTIGATIONS E.S.R. 81 mm./hour. Platelets 102,000/c.mm. Prothrombin concentration 68%. Chest radiograph: pulmonary vascular markings heavy and prominent, nodular shadows in both lower zones. Barium meal: no oesophageal varices seen, no ulceration of stomach or duodenum. Oesophagoscopy: definite varices seen. Pulmonary function tests were repeated and arterial unsaturation, more pronounced on exercise, was again demonstrated as well as a low CO diffusion. On breathing oxygen the patient failed to saturate fully his arterial blood, suggesting intrapulmonary shunting of blood, but radio-krypton studies again failed to show any shunt.

Following this admission his condition remained unchanged for 15 months until November 1965, when he was admitted to hospital after a large haematemesis, presumably from oesophageal varices. Within hours of admission he went into profound coma and died in hepatic failure.

NECROPSY

Necropsy carried out 48 hours after death showed the liver (wt. 1,500 g.) surface to be irregularly nodular with marked areas of fibrosis and regenerating nodules. The portal vein was patent. The pancreas appeared normal.

HEART AND LUNGS The lungs and heart were available for injection studies. The pulmonary artery was injected by placing a catheter in the right ventricle and into the pulmonary artery into which it was tied. Micropaque-gelatin suspension was used, the injection pressure being 110 cm. of water and the overall injection time 7 minutes. Due to the viscosity of the injection mass, an injection pressure higher than the physiological pulmonary artery pressure must be used. The

pressure and the conditions of the injection are standardized; it is known that the injection mass does not enter vessels of less than 30 μ in diameter, and in normal lungs it never passes into pulmonary veins. We do not think artefacts in vessel demonstrations are produced by this method. Within the pericardium the four main pulmonary veins were exposed; each was encircled by two ligatures between which the vein was opened so that venous reflux from each lobe could be assessed.

Two minutes after the injection was started 'spiders' could be seen coming up over the lung and an occasional vessel at the lung edge. Then between two and four minutes venous reflux occurred from each lobe in the following order: the right lower, right upper, and the left upper and left lower (this means that precapillary arteriovenous shunts were present in each lobe but they were evidently not very large, since in the presence of a large shunt the injection medium floods almost immediately from the veins). As reflux was identified, the ligatures were tied to prevent loss of the injection medium and to enable pressure to build up within the injection system. Dilated vessels were numerous at the edge of both lungs, mainly below the hilar level, and here continuity between arteries and veins could be traced.

Spider naevi were best seen over the medial and lateral flat surface, the fissural surface being relatively free. The spiders were denser over the lower lobe than the upper, but in all many hundreds of naevi (700 were counted) could be distinguished over each lung (Figs 3 and 4). In view of the large amount of pleural filling it was striking that there was little in the way of perihilar injection, no large anastomotic vessels being seen on the pleural surface. Nor was there any reflux from vessels around the bronchus.

In slicing the lungs, some filling of the bronchial arteries at the hilum was seen, but it was not striking. The bronchial wall did show the occasional stellate pattern of vessels, characteristic of venous filling, each cluster being about 1 cm. in diameter. The fact that the regions of venous filling were usually isolated from each other suggests that there was no widespread arteriovenous shunt within the bronchial wall.

The cut surface, although showing a denser pattern of fine vessels than is seen in the normal, gave no indication of arteriovenous anastomosis. This was really apparent only on the diaphragmatic pleura and on the pleura of the infrahilar part of the lung, where it was possible to trace arteries to veins.

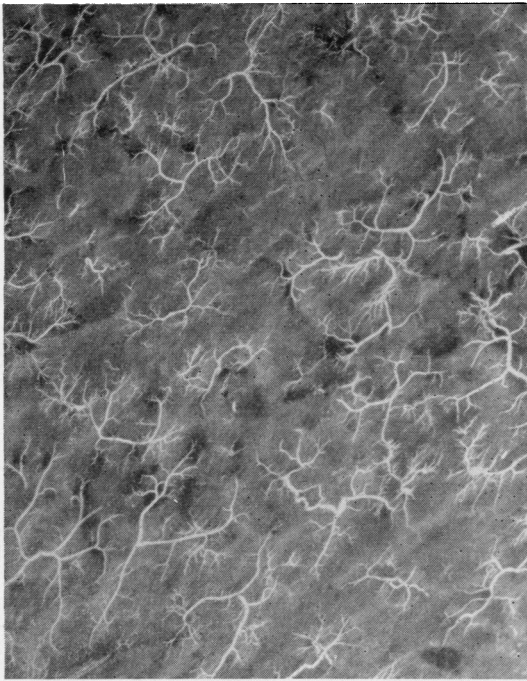


FIG. 3. *Pleural surface showing the numerous mostly discrete spider naevi injected with Micropaque barium suspension present over the surface of the lung.*

On the diaphragmatic surface of the left lung an adhesion was present and pulmonary artery injection showed that it included a large number of fine blood vessels (Fig. 5). Several similar but smaller adhesions were present over the diaphragmatic surface of the right lung.

The ventricles of the heart were dissected free of fat and valves and weighed separately after Fulton's method (Fulton, Hutchinson, and Jones, 1952). The left ventricle weighed 272 g., the right 65 g., giving a left to right ventricular ratio of 4:1 and pointing to left ventricular hypertrophy.

In summary, pulmonary artery injection showed numerous but small precapillary arteriovenous shunts in each lobe and mainly in the infrahilar region: continuity between arteries and veins could be traced mainly on the pleural surface. Pulmonary-bronchial artery shunts were not a feature, but there was widespread vasodilatation of small arteries, and numerous spider naevi were present on the pleura.

DISCUSSION

Cyanosis occurs in a proportion of patients with hepatic cirrhosis, but the mechanism has not been

fully explained. In this case a history of nose bleeds affecting the patient and two members of his family suggested hereditary haemorrhagic telangiectasia, which may be associated with liver disease (Martini, 1955), but no evidence of cutaneous or mucosal telangiectasia was found on examination of the patient and his family. Increasing breathlessness, slight cough with yellow sputum, finger clubbing, crepitations at both bases, and nodular shadowing in both lower zones of the lungs led initially to a tentative diagnosis of interstitial pulmonary fibrosis in addition to that of hepatic cirrhosis. Pulmonary function tests showed a reduced diffusing capacity, but failure to reach the predicted arterial oxygen tension on breathing 100% oxygen indicated that the cyanosis was primarily due to arteriovenous shunting and not to a failure to oxygenate blood perfusing ventilated alveoli. Precapillary arteriovenous shunting was in fact later demonstrated on pathological

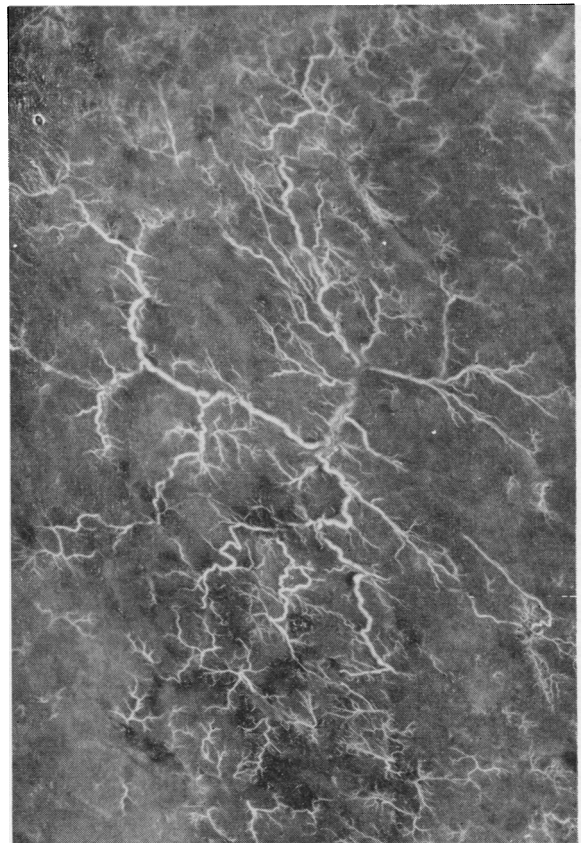


FIG. 4. *Numerous small spider naevi and a larger intercommunicating system of dilated vessels.*



FIG. 5. The diaphragmatic surface of the left lower lobe showing, to the right, spider naevi and an injected vein with, over most of the surface, numerous adhesions consisting mainly of small dilated vessels.

examination of the lungs, when Micropaque-gelatin suspension injected into the pulmonary arteries escaped through the pulmonary veins, evidently bypassing the capillaries since the injection medium does not fill vessels below $30\ \mu$. Continuity between arteries and veins could be traced on the pleural surface and infrahilar region. Several adhesions on the diaphragm contained numerous blood vessels similar to the arteriovenous fistula found in one of the cases reported by Berthelot *et al.* (1966), in which numerous arteries and veins were intertwined in a localized region on the diaphragm. The large number of pleural spider naevi offered additional channels through which blood could be shunted away from the respiratory surfaces into the pulmonary veins. The diffuse vasodilatation also previously reported was present throughout the lungs. The severe fall of arterial oxygen saturation from 91% at rest to 68% on exercise may reflect a relative increase in flow to these sites. The chest radiograph in this case showed the nodular shadows in the lower zones noted by Berthelot *et al.* (1966). They were present in all films taken over several years and seemed to represent the diffuse vasodilatation, since no other cause was found on pathological examination of the lungs.

The significance of the reduced diffusing capacity in this patient remains uncertain. Pathological examination of the lungs showed no evidence of interstitial fibrosis or other conditions which could interfere with transfer of oxygen across the alveolar wall. The diffusing capacity has been reported to be normal in patients with liver cirrhosis (Williams, 1960; Heinemann, Emirgil, and Mijnsen, 1960) as well as in patients with pulmonary arteriovenous fistulae (Bates and Christie, 1964). Two patients with pulmonary arteriovenous fistulae seen personally also had a normal diffusing capacity.

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