Cor Pulmonale in a Case of Interstitial Fibrosis of the Lungs with Death in a Sickle-Cell Crisis

By Walton R. Akenhead, M.D., Ronald A. Welsh, M.D., and Edgar Hull, M.D.

The patient, a 30-year-old Negro laborer, was referred to the Charity Hospital Outpatient Clinic in December 1952 with a history of shortness of breath that had been progressive since its onset, approximately 2 years previously. Mild cough productive of small amounts of white sputum had been present for several months. There had been no chest pain, fever, hemoptysis, or pedal edema. There was no history of heart disease, rheumatic fever, syphilis or exposure to noxious agents. His work in a sugar refinery did not expose him to bagasse dust. Physical examination was recorded as essentially negative except for slight increase in pulse and respiratory rates. Initial laboratory work showed the following: Hemoglobin 12 Gm., red blood cell count 4.2 million, white blood cell count 22,760 with a normal differential count. There was less than 5 per cent sickling in 24 hours. No acid fast bacilli were noted on direct smear of the sputum. An electrocardiogram was normal. Digitalis therapy over the next several weeks gave no improvement.

He was admitted to a Veterans Hospital in February 1953 and 8 weeks later was transferred to Charity Hospital for further study. Additional history revealed jaundice of unknown duration at the age of 12 and "rheumatism and tonsillitis" at the age of 13. He was febrile during the latter illness and remained in bed for about 3 months.

Physical examination in April 1953 revealed a well developed and nourished Negro who did not appear particularly ill. Blood pressure was 124/76, pulse 88 per minute, temperature 98.6 °F, ventilatory rate 24 per minute. Aside from a soft apical systolic murmur the physical examination was normal. Venous pressure was 140 mm. of water. Circulation time (arm to tongue) was 25 seconds. Routine hemogram was essentially normal except for mild leukocytosis. X-ray of the chest revealed prominence of the pulmonary conus with a heart of normal size. Fluoroscopy gave the impression of a prominent, actively pulsating pulmonary artery with slight prominence of the right ventricle. An electrocardiogram was within normal limits but there had been definite shift of the QRS axis toward the right as compared to the record of December 1952 (fig. 1A and B). Muscle biopsy was normal.

The patient was hospitalized several times during the next few months. His dyspnea was becoming more severe and was not responsive to digitalis, bronchodilators, or steroids.

Pertinent aspects of the pulmonary function studies were as follows:

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<th>Vital capacity</th>
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From the Charity Hospital of Louisiana at New Orleans and the Louisiana State University School of Medicine, Departments of Medicine and Pathology, New Orleans, La.
Cardiac catheterization showed pulmonary hypertension (75/35) with no evidence of left-to-right shunt.

Numerous routine laboratory determinations showed no abnormalities except for a rather persistent mild leukocytosis. No sickle-cell preparations were done except the one done upon his initial admission to the Outpatient Clinic. Many target cells were noted in one smear. Electrocardiograms taken in August and September 1953 showed progression of QRS axis deviation to the right with the R waves in V1, V2, V3 becoming higher.

He entered the hospital on his final admission, September 29, 1953, complaining of dyspnea, mild lower right chest pain, severe cramping pain in the legs and arms, and a transient episode of syncope. Physical examination revealed a blood pressure of 114/92, pulse 144, respiratory rate 34. Mucous membranes were cyanotic. A harsh systolic murmur at the mitral area was heard. The heart was not clinically enlarged. The lungs were clear. Blood calcium was 11.5 mg. per cent and serum bilirubin was 4.5 mg. per 100 ml. (direct 1.6, indirect 2.9).

The patient died several hours after admission.

Dr. Walton R. Akenhead: This man's illness apparently lasted about 1½ years and initially featured increasing dyspnea subsequently attended by evidence of right ventricular hypertrophy and arterial oxygen unsaturation and finally ended in an episode characterized by jaundice and pain in the chest, arms and legs.

Since this patient's initial clinical manifestation was shortness of breath unattended by evidence of cardiac disease or severe anemia, it seems clear that his dyspnea was pulmonary in origin, with the pathologic process involving the lung parenchyma or pulmonary vasculature or both.

The pulmonary function studies show reduction in both vital capacity and maximum breathing capacity but only slightly so, and certainly not to the degree expected in gross ventilatory dysfunction. The arterial oxygen saturation studies though not uniform do show progression to the point where there is diminished arterial oxygen saturation with exercise when the patient breathed air or 100 per cent oxygen. These findings tend to place the difficulty in the category of a right-to-left shunt or a severe defect in gas diffusion or block at the alveolar capillary membrane.

Cardiac catheterization revealed the presence of definite pulmonary hypertension and failed to show any evidence of atrial or ven-
tricular septal defect. The several electrocardiograms showed steady progression from a normal tracing to one consistent with right ventricular hypertrophy. This finding would suggest and fortify the impression that this patient's cardiac involvement is secondary to the pulmonary hypertension.

If we are agreed that this patient had some sort of rapidly progressive pulmonary or pulmonary vascular disease leading to arterial oxygen unsaturation, cor pulmonale, and death, then we may discuss some of the diagnostic possibilities.

Perhaps the most common lung condition leading to cor pulmonale is emphysema. It is the time-honored concept that pulmonary hypertension is secondary to the increased resistance resulting from the reduction in capillary bed occasioned by the breakdown of alveolar septa. There is much thought and some evidence at present that this explanation is far too simple. It seems more likely that some complex mechanism involving communication between the low-pressure pulmonary vascular system and the high-pressure bronchial vascular system may be at fault. In this case the relatively normal maximum breathing capacity and the diminution of oxygen saturation during exercise would rule out obstructive emphysema as the cause of this patient's pulmonary hypertension. In emphysema the maximum breathing capacity is reduced out of proportion to the vital capacity because of expiratory "air trapping" when the patient attempts rapid, deep breathing. In the usual case of emphysema with oxygen unsaturation, exercise results in better ventilation and distribution of air and oxygen, with some rise in oxygen saturation of the arterial blood. It would be distinctly unusual for emphysema to begin so abruptly and terminate so rapidly in a person of this age without obvious bronchial disease. Moreover, emphysema is not a common disorder in the Negro.

We are becoming more aware of sickle-cell disease as a cause of pulmonary hypertension with eventual cor pulmonale. The basic defect in sickle-cell disease is the abnormal architecture of the hemoglobin molecule. This readily explains the abnormal shape of the cells which, together with the tendency of these cells to stagnate, conglutinate, and thrombose in small vessels, is the key to the pathology of the disease. It has long been recognized that patients with sickle-cell states are prone to thrombosis. The frequent occurrence of splenic and cerebral infarction and the common ischemic leg ulcers are clinical and pathologic events that attest to the thrombotic propensity of these patients. It has also been long recognized that low oxygen tension is the most powerful of the "sickling potentiators." Patients with sickle-cell disease show 3 or 4 times more "sickling" in venous blood than in blood from the arterial side of the greater circulation. Individuals exhibiting the heterozygous sickle trait are prone to "thrombotic crises" when at high altitudes in an atmosphere of low oxygen tension. In view of the above observations it would follow that one could expect small vessel thrombosis in the lungs where oxygen tensions are low and flow is comparatively slow. This tendency would be increased should blood be flowing through poorly aerated areas of the lung. How much reduction of the capillary bed of the lung by repeated small infarctions is necessary for production of pulmonary hypertension and cor pulmonale is not known but judging on clinical grounds alone the amount of pulmonary involvement required to compromise the pulmonary circulation must be considerable. However, should an oxygen diffusion defect occur as a consequence of widespread fibrosis due to repeated small, subclinical infarctions, arterial hypoxia might contribute to the development of pulmonary hypertension. With the better methods of identification of the various combinations of abnormal hemoglobin values that comprise sickle-cell disease and its variants it is more than likely that many cases of pulmonary hypertension heretofore regarded as "primary" will be ascribed to repeated small pulmonary infarctions. The more judicious
use of transfusions and the better armamentarium against infections will no doubt allow many of these patients afflicted with abnormal hemoglobins to live sufficiently long to manifest the ultimate result of these pulmonary infarctions.

In this case it is unfortunate that more definitive studies relating to hemoglobin structure were not done. The demonstration of "less than 5 per cent sickling" and target cells in the absence of anemia, jaundice, or other hallmark of sickle-cell disease would lead one to believe that this patient had one of the heterozygous sickle-cell variants rather than the homozygous sickle-cell disease. However, it should be mentioned that occasionally one may see the first clinical manifestations of the homozygous sickle-cell state in well developed, apparently healthy Negro adults with no history or evidence of anemia, jaundice, hemolytic crisis, leg ulcers, skeletal abnormalities, or other hallmarks of the disease that are usual from childhood in the classic case of sickle-cell disease.

The final episode of the patient's illness is worthy of some comment. In addition to his increasing dyspnea, the patient had an episode of syncope and complained of right lower chest pain and severe cramping pain of the arms and legs. Jaundice was noted for the first time. This type of exitus may be seen in patients with sickle-cell disease as a result of widespread conglutination of sickle cells with thrombosis, obstruction, or impairment of circulation with resultant infarction or ischemia. It is unfortunate that blood studies were not done during the few hours of his last hospitalization. It is inviting to speculate that his increasing arterial and venous oxygen unsaturation may have potentiated his "sickling" tendency.

The diagnosis of periarteritis nodosa of the pulmonary arteries is suggested by the persistent leukocytosis and the rapid course of the disease. The absence of fever and the negative muscle biopsy militate against this diagnosis but do not in any way rule it out. A lung biopsy would be necessary to establish or thoroughly to negate such a diagnosis.

The opinion generally held by the staff who cared for this man was that his basic difficulty was interstitial fibrosis of the lungs of the variety described by Hamman and Rich. The rapidly progressive course with increasing dyspnea and cyanosis and eventual evidence of right ventricular hypertrophy is almost a carbon copy of the cases originally described by Hamman and Rich. In the usual case of interstitial fibrosis with alveolar capillary diffusion block the already reduced arterial oxygen saturation during the breathing of air will further diminish with exercise, but the breathing of 100 per cent oxygen will usually result in complete saturation at rest and after exercise. In this case this was essentially true when studies were done early in his hospitalization. Later on, studies showed that arterial oxygen unsaturation was present at rest, breathing air or oxygen, and that this unsaturation was increased by exercise whether the patient was breathing air or oxygen. In this regard the findings are those of a right-to-left shunt. This is not altogether surprising, since it seems reasonable that if the alveolar-capillary interface is sufficiently thickened the diffusion of oxygen into capillaries will be so seriously compromised that the existence of blood flow in areas so involved will, in essence, be a right-to-left shunt.

Dr. Ronald A. Welsh: The significant findings at necropsy were limited to the lungs, heart, and spleen. There were diffuse fibrous adhesions in both thoracic cavities. Both lungs were essentially similar in gross appearance, firm in consistency throughout all lobes. The cut sections demonstrated a diffuse coarsening of lung architecture with no evidence of gross hemorrhage, edema, or consolidation. The hilar lymph nodes were not significantly enlarged. The right ventricle of the heart was hypertrophied and dilated. An unexpected finding was an extremely small fibrotic spleen, weighing only 14 Gm. The remainder of the organs were essentially normal on gross examination.

Microscopic examination of the lungs revealed diffuse interstitial fibrosis of a type
similar to that described by Hamman and Rich (fig. 2). The alveolar walls were thickened and contained an increased amount of collagen along with an apparent increase in capillaries. There were small numbers of lymphocytes and occasional plasma cells in the interstitial tissue. The alveolar spaces were almost uniformly lined by cuboidal cells, and contained variable numbers of histiocytes and occasional red blood cells. There were patchy areas of compressed and collapsed alveoli with adjacent areas of dilated emphysematous spaces. The red blood cells showed marked sickling in the vessels of the lung, as well as in all organs examined. Although no definite recent thrombi could be demonstrated, several pulmonary arteries were found showing old, recanalized thromboses (fig. 3). The splenic pulp was completely replaced by fibrous tissue containing large masses of calcium and hemosiderin. A section of bone marrow was hyperplastic, with an increased erythroid component.

This case presents several interesting features for pathologic correlation. First, the arterial oxygen studies initially were consistent with an alveolar gas diffusion block, but in the later studies there was a change with evidence pointing to a right-to-left shunt in the pulmonary circulation. In examining these lungs microscopically, one is struck by the marked over-all vascularity in the individual alveolar walls. This feature of pulmonary "angiosis" in the Hamman-Rich syndrome has been pointed out by Golden and Bronk, and it appears that in this case in many areas there has been a definite increase in capillaries in the alveolar walls. Although an actual gross right-to-left shunt has not been accurately identified in this case, there is definite anatomic evidence of an abnormal vascular pattern, and injection studies in future cases may shed light on the exact nature of the vascular cross connection suspected physiologically by Dr. Akenhead in the studies of arterial oxygen saturation.

This case is complicated by the associated clinical evidence of a terminal hemolytic disease, which is accompanied by pathologic evidence of normoblastic hyperplasia of the bone marrow, pronounced sickling of the erythrocytes, and a shriveled, fibrotic spleen. I am interested in the original sickling preparation reported on this patient as 5 per cent sickled cells present. Certainly in the autopsy tissues there is more than 95 per cent sickling seen. It is probable that the original preparation did not reproduce the severe oxygen deprivation seen in the tissue, or the original preparation may have been examined too early. In our experience, a shrunken fibrotic spleen such as in this case is ordinarily seen in true sickle-cell disease of homozygous "S"-hemoglobin type. When changes in the size of the spleen occur in the heterozygous "S"-hemoglobin individuals, there is usually splenomegaly, although it is probable that future anatomic studies of...
large groups of individuals with heterozygous sickle-cell hemoglobin will disclose rare instances of a similar, severe, splenic atrophy.

The sickle-cell disease is most likely a coincidental associated disease, and to my knowledge does not produce diffuse interstitial fibrosis of the lungs of the Hamman-Rich type. The recanalized thrombi in the pulmonary arteries may represent the effect of previous sickle-cell crises and may contribute to the cor pulmonale. Examination of reported cases of Hamman-Rich syndrome reveals no significant association with sickle-cell disease; actually the syndrome has been found in about equal proportions in the white and Negro races. Sickle-cell disease was undoubtedly a potent contributory factor in this patient's demise, particularly in view of the hemolytic crisis that was observed clinically.

The pathologic diagnoses were diffuse interstitial fibrosis of the lungs (etiology unknown); hypertrophy of the right ventricle; sickle-cell disease, normoblastic hyperplasia of the bone marrow, and atrophy of the spleen.

Dr. Edgar Hull: I first saw this patient at a clinical conference in April 1953, and my recorded opinion was that he had "diffuse interstitial fibrosis of the lungs." I did not consider the possibility of a sickling state as a factor in his illness, either then or on the 2 or 3 other occasions when I saw him or discussed his case. Probably because he was never anemic and because of the single negative sickle preparation, none of the others who followed his course mentioned the sickle state as a possible factor in the pathogenesis of his pulmonary hypertension, although we knew that pulmonary hypertension and cor pulmonale are common enough in sickle-cell disease. We have been aware of this complication since the report of Yater and Hansmann in 1936, and we recognize that some of the unusual murmurs (particularly the very loud systolic murmurs and the occasional diastolic murmurs heard to the left of the upper sternum) are due to dilatation of the pulmonary artery. We frequently recognize pulmonary infarction in patients with sickle-cell disease; even in the absence of "clinical" signs of pulmonary disease transient densities are often seen in the chest x-rays of these patients.

I recall that during the admission of July 1953, when the arterial oxygen saturation of this patient failed even to approach 100 per cent while breathing oxygen, there was spec-
ulation that he must have, in addition to the primary pulmonary disease, an anatomic patency of the foramen ovale, through which right-to-left shunting occurred as right ventricular failure developed and right atrial pressure increased. Like Dr. Akenhead, I thought that the "shunt" bypassed the air in the alveoli, but not necessarily the lungs—that it was probably intrapulmonary.

Dr. Welsh has told us that in this case the sickle state was probably not concerned in the pathogenesis of the pulmonary fibrosis, but that it was undoubtedly an important factor in his death. This opinion I accept, particularly since in part it substantiates our clinical diagnosis though it does not lessen our chagrin over missing half of the boat.

I wonder, however, whether the fibrosis may have been related to repeated subclinical episodes of small vessel, perhaps capillary, thrombosis, occurring over the years. This man may have been a heterozygous sickler, yet his spleen was as small and fibrotic as that of any S-S sickler. Indeed, Moser and Shea\(^4\) have reported pulmonary hypertension and cor pulmonale in heterozygous sickle states.

Further and finally, at this time we have in the hospital a Negro man, age 52, whose illness, to use Dr. Akenhead's words, is almost a carbon copy of that in the case under discussion. He has been short of breath on exertion for about 7 months; on 2 occasions he has fainted during exertion. He has a big right ventricle (fig. 4A and B); electrocardiographic signs of right ventricular hypertrophy (fig. 5); signs of an oxygen diffusion defect without great reduction in maximal breathing capacity. He is not anemic (hematocrit 49 per cent); his sickle test is positive; electrophoretically he is heterozygous A-S. Is he, too, a case of the Hamman-Rich syndrome, or is his cor pulmonale due solely to the consequences of the sickle state?

**Dr. Welsh:** The possibility that the entire clinical picture can be ascribed to sickle-cell disease alone is tempting to consider; however, I would like to clarify further that the old pulmonary thromboses in this case were too few in number to have resulted in such a degree of interstitial fibrosis. Likewise, if tiny capillary thrombi were a mechanism, as postulated by Dr. Hull, again we would expect to see diffuse interstitial fibrosis of this type in a higher frequency in the Negro race with sickle-cell disease, but apparently this is not the case.

**Dr. Akenhead:** In conclusion, we have presented a patient with diffuse interstitial fibrosis of the lungs with eventual development of pulmonary hypertension and cor pulmonale whose exitus was attended by a "sickle-cell crisis."

The altered cardiopulmonary physiology occasioned by the pulmonary pathology and the possible relationship between the hemoglobinopathy and the pulmonary fibrosis have been discussed. I suspect, as is usual in these sessions, that we have raised more questions than we have settled.

**REFERENCES**

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