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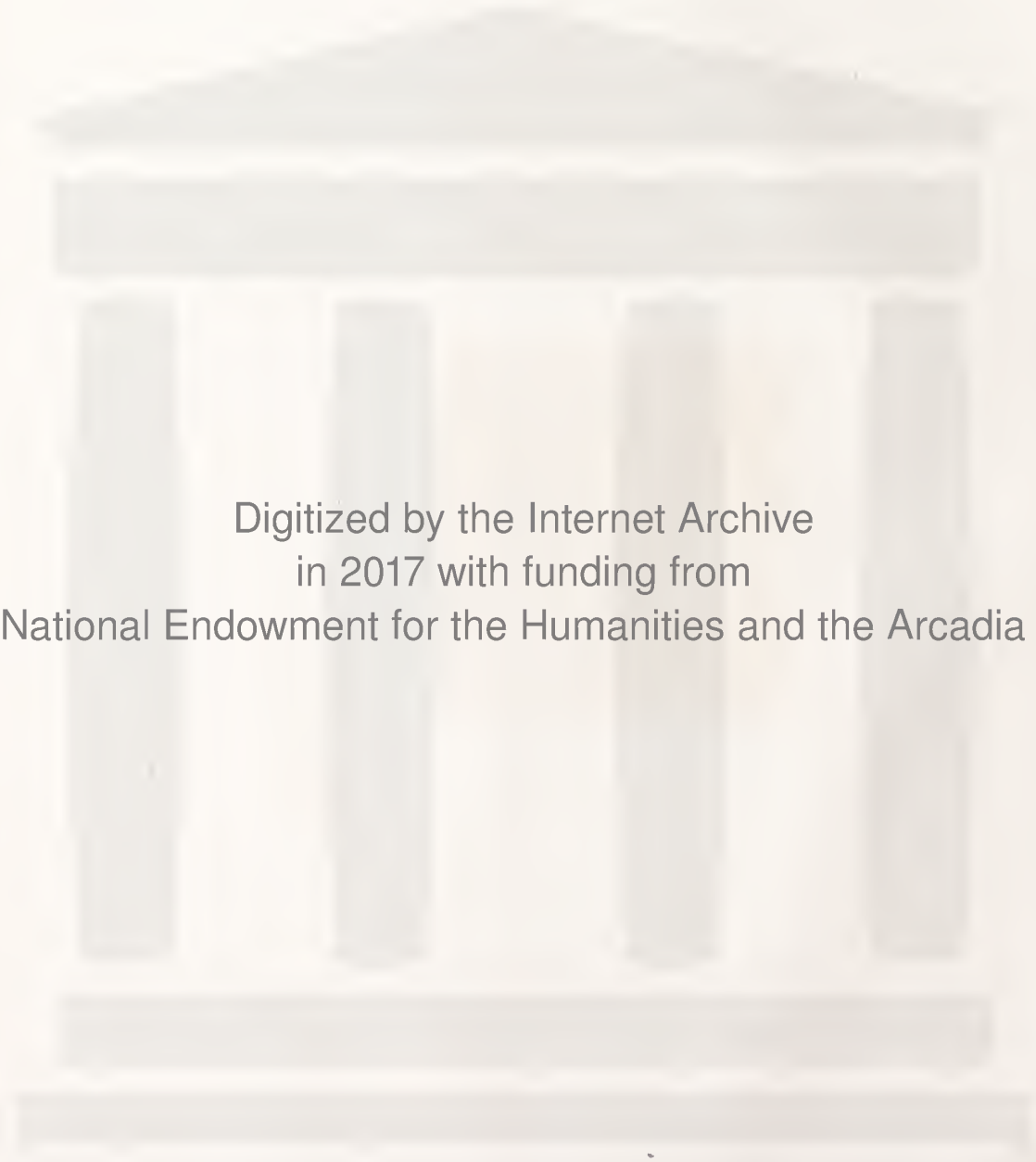

Pulmonary Manifestations of Sickle Cell Disease

A Thesis

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Introduction

The interaction between hemoglobin and oxygen which occurs in the lung is necessary for life, but in those with sickle cell disease, it has an added, critical importance. Deoxygenation, acidosis, and hypertonicity all favor sickling of erythrocytes carrying the abnormal S hemoglobin. If the blood is not sufficiently oxygenated in the lungs, arterial PO_2 will drop. Below a critical PO_2 extensive sickling in the microvasculature of the tissues occurs. In many patients a small, but constant percentage of the circulating erythrocytes is always sickled (Milner, 1974). Sickled erythrocytes may occlude the vascular channels, resulting in oxygen deprivation of the tissues, more sickling, and eventually infarction.

The significance of sickling and its effect on the spleen, leading to autoinfarction, and on the kidney, resulting in loss of concentrating ability, have been well documented. However, the effect of sickling on the lungs, which receive the most deoxygenated blood in the body and then reoxygenate it, is not

definitively established.

The first portion of this paper reviews the literature on pulmonary disease in sickle cell anemia. The second portion consists of a clinical study which 1) Presents clinical data on pulmonary episodes in sickle cell patients seen at Yale-New Haven Hospital and 2) Examines pulmonary function in asymptomatic patients with sickle cell disease. This study will document that there is a high incidence of acute pulmonary disease in the sickle cell population and will delineate the characteristics of pneumonia in this population. Pulmonary function studies documenting an impairment in gas exchange will be described. The hypothesized underlying pathophysiology of pulmonary disease in the sickle cell population will be discussed. Lastly problems of management of acute pulmonary disease in the sickler and the direction of further studies will be examined.

Literature Review

It is known that those with sickle cell anemia are more prone to pneumonia, and also that they may have episodes of pulmonary infarction. Distinguishing acutely between infarction and pneumonia frequently constitutes a diagnostic dilemma. In addition the acute and chronic effects of sickling on the lungs are not well established. It has been reported the sickle cell

patients have impaired lung function and progress to develop cor pulmonale, but there is controversy regarding the frequency of this complication. In the following section of this thesis the literature on pulmonary manifestations of sickle cell disease will be examined with regards to: 1) Infection, 2) Infarction, 3) Radiographic changes, 4) Cardiovascular function, 5) Pulmonary function, and 6) Pulmonary pathology.

Infection

An acute pulmonary event is the most common cause of hospitalization in the sickle population (Barrett-Connor, 1971-b). The relative incidence of pneumonia in the sickle population is at least 20 to 100 times that in normal blacks (Bromberg, 1974; Barrett-Connor, 1971-a). Of 54 sickle cell patients (mean age 21.2, range 5 to 50) reviewed by Henderson, there were 105 admissions to the medical service over a ten year period. Of these 14 were for pneumonia and 13 had an associated crisis. Barrett-Connor reported that for 166 patients with sickle cell disease followed over a period of 11 years (average of 5 years, with a total of 864 patient-years) there were 200 hospitalizations for an acute illness with an infiltrate on chest x-ray (Barrett-Connor, 1971-a). This population was somewhat younger than Henderson's,

with a mean age of 12 and a range of 7 weeks to 47 years. In another study 98 sickle cell patients had 63 episodes of bronchopneumonia occurring in 42 of the group (Karaylacin et al., 1975). Clearly the incidence of acute pulmonary disease is significantly increased in sickle cell anemia.

The clinical manifestations of acute pulmonary disease in sickle cell anemia differ from those of the normal population. Consistently prolonged fever, lasting as long as 41 days, characterizes pneumonia in patients with sickle cell anemia. (Petch and Serjeant, 1970; Petch et al., 1970; Barrett-Connor, 1973; Henderson, 1950). Frequently there is a history of previous pneumonia, and if pneumonia occurs before the age of 5 the individual is more likely to have recurrent episodes (Petch et al., 1970; Barrett-Connor, 1971-a). A history of preceding upper respiratory tract infection is common. Sputum and blood cultures are often negative, and antibiotic response is inconclusive. The white blood count reaches higher levels in sickle cell patients with pneumonia versus controls with pneumonia. Petch et al. (1970) found on admission mean white counts of 23,400/mm^3 with a range of 9,300 to 52,000/mm^3 in sicklers versus age-matched controls with mean white counts on admission of 12,500/mm^3 with a range of 5,100 to 34,000/mm^3. In addition to the prolonged course of fever and high white blood cell counts, sickle cell patients also tend to have repeated bouts of pneumonia during one hospitalization. Frequently more than one lobe is involved; in one study the incidence of multilobar involvement was 41%

(Barrett-Connor, 1971-a).

Mycoplasma pneumonia tends to be particularly severe in patients with sickle cell anemia. Shulman et al. (1972) reported 5 cases of mycoplasma in children. The illnesses were characterized by multilobar involvement, white blood counts greater than 25,000/mm^3 (versus the usual absence of leukocytosis in normal patients with mycoplasma), a prolonged fever course of greater than 7 days, pleuritic pain, and pleural effusion in 2 out of the 5 cases. Significantly no dramatic response to erythromycin occurred, although the cases were all well-documented with a rise in cold agglutinin titer, positive cold agglutinins, and/or a positive mycoplasma complement fixation titer. The increased severity of mycoplasma pneumonia in patients with sickle cell disease was also noted by Putnam et al. in their review of radiological manifestations of mycoplasma (Putnam et al., 1975).

There is increasing evidence that patients with sickle cell disease have impaired antimicrobial defense systems. Pearson et al. have documented that at an early age sickle cell patients have a functional asplenia (Pearson et al., 1969; Pearson et al., 1970). Sickle cell patients are particularly susceptible to pneumococcal infection (Barrett-Connor, 1971-b). Studies of serum from sickle cell patients versus normal controls demonstrated that the sickle cell serum has abnormally low levels of heat-labile opsonizing activity for the pneumococcus. On the other hand the levels of serum opsonizing

activity for salmonella do not differ significantly between the two groups, and both groups have similar hemolytic complement activity (Winkelstein and Drachman, 1968). In vitro leukocyte phagocytosis in both groups is indistinguishable. Johnston et al.'s work indicates that the defect in opsonization observed in sickle cell patients' serum is due to a defect in the alternate (properdin) pathway by which C-3 is directly fixed to antigen (Johnston et al., 1973). They propose that synthesis of a component of the alternate pathway is depressed as a result of either splenic or reticuloendothelial dysfunction. This dysfunction of the reticuloendothelial system in particular could be accounted for by the overload of erythrophagocytosis and secondary iron overload resulting from the sickling of erythrocytes. More work remains to be done in this area to fully elucidate the cause of the increased susceptibility of the patient with sickle cell anemia to infection, particularly pneumococcal, on the cellular level.

Another factor in susceptibility to infection may be impaired phagocyte function. Alveolar macrophages are highly dependent on aerobic glycolysis, much more so than other macrophages. Low oxygen tensions inhibit phagocytosis in alveolar macrophages (Green, 1968). In addition oxygen

is needed for the respiratory burst involved in the destruction of microorganisms by phagocytes (Babior, 1978). Thus low oxygen tensions both in the pulmonary capillary blood and in the alveoli (this will be further discussed later) may be a critical factor in impairing the function of alveolar macrophages in the sickle cell patient.

The two other hemoglobinopathies with similar clinical manifestations to SS disease are SC and S-Thalessemia, S-Thalessemia occurs in 0.3% of American blacks (Wintrobe, 1974). In a population of 21 patients with documented S-Thalessemia, age range 17 to 53 years with a mean of 25.8 had documented pneumonia and 6 had more than one episode (Reynolds et al., 1973). SC disease occurs in 0.8% of the American black population (Wintrobe, 1974). In her series of 24 patients with SC disease, Barrett-Connor observed that 10 patients had at least one hospitalization for infection (Barrett-Connor, 1971-c). In this group, which had been followed for a total of 68 patient-years, there were 7 episodes of pneumonia, of which 3 were pneumococcal. In addition there were two episodes of pulmonary infarction documented by angiography. River et al. (1961) also reviewed the incidence of acute pulmonary disease in patients with SC hemoglobin. They observed a high incidence of chest pain, fever, cough, and leukocytosis, accompanied by infiltrate on chest x-ray. Thirty patients in their group

had a total of 46 episodes of acute pulmonary disease, which is a greater incidence than one would expect in a normal population. Although the data for S-Thalessemia and SC disease are more limited and more preliminary than for SS disease, it is certainly indicative of a higher than normal incidence of pulmonary disease in these two populations as well as in the SS population.

Typically, then, pneumonia in patients with sickle cell disease tends to be characterized by a prolonged course. Frequently the response to antibiotics is poor, even when there is documentation that the antibiotic is the drug of choice. Multilobar involvement occurs often, and the pneumonia can progress, despite appropriate treatment, from one lobe to another during the course of hospitalization. Furthermore no pathogen can be isolated in many episodes of pulmonary disease in sicklers. Whether this pattern holds true for SC disease and S-Thalessemia has yet to be established. The preliminary data indicate that both groups have a higher incidence of pulmonary disease, which is more severe than in the normal population. There is some evidence to suggest that the increased incidence of pulmonary disease is not as great in SC disease as in SS disease (Barrett-Connor, 1971-c).

Embolization and Pulmonary Infarction

The diagnostic dilemma in sicklers who present with acute pulmonary disease remains whether it has infection or infarction as its etiology. Reynolds et al. in reviewing radiologic findings in 22 sicklers found 4 episodes of pulmonary infarction documented by lung scan (Reynolds et al., 1973). In this same group of 22 patients they observed pneumonia in 8 patients with 6 patients having repeated episodes. The 4 cases of pulmonary infarction were accompanied by infiltrate on chest x-ray, transient right axis deviation on electrocardiogram, as well as moderate cardiomegaly. In another review of 89 patients followed for an unspecified number of years, there were 11 episodes of pulmonary infarction (method of diagnosis not given) versus 63 episodes of pneumonia (Karayalcin et al., 1975).

Certainly the incidence of pulmonary infarction is significantly increased over that in the general population. The difficulty of diagnosis remains. Repetitive, closely spaced bouts of pulmonary disease, which in the normal population would be interpreted as indicative of infarction, are not helpful in making the diagnosis in sickle cell patients. In Barrett-Connor's study half

of the patients for whom it was proved that they did not have pulmonary infarction by lung scan, angiography, or autopsy had multiple closely spaced episodes of pulmonary disease (Barrett-Connor, 1973).

There are other signs and symptoms which can be helpful in diagnosis. Onset with a chill favors pneumonia (Barrett-Connors, 1973). Gross hemoptysis, considered in the normal population as suggestive of infarction, was not observed in any of Barrett-Connor's (1973) documented cases of pulmonary infarction. Furthermore Petch and Serjeant (1970) observed hemoptysis in 18 of 28 normal patients with acute lobar pneumonia and in only 1 of 28 sickle cell patients with "pneumonia". The simultaneous presence of thrombophlebitis and acute pulmonary disease in the normal population is considered highly suggestive of embolization and infarction. In sickle cell anemia thrombophlebitis is unnecessary. Infarction can follow fat or marrow embolization to the lung accompanying crisis, or can occur secondary to *in situ* sickling or thrombi of sickled cells. Thus a preceding or concurrent crisis would be expected to tend to favor infarction, and observations supporting this have been made (Barrett-Connor, 1973).

Chest x-ray findings are not pathognomonic. Location

of an infiltrate in the lower lung fields, assymmetry if the infiltration is bilateral, segmental involvement, moderate elevation of the diaphragm early in the course, and acute increased prominence of the pulmonary artery all favor infarction (Reynolds, 1965). The five episodes of pulmonary infarction which Barrett-Connor reviewed indicated that older age, single lobe involvement, and associated clinical crisis are suggestive of the diagnosis of infarction (Barrett-Connor, 1971-a). Four of these 5 patients had jaundice and serum bilirubins greater than 5 mg. per 100ml., while only 25% of patients with pneumonia had pain suggestive of crisis and only 2 of the patients had a similar increase in serum bilirubin.

Several investigators have observed the presence of blister cells in the peripheral blood smears of patients with sickle cell anemia and pulmonary emboli and/or infarction (Barreras et al., 1968; Petch and Serjeant, 1970; Karaylacin et al., 1972). These cells are characterized by the presence of "blebs" or "blisters" on their surfaces and are actually poikilocytes (Barreras et al., 1968). As the symptoms of the pulmonary episode resolved, the blister cells were noted to disappear from the peripheral blood by these investigators. Barreras et al. (1968) examined the peripheral blood smears of several sickle

cell patients with pneumonia, crisis, osteomyelitis, or other infections, and they found that none of these demonstrated blister cells. The examination of smears from patients with pulmonary emboli, but without sickle cell disease was inconclusive (Barreras et al., 1968). It remains to be seen if the observation of blister cells on the peripheral smear can be a reliable diagnostic finding for pulmonary infarction in sickle cell disease. A key point is that G6PD deficiency will cause poikilocytes, or blister cells, and it is important to rule out this possible etiology for the presence of these cells in patients with pulmonary infarction. Before these observations on the presence of blister cells accompanying pulmonary emboli and infarction in sickle cell disease can be conclusive it is necessary that G6PD levels be demonstrated to be normal in the patients studied.

In the sickle cell patient infarction of pulmonary tissue can occur through several mechanisms. Sickle crisis can be accompanied by embolization of both fat and marrow from bone marrow to the lungs (Shelley and Curtis, 1958). Thrombus can embolize to the lungs; thrombus formation may occur as a complication of pregnancy, frequently late in pregnancy or in the post-partum period. There are numerous case reports in the

literature of embolization, fat and marrow embolization (accompanying crisis), and pulmonary infarction (often without any source of emboli) occurring in patients with SS, S-Thalessemia, and SC disease (Jewett, 1976; Bashior and Lindsay, 1975; Karayalcin et al., 1972; Dunn and Haynes). The incidence of these complications has not been documented in pregnant women with sickle cell disease or the SC or S-Thalessemia variants. Nor is the incidence of marrow and fat embolization in association with crisis known. Clearly as these events can range from "silent" microemboli to multiple microemboli or massive emboli it would be difficult to document an estimate of incidence. However, it should be possible to document the frequency of major episodes of embolization and infarction in both the sickle cell population overall and in sickle cell patients who are pregnant.

In addition to fat, marrow, and thrombus embolization there is also the possibility of in situ sickling in the lungs. A precipitating stress might be a factor in this. For example, pregnancy further lowers the PO_2 of venous blood returning to the lungs, and in a situation which is already precarious this might be enough to tip the balance and precipitate significant sickling within the lungs such that occlusion of pulmonary vasculature occurs. Or, a mild

infection might precipitate sickling in the pulmonary vasculature when it otherwise might not have occurred, and thus lead to infarction. Thus even if the initial event is a pneumonia, it can in theory be potentially complicated by pulmonary infarction. One can also postulate that once a sickling cycle is set off within the pulmonary vasculature this can lead to an acute episode of massive pulmonary hemorrhage and infarction. (1967; Rywlin et al., 1963; and Shelley and Curtis, 1958). Significantly many of these cases occurred in women who were pregnant or taking oral contraceptives. Frequently the hemoglobinopathy was unsuspected prior to the occurrence of pulmonary infarction.

Diagnosis of pulmonary infarction in sickle cell patients remains difficult because of the somewhat confusing manifestations of pulmonary disease in these patients, and also because of the inherent risks in some diagnostically definitive procedures such as angiography, which can potentially precipitate sickling. An alternative is the lung scan, but this can be less satisfactory as its accuracy, depending on the medical center, varies, and there can be a high rate of false negatives, and or false positives. Also the smaller the emboli, the less likely that the scan will be positive. More will be said on the potential role of lung scans in the latter part of this paper.

Radiologic Findings

There are a number of different findings on the chest radiographs of sickle cell patients. The occurence of cardiomegaly in virtually all patients with sickle cell disease has been well documented (Henderson, 1950; Shubin et al., 1960; Reynolds, 1965; and Karayalcin et al., 1976). Pulmonary vascular markings tend to have increased prominence in all sickle patients, and this has been interpreted as due to increased cardiac output secondary to chronic anemia (Reynolds, 1965). In addition there is a range of findings in the lung fields, the frequency of which has not been established. Findings consistent with pulmonary hypertension and cor pulmonale occur. Karayalcin et al., (1976) reported engorgement of the hilar vessels in 29 of 125 patients (age range 3 months to 50 years, mean 18 years) and a prominent pulmonary conus in 6 of the 125 patients. Zones of increased radio-lucency occur as well as transient patchy infiltrates. The latter have been described as, "faint, finely mottled and reticular in pattern", consistent with interstitial infiltrates (Reynolds, 1965).

It is these findings that Reynolds (1965) defines as sickle cell lung. In sickle cell patients at Parkland Memorial Hospital Reynolds estimated that less than 10% had radiographically what he defines as sickle cell lung disease. In addition he noted that in the population at Parkland he observed overt signs of pulmonary hypertension only in males over thirty (Reynolds, 1965). The significance of this last observation is not clear, and it may reflect some peculiarity of this particular patient population, particularly as no other reports have indicated that pulmonary hypertension is observed exclusively in males with sickle cell disease.

Cardiac Function

No examination of the effect of sickle cell disease on pulmonary function can ignore cardiovascular function. Anemia alone has cardiovascular manifestations. These usually occur with a hemoglobin of 7gm% or less, and include increased cardiac output, decreased A-V 0_2 difference, decreased peripheral resistance, and normal atrial pressure (Brannon et al., 1945; Varat, 1972).

Clinically patients have tachycardia, bounding arterial pulses, increased splitting of S_2, a prominent S_3, and systolic murmurs, which are usually most prominent in the second left intercostal space (Fowler, 1978). These findings are felt to be secondary to the increased flow resulting from increased blood volume and increased cardiac output. In sickle cell anemia signs of altered cardiac function, such as cardiomegaly, a systolic murmur, and increased cardiac output, are evident at much higher hemoglobins than in other anemias, and commonly occur with hemoglobins as high as 9 to 10 mg% (Varat, 1972).

During the 1950's and early 1960's investigators performed several studies involving right heart catheterizations in asymptomatic sickle cell patients. Sproule et al. (1957) catheterized 6 adults with SS disease. None of these patients had known pulmonary disease. Leight et al. (1954) studied 13 patients with SS disease ranging in age from 12 to 39. All 13 had systolic murmurs and evidence of cardiac hypertrophy and/or dilatation on electrocardiogram or chest x-ray. Only two of these patients had a history of heart disease. The youngest was a 12 year old girl with a documented history of rheumatic heart

disease; the oldest patient was a 39 year old male who had been admitted in congestive failure. He had no evidence of primary pulmonary disease, but had the hemodynamic pattern of cor pulmonale. Brannon et al. (1945) examined two patients with sickle cell disease in their study of cardiac dynamics in chronic anemia. Hemoglobin electrophoresis results are not available on these two patients. It is assumed that they represent SS disease. The final study examined 7 children with SS disease ranging in age from 6 to 16 (Shubin et al., 1960). All 7 had some dyspnea and fatigue chronically. At least 4 of the 7 had cardiac murmurs (not described) and at least 2 of the 7 (patients #2 and 5) had a history of pneumonia.

The data from these studies is summarized in Table I along with normal values. Data is available on a total of twenty-eight patients, ranging in age from 6 to 39. 8 of the patients are less than 15 years old. 5 patients are known to be in their 30's, while the ages of 4 of the adults are not available. In this patient group there is one documented case of cor pulmonale. None of these patients is reported to have any form of pulmonary disease or any major medical disease other than sickle cell anemia, except for the two patients with rheumatic heart disease and cor pulmonale, already cited.

Hemoglobin values ranged from 4.5 gm.% to 10.8% with

Table I — Catheterization Data

Study	Age/sex/Hgb	Hgb	RA	RV	PA/Ex.	Wedge	C.O.	Cardiac Index Room Air	Cardiac Index 100% O_2	Blood Vol. ml/Kg	Arterial O_2 Sat.	A-V O_2 Difference cc/L
Sproule et al. (1957)	35/SS		4	25/3	20/8	8.0		5.3	4.9	126		
	SS		8	49/9	43/12	15.0		5.4	4.3	121		
	SS		8	19/3	21/10	8.0		4.8	3.9	73		
	SS		6	30/6	26/10	7.9		4.9	6.1	135		
	SS		6	—	—	—		3.6	2.6	72		
	36/SS		2	17/0	18/8	4.5		4.9	7.7	—		
Leight et al. (1954)	12/F	9.7			28//37	23	6.5	5.4			97.4	29.3
	39/M	7.7			31//44	7	10.2	6.2			82.9	28.5
	27	10.8			20//26	14	9.3	5.4			86.9	27.3
	20	6.0			20//21	14	8.9	6.4			89.3	19.2
	19	5.8			17//28	13	6.9	5.1			88.5	26.5
	13	6.7			11//19	8	7.1	5.9			91.1	28.5
	17	8.3			17//19	13	14.5	7.5			97.5	21.0
	37	8.6			17//18	9	10.3	6.1			93.4	30.4
	15	7.7			18//16	11	19.2	15.9			96.1	19.4
	25	8.4			17//23	12	9.2	5.8			92.1	22.1
	25	7.0			15 NA	9	10.1	5.9			94.2	24.3
	19	7.0			15//18	10	10.6	7.5			89.4	21.5
	18	6.1			20//15	15	8.5	5.5			93.4	22.1
Shubin et al. (1960)	6/F/SS	8.4	7/4	35/5	28/12	7/4		7.2	—		86.8	
	8/F/SS	7.4	8/5	35/6	27/11	—		8.2	90.5		76.5	
	9/F/SS	6.5	8/4	30/6	27/12	11/6		7.2	86.8		79.3	
	12/F/SS	7.0	5/2	27/33	25/13	12/6		4.6	67.7		88.5	
	13/F/SS	6.3	5/3	23/3	22/10	—		11.7	119.8		80.2	
	10/M/SS	7.4	5/1	30/4	28/9	10/4		8.5	109.5		78.8	
	16/F/SS	9.5	7/2	32/2	29/8	10/5		3.8	91.4		89.0	
Brannon et al. (1945)	17/F	4.5	2.6				10.3	6.2				
	35/M	6.4	1.0				13.1	7.6				

Key to symbols: hgb-hemoglovin, where not listed,unknown. RA- right atrial pressure, mean or systolic/diastolic;RV-right ventricle pressure, systolic/diastolic;PA//Ex.- pulmonary artery pressure either systolic/diastolic or mean at rest//mean with exercise; wedge-pulmonary artery wedge pressure; C.O.-cardiac output, L./min.; Arterial O_2 saturation in percents;A-V O_2, arterial-venous O_2 difference; All pressures in mmHg, where necessary values have been converted to mmHg.

Normal Values:

Schlant(1978) RA 2-14/-2 - +6; RV 15-28/0-8; PA 15-28/5-16, mean 10 - 22; Wedge 9-23/1-12, mean 6-15; Arterial O_2 Sat. 94-100%; A-V O_2 difference 30 - 48.

a mean of 6.9% in this patient group. Cardiac output was increased markedly in all of the patients compared with a normal of 5 to 6 L/min. The cardiac index was also strikingly elevated in all patients except for one 16 year old female in Shubin et al.'s study who had a cardiac index of 3.8 L/min., which is upper normal.

Blood volume per kilogram of body weight was assessed in two studies (Sproule et al., 1957; Shubin et al., 1960). The values are notably elevated in all except one patient, when the values are compared with the normal values of 69 ml/kg for males and 65 ml/kg for females.

Right heart catheterization showed normal right atrial pressures (Sproule et al., 1957; Shubin et al., 1960; Brannon et al., 1945). Right ventricular pressures were elevated in 2 out of 6 patients studied by Sproule et al. (1957) and in 5 out of 7 patients in Shubin's study. Two of the patients in the latter study had known heart disease as mentioned previously (rheumatic heart disease and cor pulmonale). The pulmonary artery pressures measured in these two studies were markedly elevated in 1 of the 5 patients and were upper normal in a second patient in the first study. Both of these patients had elevated right ventricular pressures. Pulmonary artery pressure was elevated slightly in one patient in Shubin's study and top normal in the remaining 6 patients. Moser et al. reported an increased mean

pulmonary artery pressure in 3 of 10 patients in another study (1960). Leight et al. (1954) measured pulmonary artery pressures at rest and with exercise in their patients. At rest pulmonary artery pressure has a mean of 12 mm Hg with no significant change in this value from 4 to 70 years of age (Blount and Grover, 1978). Pulmonary artery pressure should remain the same or decrease with exercise (Luchsinger et al., 1957). An exception to this has been observed in normal supine patients with severe exercise on a bicycle ergometer such that cardiac output is tripled. Under these conditions pulmonary artery pressure has been observed to increase as much as 15 mm Hg (Blount and Grover, 1978). The decrease in pulmonary artery pressure with moderate exercise reflects vasodilatation and perfusion of portions of the capillary bed which are either underperfused or not perfused at rest. Leight et al. found that mean pulmonary artery pressures were normal to top normal at rest in all but two of the patients, who had rheumatic heart disease or cor pulmonale. With exercise the pulmonary artery pressure increased in seven of the thirteen patients. Wedge pressures in these patients were normal except for a markedly elevated wedge pressure in the patient with rheumatic heart disease. Other investigators have also observed an abnormal increase in pulmonary artery pressure with moderate exercise in patients with SS disease (Moser et al., 1960).

Echocardiographic studies on 23 asymptomatic patients with SS disease and a mean age of 29.5 years (range 16 to 53) showed normal mean right ventricular dimensions for the group when compared with nine healthy controls (Gerry et al., 1976). However, three of the sickle cell patients did have elevated right ventricular dimensions. No paradoxical septal motion was noted. When the patient group was split into two subpopulations on the basis of age, group I (mean age 22.1) versus group II (mean age 43.5), no significant difference was noted between the two groups for the mean right ventricular dimensions. Examination of the left side of the heart showed increased atrial and ventricular cavity size as well as increased left ventricular mass and stroke volume. Gerry and his coworkers concluded that the findings could be accounted for by the chronic volume overload secondary to anemia, and that the lack of significant difference between younger and older patients (again comparing the two subgroups) indicated that this volume overload was well tolerated by the left ventricle.

The question is, does progressive pulmonary hypertension and cor pulmonale occur in at least a subpopulation of those with sickle cell anemia. Of the 28 patients catheterized as part of the studies discussed here, only one, a 39 year old male, had cor pulmonale. Only 5 of the patients in this group are known to have been in their

thirties. The majority are much younger. It would be logical to reason that pulmonary hypertension might arise both from microemboli of sickled erythrocytes, fat, and marrow, and from *in situ* sickling in the lungs. All of these might be expected to accompany sickle crises. The result of these phenomena would be occlusion of microarteries in the lung, and would lead to a reduction in the cross-sectional area of the pulmonary vasculature. The importance of this cross-sectional area will be discussed later.

The life course of sickle cell anemia is punctuated by crises of varying clinical severity and varying frequency. Both aspects of the disease differ from patient to patient; some patients have severe disease diagnosed early in childhood; other patients have seemingly mild disease not diagnosed until adulthood, and even then only as an incidental finding in the course of an examination for other reasons. But, given the chronic pattern of sickle cell disease, one would expect to see pulmonary hypertension more frequently as the age of the patient population increases, and also more frequently in those with more severe disease, as measured by frequency and severity of crises. Yet in the single echocardiographic study done, only three patients had increased right ventricular dimensions, and no significant difference was noted between two patient subpopulations divided by age.

However, enlargement of the right ventricle would be expected to occur late in the course of pulmonary hypertension so one would not anticipate that right ventricular enlargement would be present in a large percentage of patients. Furthermore, the incidence would also vary with the severity of the sickle cell disease, and no information on this was provided in this study. Less severe sickle cell disease tends to favor longevity. And, lastly, no information is provided on the incidence of acute pulmonary episodes in this patient population, which as will be discussed later, is a significant factor.

Although only one of the 28 cases who underwent cardiac catheterization had cor pulmonale, 5 additional cases showed an abnormal increase in pulmonary artery pressure with moderate exercise. A similar observation was made in 3 of 10 patients in another study (Moser et al., 1960). This indicates a reduced pulmonary capillary bed reserve in these patients (Luchsinger et al., 1957). The pulmonary vascular bed normally possesses considerable reserve; a significant increase in pulmonary artery pressure does not occur until the total cross-sectional area of this vascular bed has been reduced by more than 50% (Blount and Grover, 1978).

Blount and Grover (1978) in their discussion of pulmonary hypertension list three etiologies: (1) increased pulmonary capillary or left atrial pressure,

(2) reduced cross-sectional area of the total pulmonary vascular bed, (3) significantly increased pulmonary arterial blood flow. They also cite pulmonary blood volume, blood viscosity, intrapulmonary pressure, and intrathoracic pressure as possibly contributing a minor role in the development of pulmonary hypertension. The data indicate that the patients examined in the studies discussed here had normal pulmonary capillary and left atrial pressures as reflected by normal wedge pressures. Recurrent microemboli occur in sickle cell patients accompanying crises, and in situ sickling in the lung is a possible second mechanism of vascular occlusion. Both of these phenomena, microemboli and in situ sickling, can lead to occlusion of microarterioles and a reduction in the cross-sectional area of the pulmonary vasculature.

All of these patients (who underwent cardiac catheterization) had markedly increased cardiac outputs. In the absence of right to left shunting this increased cardiac output must also be reflected in an increased blood flow to the lungs. Significant increases in pulmonary blood flow alone, as seen with major shunts such as occur with left to right shunting in intraseptal defects can cause pulmonary hypertension. The combination of increased pulmonary blood flow (of lesser magnitude than that seen with a major shunt) with a somewhat decreased pulmonary vascular bed cross-sectional area can result in an increase

in pulmonary resistance and in pulmonary hypertension (Blount and Grover, 1978). As already discussed, a decrease in the pulmonary vascular bed is a potential long term complication of sickle cell disease and the likelihood of its occurence can be anticipated to be a function of the severity of the sickle cell disease in terms of frequency of crises. Also, it can be deduced that pulmonary blood flow in these patients is increased, as their cardiac outputs are increased. This is supported by two studies demonstrating an increase in the volume of pulmonary capillary blood (Femi-Pearse et al., 1970; Miller and Serjeant, 1971). The magnitude of the increase in pulmonary blood flow would depend upon the severity of the anemia, which would again reflect the severity of the sickle cell disease. So, if pulmonary hypertension and cor pulmonale are long term complications of sickle cell disease, one would anticipate that this complication would supervene in the older sickler with more severe disease. The only catch to this is that these patients most likely succumb at an early age to other complications of sickle cell disease.

Pulmonary Function

Several investigators have done studies examining

pulmonary function in patients with sickle cell disease. Femi-Pearse et al. (1970) studied 6 patients with SS disease ranging in age from 17 to 31. Bromberg and Jensen (1967) did pulmonary function tests on 10 patients with SS disease ranging in age from 16 to 49. Young's studies involved 9 patients with SS disease ranging in age from 16 to 49 (Young et al., 1976). The final study in which detailed tables of the findings are given is that of Miller and Serjeant (1971). They compared two groups of SS patients. Thirteen had a history of pulmonary "episodes," which they defined as pneumonia, pleurisy, hemoptysis, and acute chest illness of at least one week's duration, or isolated attacks of wheezes and breathlessness in a nonasthmatic. In addition, they broke their patients down as to smokers and nonsmokers, and compared these two groups as well. The data from these four studies are summarized in Table II along with normal values. For many pulmonary function tests normal values are determined by parameters specific for each patient, such as height, weight, and age. Therefore, where investigators have provided data as to the predicted value for a given test for a given patient, or for the percent of the predicted value, these data are listed in the table.

Total lung capacity was consistently less than the predicted value for all but one patient out of these four studies. Others have also observed a consistent reduction in total lung capacity (Diggs, 1969). Vital capacity is

Table II — Pulmonary Function Test Data

Study	age/sex/hgb	VC(L)	VC/VPC	TLC	%Pred.	RV/TLC	FRC	%Pr	FVC	%Pred.	FEV_1	FEV_1/FVC	FEF_{25-75}	Vmax	D_L	Vc(ml)	D_M	$AaPO_2$	SaO_2%	Shunt(calculated)
Bromberg & Jensen (1967)	41/F/SS	2.23	75	-	-	-									13.8			7	97	4.8
	17/F/SS	2.08	60	-	-	-									6.0			37	80	19.3
	21/F/SS	2.26	68	2.72	69	17									8.6			37	86	17.4
	21/M/SS	3.70	81	5.13	94	28									12.7			25	86	14.3
	39/M/SS	3.09	76	4.74	94	35									10.0			20	90	2.8
	16/F/SS	2.62	76	3.39	83	23									8.2			20	90	2.5
	49/F/SS	2.73	70	-	-	-									-			-	87	-
	20/F/SS	3.50	108	-	-	-									10.6			27	88	4.0
	17/M/SS	2.83	67	-	-	-									14.0			28	79.5	7.9
	16/F/SS	3.13	90	-	-	-									6.5			15	94.5	13.2
Young et al.(1976)	26/M/SS	4.33	86			32	3.96	94	4.10	82		75	2.60	10.1	15					
	49/M/SS	2.72	66			22	2.31	71	2.66	64		81	2.52	9.6	24					
	38/F/SS	2.58	74			22	1.66	64	2.57	74		87	4.18	6.9	15					
	37/M/SS	4.61	85			25	2.84	71	4.53	83		80	4.55	8.2	19					
	24/F/SS	2.13	57			28	1.77	53	2.08	55		88	2.92	8.0	12					
	23/M/SS	3.05	65			27	2.81	85	2.96	63		88	3.50	5.3	21					
	28/M/SS	3.46	64			41	3.44	74	3.57	66		63	1.45	5.5	17					
	21/F/SS	1.92	52			-	-	-	1.92	52		80	1.90	-	18					
	44/M/SS	3.18	69			45	3.89	100	3.18	69		80	3.20	-	21					
Femi-Pearse et al.(1970)	18/M/SS	3.9	80	4.9	79	20									23	70	47			
	17/M/SS	4.0	79	5.2	103	23									20	89	39			
	20/M/SS	3.8	93	4.6	87	17									22	69	48			
	31/M/SS	4.0	78	5.1	79	22									32	92	66			
	17/M/SS	2.9	76	3.8	77	24									20	77	41			
	18/F/SS	4.2	72	5.4	75	22									27	95	45			
	values listed here are means +/- S.D. All subjects are SS.													mean	24(29	82(67)	*48(65)*			
Miller & Serjeant (1971)	16 males	3.39		4.9		32	2.74		3.13		2.55	81.9			89.6	45.7				
	28.2+/-8.7	+/-.73		+/-.80		+/-8					3.14	81.7			69.6	63.0				
	Predicted	4.15		5.61		26+/-3	3.27				p<.001	n.s.			p<.01	p<.001				
	values	p<.001		p<.001		p<.001	p<.01													
	9 Females	2.44		3.94		38	2.34		3.80		2.10	84.2			78.0	29.0				
	27.8+/-10.9	+/-.24		+/-.5		+/-7			p<.001		2.37	81.5			61.0	44.7				
	Predicted	2.96		4.42		32	2.64				n.s.	n.s.			p<.05	p<.001				
	values	p<.001		p<.01		p<.01	n.s.		2.47						97.5	36.8				
																60.9				
																p<.001				
	M,APE(8)	2.96																		
	Predicted	4.06							2.88						81.8	55.2				
		p<.001													n.s.	65.1				
	M,NP(8)	3.82														n.s.				
	Predicted	4.25																		
		p<.05																		
	F,APE(5)	2.41													81.0	28.6				
	Predicted	3.04														44.7				
		p<.001														p<.001				
	F,NP(4)	2.48													74.3	29.4				
		n.s.													n.s.	44.6				
																p<.001				

Symbols:hgb=hemoglobin;VC=vital capacity;VPC=predicted vital capacity; TLC=total lung capacity; Pred.=predicted;RV=residual volume;FRC= Functional residual capacity;FVC=forced vital capacity;FEV_1= forced expiration in 1 second;FEF=volume of mid-expiratory flow;Vmax= peak expiration;D_L-CO diffusing capacity; Vc= volume of pulmonar capillary blood(ml); D_M=pulmonary membrane diffusing capacity; symbols(cont.)$AaPO_2$= alveolar-arterial PO_2 difference; SaO_2%= percent arterial oxygen saturation;M,APE= males with a history of acute pulmonary episodes, eight in all;M,NP= males with no history of acute pulmonary episodes; five in all; F,APE & F,NP denote the same for females; n.s.= not significant.

*mean values for 30 normals measured by Femi-Pearse et al.(1970

reduced as well. Miller and Serjeant (1971) found vital capacity to be significantly reduced below that predicted for both males and females ($p < .001$). However, when they broke their patient population down into four subgroups (subjects with and without a history of acute pulmonary disease and each of these groups divided by sex), they found vital capacity to be significantly reduced in all groups, except in females without any history of acute pulmonary episodes.

Residual volumes as a percent of total lung capacity were significantly increased in both males ($p < .001$) and females ($p < .01$) in Miller and Serjeant's study (1971). Other reports of residual volume as a percent of total lung capacity do not provide predicted values. The values reported (as listed in Table II) are within the range of normal with the exception of four subjects who show an increased residual volume.

Only two of the studies examined additional parameters of ventilatory capacity. Functional residual capacity was found to be significantly ($p < .01$) less than the predicted value for males, but for females there was no significant difference between predicted and measured values (Miller and Serjeant, 1971). In the other study functional residual capacity was reduced in all but one of the patients (Young et al., 1976). Forced vital capacity is markedly reduced below the predicted value in both sets

of patients studied (Young et al., 1976; Miller and Serjeant, 1971). Only Miller and Serjeant measured the forced expiratory volume in one second (FEV_1). They found it to be significantly decreased in males ($p < .001$), but to not be significantly decreased in females. They also calculated FEV_1/FVC and found no significant difference between the predicted value and that measured (Miller and Serjeant, 1971). This concurs with the findings of Young et al. (1976) which demonstrated FEV_1/FVC to be normal in all but one subject. Young et al. also measured the FEF_{25-75} which reflects the volume of air expired during the midperiod of expiration. In 2 of 9 patients it was increased over the expected, while in the other seven it was reduced. In the seven patients in whom they measured V_{max} (peak flow during forced expiration) they found the values to be normal to elevated in four and reduced in three.

So, in summary, studies of ventilatory capacity show a reduced vital capacity and total lung volume. Residual volume is normal to increased. Functional residual capacity is normal to reduced. Forced vital capacity is also reduced. FEV_1 is normal to reduced, and FEV_1/FVC is normal. This pattern is one that is more consistent with restrictive disease rather than obstructive disease.

Investigators have examined airway function and ventilation distribution in sickle cell patients. Young

et al. (1976) using the nitrogen delta test found abnormal gas diffusion in only 1 of 5 SS patients. None of the 6 patients examined by Femi-Pearse and his coworkers (1970) using a helium mixing index demonstrated abnormality in gas distribution, nor did any of these patients have evidence of airway obstruction. Young et al. (1976) also found normal small airways in 5 patients using the closing volume test. Assessment of large airway function with a body plethysmograph showed evidence of obstructive disease in only 1 of 9 patients (Young et al., 1976). The numbers of patients examined in these two studies is small, and further studies confirming these results would be useful. The findings of these two sets of investigators are indicative of normal airway function and normal ventilation distribution in these patients.

Measurements of parameters of gas exchange in the lung showed D_m (pulmonary membrane diffusing capacity) to be reduced. Interestingly, Miller and Serjeant (1971) found that D_m was reduced significantly in those subjects with a history of acute pulmonary episodes, both male and female, but D_m was not reduced significantly in those subjects with no history of acute pulmonary episodes. Furthermore, they found that D_m was reduced in nonsmokers, but not in smokers. They interpreted this as reflecting either that carbonmonoxyhemoglobin S formation might be protective, or that those with more severe sickle cell

disease and poorer pulmonary function would self-select and choose not to smoke.

The carbon monoxide diffusing capacity (D_LCO) in sickle cell patients is also reduced. Although all investigators found D_LCO to be reduced, only Femi-Pearse and his coworkers interpreted the D_LCO as high relative to the anemic state of these patients. However, other investigators interpreted D_LCO as reduced, even after taking into account the patients' anemia. None of the investigators applied the formula of Dinakara and his coworkers (1970) which corrects D_LCO for the degree of anemia present. Anemia alone will give a falsely reduced D_LCO which reflects the anemia, and not pulmonary function.

Arterial blood gases in sickle cell patients show a reduced arterial PO_2 as well as a reduced oxygen saturation (Leight et al., 1954; Shubin et al., 1960; Bromberg and Jensen, 1967). The alveolar-arterial oxygen gradient ($AaPO_2$) is increased in sickle cell subjects (Fowler et al, 1957; Moser et al., 1960; Jensen and Bromberg, 1967; Diggs, 1969; and Miller et al., 1973). With exercise the $AaPO_2$ gradient increases in sickle subjects (Miller et al., 1973; Moser et al., 1960). Miller et al. (1973) found V_d/V_t, which measures physiologic dead space, failed to drop below resting values upon exercise in 10 of 20 subjects. In addition they found that in 9 of 10 subjects thirty minutes of breathing

100% oxygen failed to raise the PaO_2 above 500 mm Hg. This result concurs with that of Sproule and his coworkers (1957) who found an average Aa gradient of 165.4 mm Hg while breathing 100% oxygen in those patients who had arterial oxygen desaturation on room air. Bromberg and Jensen (1967) also found the arterial PO_2 to be reduced on 100% oxygen with 4 of 9 patients failing to reach a PaO_2 of 500 mm Hg. Sproule et al. (1957) calculated an average shunt in their patients of 11.96%, while Bromberg and Jensen (1967) calculated shunts ranging from 2.5 to 13.2% (see Table II for data). The failure of hypoxemia to disappear on breathing 100% oxygen indicates shunting (West, 1974). All of these investigators interpreted these findings as consistent with venous shunts and with pulmonary thromboembolism.

There have been mixed reports concerning the oxyhemoglobin dissociation curve in sickle cell disease. Diggs (1969) observed a marked rightward shift in the oxygen dissociation curve which confirmed the observations of others (Becklacke et al., 1955; Fowler et al., 1957). However, Young et al. (1976) found no abnormality in the oxyhemoglobin dissociation curve. There are several possibilities which could account for the discrepancy between Young's data and that of other studies. High levels of hemoglobin F (10% or more) can shift the oxyhemoglobin curve towards normal (Milner, 1974), and this

could possibly account for at least some of the difference. If the subjects in Young's study had high levels of hemoglobin F this would have shifted the dissociation curve. The electrophoresis patterns of the subjects, however, were not reported beyond that they were SS. Also, the technique they used in assessing the saturation values they obtained may have contributed to their finding no difference from normal. Rather than measuring oxygen saturations of blood from normal and sickle subjects at various PaO_2 values, and then using this data to derive a normal curve and a sickle curve, they made a single determination of the oxygen saturation of the blood of each of the nine subjects in their sample. They then applied this data to a standard curve and observed that their data more or less fit the normal curve. The imprecision inherent in this method and the lack of normal controls performed in their own laboratory to standardize their technique could have caused them to obtain different results than all the other investigators.

The studies which have been done on sickle cell patients indicate three possible abnormalities in pulmonary function: (1) restrictive disease, as evidenced by measurements of ventilation capacity, (2) diffusion deficiency as evidenced by a reduced D_m, a reduced D_L, and arterial oxygen unsaturation, and (3) venous shunting as evidenced by a persistent alveolar-arterial O_2 gradient

while breathing 100% O_2. Repeated bouts of pneumonia, embolism, and infarction can potentially lead to scarring which would result in restrictive type disease. Micro-emboli to small distal arteries in the lung are more likely to result in intralveolar hemorrhage and pulmonary infarction than major emboli (Dalen et al., 1977). Multiple episodes of pneumonia, embolism, alveolar hemorrhage, and infarction can result in scarring and thickening of the alveolar-capillary membrane. This would impair gas exchange. Furthermore, increased pulmonary blood flow, particularly across a reduced vascular bed, can result in a reduced transit time across the pulmonary capillaries, and thus reduced contact with the alveolus. In the normal lung only one third of the transit time is necessary for equilibration between alveolar gas and the blood (West, 1977). If this transit time is reduced as a result of increasing the velocity of the blood, the net result could be impairment of gas exchange. It is clear that the critical value would be a tripling of the rate of blood flow, which is a significant increase. Nonetheless, the combination of an increase in blood velocity with scarring and thickening of the alveolar membrane could result in impaired gas exchange at lower blood velocities. The third abnormality, venous shunting, could arise as a result of gross V/Q mismatch, again as a result of infarction and scarring. The possibility of bronchopulmonary anastomoses

has been raised by finding such anastomoses in the autopsy of one sickle cell patient (Heath and Thompson, 1969). Such anastomoses might contribute to shunting, but the observation has yet to be confirmed.

A diffusion defect across the alveolar-capillary membrane can give rise to hypoxemia in the pulmonary capillary. The response of the pulmonary capillary to hypoxemia in a given area is vasoconstriction in that area. This hypoxic vasoconstriction would decrease the pulmonary vasculature cross-sectional area. Potentially this can result in increased pulmonary pressure if the cross-sectional area is already critically reduced. It is possible that exercise by increasing the cardiac output and blood velocity decreases the transit time in the pulmonary capillaries resulting in hypoxemia in a portion of the pulmonary vasculature. This would then cause vasoconstriction and could cause increased pulmonary pressure if the pulmonary vascular bed is already reduced. This could account for the increase in pulmonary artery pressure observed in a number of sickle cell patients with moderate exercise.

The onset of pulmonary disease in sickle cell patients can be anticipated as being insidious. Rather than major embolic episodes resulting in pulmonary impairment, multiple episodes of small, frequently "silent" or unnoted microembolizations and <u>in situ</u> sickling accompanying crisis

result in a gradual impairment of pulmonary function. More than 50% of the pulmonary vascular bed must be obliterated before pulmonary hypertension will be evident. Thus pulmonary disease would evolve over a long period of time, and would be expected to be more likely to occur in those with more severe sickle cell disease and to be most often evident in the older population of sicklers. However, as mentioned previously, those most likely to survive into their thirties and forties are those with less severe disease. Nonetheless there have been a number of reports of cor pulmonale in sickle cell patients in the literature, and this would represent the end-stage of pulmonary disease in sicklers (Yater and Hansmann, 1936; Moser and Shea, 1957).

In addition to the development of pulmonary disease over the chronic course of sickle cell disease, an acute counterpart to this process is also possible. Two mechanisms, embolization and in situ pulmonary sickling, can potentially cause severe acute disease of the lung. Both can result in alveolar hemorrhage, infarction, and vasoconstriction. In turn an increase in pulmonary artery pressure can occur. For reasons already detailed a reduction in the oxygenation of the blood can occur. This can set up more vasoconstriction. Also this will potentiate both sickling in the pulmonary vasculature and elsewhere as well. Furthermore low oxygen tensions

impair macrophage function and this predisposes the patient to pulmonary infection. Pneumonia will further reduce lung function and oxygenation of the blood. Thus a vicious cycle can be set up which potentially leads to pulmonary failure.

Pathology

Several reports of pathological findings in the lungs of patients with sickle cell disease have appeared in the literature. Yater and Hansmann (1936) reported two cases of cor pulmonale in patients with sickle cell disease. One of these was acute in onset. Autopsy of the first showed many thrombi in small and medium sized arteries in different stages of organization. In addition arteriole thickening and hyalinization were present. The lungs were edematous with bleeding into the alveoli of the lower lobes. No gross infarct was evident. Autopsy of the second patient showed cardiac dilatation, hepatomegaly, and emphysematous lungs. Microscopic examination was not performed.

In a review of the autopsy findings of 72 patients with sickle cell disease, 62 of whom had SS, Diggs reported finding sickling in pulmonary blood vessels, proteinaceous material in alveoli, emboli in pulmonary

arteries, serofibrinous pleural effusions, and pleural adhesions (Diggs, 1969). Emboli consisted of thrombi, sickled erythrocytes, fat, marrow, and bone. Emboli and infarcts were observed only in one of 32 children less than 10 years of age. Fresh and organized pulmonary emboli were present in 18 of 30 patients, and gross infarcts were present in 12.

Oppenheimer and Esterly (1971) reviewing autopsies on 36 patients with sickle cell anemia ranging in age from 2 months to 34 years demonstrated similar findings. Approximately two thirds of the patients had thromboemboli in various degrees of organization. Pulmonary edema was present in 23 out of 36, and 9 showed dilatation of interstitial spaces and pulmonary lymphatics. In 17 out of 36 pulmonary infection was present. Oppenheimer and Esterly noted proliferation of the arterial intima in 8 of the cases. It was not extensive and was associated with pulmonary hypertension in only one female with cor pulmonale. Over one fifth of the cases had intimal proliferation and pulmonary infarcts. Similar changes were observed in 6 patients with SC disease. In addition they reported observing hyperplasia of the pulmonary lymphoid tissue in nearly all of the cases.

Both Diggs and Oppenheimer and Esterly felt that the incidence of thromboemboli in the lungs increased significantly with age. With thrombi and sickling in the

lungs of sickle cell patients, there is always the difficulty of distinguishing what occurred pre-mortem from what occurred post-mortem. However, the thrombo-emboli reported by these investigators showed various stages of organization, indicating that they were not the result of port-mortem thrombosis and sickling.

There has been one case report of bronchopulmonary anastomoses in a 28 year old male with SC disease (Heath and Thompson, 1969). This patient died suddenly, and autopsy showed that the right ventricle was at the upper limits of normal in size. The left ventricle was normal, and no coronary fibrosis was present. Examination of the lungs revealed widespread occlusion of the elastic pulmonary arteries by thrombi in various stages of organization. Atrophy of the media under organized thrombi was present in many areas with loss of musculoelastic tissue and a marked decrease in medial thickness. In these areas Heath and Thompson reported finding disruption of the elastic fibrils and small capillaries communicating with branches of prominent bronchial arteries. These bronchopulmonary anastomoses were usually less than 100 u in diameter. There have been no other reports of bronchopulmonary anastomoses in sickle cell patients, and Oppenheimer and Esterly (1971) specifically note the absence of any such anastomoses in any of the cases they examined.

The reports of pathological findings in the lungs of

patients with sickle cell anemia are limited. The question is whether these few reports present data that would support or exclude the hypothesized progressive course marked by multiple episodes of microemboli, often silent, leading to pulmonary scarring, reduction in the size of the pulmonary vascular bed, and eventually to pulmonary hypertension and cor pulmonale.

Pathologically there are three types of pulmonary hypertension: (1) plexogenic pulmonary arteriopathy, (2) recurrent pulmonary thromboembolism, and (3) veno-occlusive disease (Edwards and Edwards, 1977). It is the second type that we would anticipate to find pathological changes for. Recurrent pulmonary thromboembolism is characterized pathologically by thromboemboli in the microscopic arteries (Edwards and Edwards, 1977). These thrombi are either embolic in nature or develop in situ in the lungs. In addition with recurrent thromboembolism secondary changes occur at the precapillary level with medial hypertrophy of the muscular pulmonary arteries (Edwards and Edwards, 1977). The alveolar capillaries and veins are normal.

The pulmonary vasculature of Yater and Hansmann's patient with chronic cor pulmonale showed arteriole thickening, but cor pulmonale was already established in this patient. 6 of the 12 adults with SS disease in Oppenheimer and Esterly's study showed intimal prolifera-

tion. Only 2 of 12 children between the ages of 3 and 14 had similar findings, and intimal proliferation was not observed in any of the 12 children with SS disease under 3 years of age. This is suggestive of a progressive change in the pulmonary arterioles with age resulting in increased intimal proliferation. They observed intimal rather than medial thickening. However, this is only one report. All of the investigators reported observing thromboemboli in the pulmonary vasculature in many of the cases. The frequency of this finding tended to increase with age. In the few reports with microscopic examination of the lungs, there was no report of medial hypertrophy. The pathology reported by these various investigators definitely demonstrates thromboembolism as a significant occurence. It is not possible to determine from these few reports the frequency of changes consistent with pulmonary hypertension and cor pulmonale. It is clear that a more extensive review of the pathology of the lungs of patients with sickle cell disease is needed in order to better define the pathological changes which occur.

The studies which have been done suggest a chronic, insidious course marked by repeated pulmonary infections, microemboli, and *in situ* sickling. This can lead to scarring and fibrosis in the lung and reduction of the pulmonary vascular bed. Increased cardiac output together with a reduction in the cross-sectional area of the pulmoanry vascular bed can result in pulmonary hypertension and eventually cor pulmonale. Cor pulmonale may not be seen frequently because those one would postulate as being most likely to develop it, those with the most severe sickle cell disease, are more likely to succumb early to other complications of their disease. Evidence indicates an impaired immune system and possibly impairment of alveolar macrophage function. Impairment of alveolar macrophage function has yet to be demonstrated *in vivo*, but it can be suspected on the basis of reduced oxygen tensions and the necessity for high oxygen tensions for alveolar macrophage function in microbial phagocytosis.

Infarction and pneumonia are both important pulmonary complications of sickle cell anemia. The prolonged course for pneumonia observed in these patients suggest that these episodes might be complicated by *in situ* sickling, pulmonary hemorrhage, and/or infarction.

These patients show cardiomegaly and other signs of

chronic anemia such as tachycardia. Cardiac catheterization studies are suggestive of increased pulmonary pressure and reduction in the pulmonary vascular bed. Pulmonary function studies which have been reported are suggestive of restrictive disease and of venous shunting. Data also indicate a diffusion defect, but more accurate studies of carbon monoxide diffusion which correct for the patients' anemia need to be done. There is some evidence of an increased Aa oxygen gradient as well, which indicates impairment of gas exchange. More information is needed on pulmonary function including confirmation of the observations which have been made. Data from pulmonary function studies done on the Yale-New Haven population of sicklers will be presented in the second section of this paper.

Pathological reports on sickle cell patients are very limited. Pulmonary microemboli are present very frequently, and their occurrence seems to increase with age. Pulmonary arteriole thickening has been reported, and there are several reports of cor pulmonale in sickle cell patients. However, the data in this area are very limited. Much more information on the pathologic findings in the lungs of sickle cell patients is needed.

Clinical Studies

Two approaches were taken to examining the effect of sickle cell disease on pulmonary function. First, clinical data for those patients followed at Yale-New Haven Hospital was analyzed. The incidence of acute pulmonary disease and the signs and symptoms of these episodes were looked at. As no data has been reported on the frequency and characteristics of acute pulmonary disease in the adult patient with sickle cell disease, this was of particular interest. Others have reported a dramatically increased incidence of pulmonary disease in populations largely made up of children, and it was of interest if this increase would also be observed in adults. Secondly, as pulmonary function studies have been inconclusive, a series of measurements of pulmonary function was done on ten patients with sickle cell disease. The next section of this paper will present these studies and their results which demonstrate a high incidence of acute pulmonary disease and definite abnormalities in pulmonary function.

Materials and Methods

Clinical Data: 28 Patients with Sickle Cell Disease

The hospital charts of all adults with sickle cell disease, SS, SC, and S-Thalessemia, were reviewed at Yale-New Haven Hospital during the period of 1970 to 1978. Charts were reviewed in their entirety, so that data is drawn from the entire period each patient was followed at Yale-New Haven Hospital. All patients greater than 15 years of age were considered adults. The diagnosis of sickle cell disease was based upon hemoglobin electrophoresis, the presence of anemia, and the family genetic history. The records of 34 patients were reviewed. Of these 34, two patients were eliminated from the study due to primary pulmonary disease (tuberculosis and sarcoid). Another four patients were excluded as they are followed primarily at other hospitals.

Twenty women and eight men comprised the patient group studied. The patients ranged from 17 to 65 years of age, mean age 28. Seventeen of the patients had SS disease, 12 women and five men; six patients had S-Thalessemia; the remaining five women had SC disease.

Patients were first seen at Yale-New Haven Hospital

within the period from 1949 to 1978, and were followed for a total of 339 patient-years (mean follow-up 12 years). Of the 339 patient-years, 113 were when these patients were in the pediatric age group (15 years or younger) and 225 were during adulthood. The mean follow-up period for patients seen during the pediatric period and adult period was similar--eight years. Since all patients were selected as adults, the pediatric data are mostly from late childhood, although some of the patients have been followed since birth.

Pulmonary Function Studies Protocol

All patients who could be contacted were asked to participate in a study of pulmonary function approved by the Yale University School of Medicine Human Investigation Committee. Nine females and one male agreed to do pulmonary function tests. Of these ten subjects, five had SS disease, three S-Thalessemia, and two SC. The age range of the ten patients was 21 to 38, average 26. A clinical history including respiratory symptoms and smoking and occupational history, was obtained for each subject. A physical examination was done prior to the tests.

Hemoglobins were measured. Posterior-anterior and lateral chest radiographs were obtained on the day of testing if a baseline chest radiograph was not available

from the previous two months.

Lung volumes were determined using the helium dilution technique, and were done with the Collins Maxi-Survey Computer System using a Stead-Wells eight liter spirometer.

Maximum expiratory flow volume (MEFV) curves were done on a flow volume device--a pneumotachygraph intergratory system of Virulto and Bouhuys (1973) and a Brush 500 high performance calibrator was used to calibrate the pneumotachygraph for air and helium. First, the subject breathed air in performing the MEFV curves, and then repeated the test breathing an 80% helium-20% oxygen mixture. Each set of curves (helium-oxygen and air) was repeated at least three times, and the curves were reproducible. Maximum expiratory flow rate at 50% vital capacity ($MEF_{50}Air$), forced expiratory volume in 1 second (FEV_1), and forced vital capacity (FVC) were determined from the air flow volume curves. The MEF_{50} for helium ($MEF_{50}He$) was determined from the MEFV curves breathing helium.

The flow rate response at 50% of the FVC breathing helium compared to air was expressed as ΔMEF_{50}helium.

$$\Delta MEF_{50}He = \frac{MEF_{50}He - MEF_{50}Air}{MEF_{50}Air} \times 100$$

A $\Delta MEF_{50}He$ of less than 20% was interpreted as suggestive of small airway disease (Dosman et al., 1975; Despas et

al., 1972).

The diffusing capacity for carbon monoxide (DLCO) was determined using the single breath method of Gaensler and Smith (1973).

Arterial blood gases were obtained at rest breathing room air in a sitting position. Following infiltration of the skin over the radial artery with xylocaine, a 21 gauge needle was inserted into the artery and a sample obtained. The arterial blood gases were repeated following 20 minutes of breathing 100% oxygen via a demand valve with a mouthpiece. All measurements were made immediately after obtaining the blood samples.

Alveolar-arterial (A-a) oxygen gradient was determined using the following equation:

$$P_AO_2 = P_IO_2 - (P_aCO_2 \times 1.25)$$

$$\text{then, } (A\text{-}a) = P_AO_2 - P_aO_2 \qquad \text{Cherniak (1977)}$$

where: P_AO_2 = alveolar O_2, P_IO_2 = inspired O_2, P_aO_2 = arterial O_2, and P_aCO_2 = arterial CO_2.

Predicted normals for (A-a) oxygen gradient were taken from Mellemgaard's measurements in a healthy population (Mellemgaard, 1966).

The magnitude of the intrapulmonary shunt was calculated as follows using arterial blood gases obtained

while the subject was breathing 100% oxygen (minimum of 20 minutes):

$$\frac{\dot{Q}_S}{\dot{Q}_T} = \frac{C\ (c' - a)\ O_2}{C\ (c' - \bar{v})\ O_2}$$

where: $\dot{Q}_S$ = shunt blood flow. $\dot{Q}_T$ = total blood flow. Cc'_{O_2} = endcapillary O_2. $C_{a_{O_2}}$ = arterial O_2, and $C\bar{v}_{O_2}$ = venous O_2. An a-$\bar{v}$ oxygen content difference of 5 ml/100 ml is assumed (Cherniak, 1977).

Predicted normal values for FVC, FEV_1, and MEF_{50} were from Higgins and Keller (1973). Predicted values for functional residual capacity (FRC) were from Bates et al. (1971), and for residual volume (RV) from Goldman and Becklake (1959). Predicted DLCO was from Gaensler and Wright (1966), and was corrected for anemia using the equation of Dinakara et al. (1970). All predicted values for lung volumes, flow-volume measurements, and DLCO were adjust by a factor of 0.85 to account for racial difference (Binder et al., 1976).

Predicted values for arterial blood gases were calculated from the equation of Bates et al. (1971).

Informed consent was obtained prior to the study with a research protocol approved by the Yale University School

of Medicine Human Investigation Committee.

Results

Clinical Data: 28 Patients with Sickle Cell Disease (Tables III-VI)

A total of 62 episodes of acute pulmonary disease were diagnosed over a period of 339 patient-years (see Table III). Thirty-three of the episodes were pneumonia; nine pulmonary infarction or embolism; nine acute bronchitis; six were of unknown etiology, likely pneumonia or infarction; and one each was pleurodynia, "pneumonitis," and pharyngitis. The latter case was included because of a chest radiograph infiltrate. In all cases in which pulmonary infarction or pulmonary embolism (from here on these will all be referred to as pulmonary infarction) was diagnosed, there was no evidence of deep vein thrombophlebitis. Other possible sources of emboli in these patients are fat and marrow from the marrow cavity and thrombi of sickled cells. All of these would arise as a result of an ongoing crisis. In situ sickling in the lungs is also a possible etiology.

Thus, the incidence of acute pulmonary disease in this sickle cell population of 28 patients is one episode

Table III — Incidence of Pulmonary Disease in the Sickle Cell Population at Yale-New Haven Hospital. Data compiled case records of all known patients with SS, SC, or S/Thalessemia.

	# Patient-Years Followed	# Episodes of Acute Pulm. Disease*	Episodes** Years	Hosp.*** Pneumonia	Hosp.Pneum. Years	Total Pneum	Total Pneum. Years
Total	339	62	1/5.5	21	1/16.1	33	1/10.3
Pediatric	113	21	1/5.4	3	1/37.7	14	1/8.1
Adult	226	41	1/5.5	18	1/12.6	19	1/11.9

* episodes of acute pulmonary disease includes pneumonia, pulmonary infarction, bronchitis, and those with pulmonary disease of unknown diagnosis(acute disease).

** Episodes/Years represents the number of patient-years divided by the number of episodes.

*** Hosp. — hospitalizations.

every 5.5 years. Twenty-five of these episodes were diagnosed and treated in the emergency room. This included 11 episodes of pneumonia in the pediatric group and one in an adult. There were 21 cases of pneumonia necessitating hospitalization. Three of these were in children and 18 in adults. Overall, pneumonia was diagnosed at an approximately equal frequency in children and adults, once every 8.1 and 11.9 patient-years respectively. At the same time, the rate of hospitalization for crisis in the same population was once every 3.3 patient years (see Table IV).

Of the nine episodes of pulmonary infarction, four were diagnosed in children (all in the same patient, D. H.) and five in adults. The diagnosis was based on exclusion of other causes (e.g. pneumonia) and on an appropriate clinical picture consisting of presence of crisis and symptoms of pulmonary disease. The characteristics of these nine episodes will be discussed in more detail.

Management

In the management of these patients hydration and analgesics were used whenever crisis accompanied the acute pulmonary episode. In addition oxygen and antibiotics were used when pneumonia was suspected. Arterial

Table IV — Incidence of Pulmonary Disease in Sickle Cell Population at Yale-New Haven Hospital.

	Pediatric		Adult	
Diagnosis	E.R.*	Hospitalized	E.R.*	Hospitalized
Pneumonia	11**	3	1	18
Pulmonary Infarct	0	4	0	5
Bronchitis	1	0	4	4
Unknown[3]	2	0	4	2
Other[4]	0	0	3	0

*Treated in emergency room and released.

**Total number of cases.

3 Acute pulmonary disease, etiology unknown.

4 Includes pneumonitis, pleurodynia, and pharyngitis. The latter included because of acute chest x-ray infiltrate.

blood gas determinations were employed in management of only one third of the adult in-patients with acute pulmonary disease, and were obtained in none of the pediatric patients, and in none of the outpatients. Transfusion was employed in the treatment of 23% of the total episodes, and 29% of these transfusions were partial exchange transfusions. Ninety-three percent of the patients were performed on adults. Sixty-four percent of the patients transfused were concurrently in crisis. Forty percent of adult inpatients were treated with transfusion in addition to other modes of therapy.

Signs and Symptoms of Pneumonia Versus Infarction

In order to better define the characteristics of pneumonia in the sickle cell patient a scale was set up to make a more definitive diagnosis (see Table V). As illustrated in the table, points were assigned to various signs and symptoms of pneumonia. The highest ratings were assigned to the most diagnostic signs and symptoms with a positive sputum culture (for a pathogen) and a positive mycoplasma titer receiving the highest number of points. Using this scale, all 62 episodes were evaluated. Points were deducted for the presence of crisis and hemoptysis, even though pneumonia and crises may be

Table V. —Scale for evaluating acute pulmonary episodes in patients with sickle cell anemia. Score of greater than five indicative of pneumonia.

Sign/symptom	Point Value
Productive cough	1
Onset Chill	3
Discrete chest radiograph infiltrate	2
White Blood Cell Count	
>10,000	1
>15,000	3
Differential Count 5% or more bands	3
Positive Gram Stain	2
Positive Culture for Pathogen	5
Positive Mycoplasma Titer	5
Crisis	-1 *
Hemoptysis	-1 *

* Subtract one point.

concurrently present. For nine of the cases there was insufficient data to evaluate on this scale. Using five points as a cut-off, all cases with a score greater than this were considered to have pneumonia. Seventy-three percent (22 or 30) cases with discharge diagnoses of pneumonia fulfilled the criteria of the scale for pneumonia by having more than five points. Three of the other cases with discharge diagnoses of pneumonia lacked sufficient data to be evaluated on the scale. Another five cases with discharge diagnoses of pneumonia when evaluated on the scale had a total of five or fewer points. These eight cases with discharge diagnoses of pneumonia which either had insufficient data or failed to fulfill the criteria of the scale were not considered in the analysis of the frequency of signs and symptoms.

In addition to the 22 cases of pneumonia, three cases of bronchitis and two of unknown diagnosis had more than a score of five. The bronchitis cases were omitted from the analysis. All nine cases which had been diagnosed as pulmonary infarction had five or fewer points.

The average age of the patients with pneumonia was 22 with a range of one to 49. Two-thirds of the cases were admitted to Yale-New Haven Hospital; the remaining one-third were treated in the emergency room. Seventy-five percent of those treated in the emergency room were children, while 83% (12 of 14) of those hospitalized were

adults.

The signs and symptoms of these 22 cases of pneumonia defined as above, were examined (Table VI). Twenty-nine percent of the patients had an antecedent URI. Forty-two percent had a concurrent crisis and 25% had an onset chill with their pneumonia. Pleuritic chest pain was present in 33% and hemoptysis occurred in one patient. While 54% had a history of previous pneumonia, just over 12% had a history of pulmonary infarction. The most common presenting symptom was productive cough which occurred in two-thirds of the patients. Although only one-fourth of the patients had an onset chill, it was a highly reliable symptom for pneumonia, and gram stains and/or cultures were positive in two-thirds (two of five) of the cases. Cultures were positive for Diplococcus pneumonia twice and for Hemophilus influenza once in those presenting with a chill. Two-thirds of those with onset chill were adults.

Significantly over 37% of the patients were afebrile on presentation, though all but two went on to develop fever. The mean duration of fever with treatment was 5.3 +/-2.9 days (mean +/- S.D.). The average length of hospitalization was 10.1 +/-4.9 days. The mean white count on presentation was 24,000, but there was a large range from 11,200 to 56,250/mm^3. A left shift was not consistently present on presentation. The average percentage of bands was 10.8 +/-8.4.

Table VI — Frequency of signs and symptoms in pneumonia and in pulmonary infarction in patients with sickle cell disease on presentation.

sign/symptom	Pneumonia (24)*	Pulmonary Infarction (9)
Fever	62% (15)	33% (3)
Crisis	42% (10)	89% (8)
Productive Cough	67% (16)	0% (0)
Hemoptysis	4% (1)	0% (0)
Onset Chill	21% (5)	0% (0)
Preceeding URI	29% (7)	11% (1)
Pleuritic Chest Pain	33% (8)	33% (3)
History of Pneumonia	54% (13)	67% (6)
History of Pulmonary Inarction	12% (3)	44% (4)
History of Oral Contraceptive Use	0% (0)	11% (1)
Chest Radiograph Infiltrate	100% (24)	22% (2)
Multilobe Involvement on Chest Radiograph	38% (9)	0% (0)
Pleural Effusion	4% (1)	33% (3)
White Blood Cell Count Above 15,000	77%** (19)	100% (9)
Differential Count 5% or more Bands	77%** (19)	44% (4)
Elevated Bilirubin		
Direct	80% (8/10)	71% (5/7)
Total	90% (9/10)	100% (7/7)

*Figures in parentheses are total numbers of patients.

**These two groups are not identical, some patients had "left shifts" and no elevation of white count and vice versa.

The chest radiograph showed an infiltrate in all patients. In over 37% there was multilobar involvement. Only one of 24 patients had a pleural effusion.

Gram stains were positive in only six of the cases. Of these half grew pathogens. Cultures from an additional two patients were positive. The organisms isolated were Diplococcus pneumoniae (three patients), Haemophilus influenza (one patient), and Staphylococcus aureus (one patient). Two of the culture positive cases of Diplococcus pneumoniae were in adults, the other in a child.

For comparison data from the nine patients diagnosed as having pulmonary infarction or embolism without pneumonia, all of whom came in on the low end of the evaluating scale, were analyzed. One of the nine had an antecedent URI. 89% presented with concurrent crisis. Pleuritic chest pain was present in one third. None had a productive cough, and none had hemoptysis. Sixty-seven percent had a history of pneumonia and 44% had a history of pulmonary infarction. One patient was taking oral contraceptives.

All patients with a diagnosis of pulmonary infarction were hospitalized for their illness. The mean age was 25 with a range of 12 to 42. The average length of stay was 9 +/- 4 days. Two-thirds were afebrile on presentation. Four patients had low-grade fevers during hospitalization, and the average duration of fever for these patients was

5 +/-2 days.

The average white blood count on presentation was 22,100/mm^3 with a range of 19,900 to 31,700/mm^3. Four of the nine patients had a left shift in their differential, and in two of these the shift was marked--20 and 30% bands respectively. The mean percentage of bands for all nine patients on presentation was 7.4%.

Reticulocyte counts were examined in view that reticulocytosis might be suppressed in the presence of infection and normal or elevated with infarction. The average count was 17 +/-13% while the average was 20.8 +/-18.7% in patients with pneumonia.

Bilirubin was elevated in the group with pulmonary infarction, but not consistently: mean direct was 1.74 mg/100 ml, mean total 2.75 gm/100 ml. Bilirubin was lower in those with pneumonia: mean direct 0.62 mg/100 ml, mean total 2.57 mg/100 ml, but values were not consistently different from the values seen in patients with pulmonary infarction.

One-third of the patients with pulmonary infarction had clear chest radiographs. Another one-third of these nine patients had pleural effusions. The chest radiograph of only one patient demonstrated the classic wedge-shaped infiltrate of pulmonary infarction. Two chest radiographs showed plate-like atelectasis, and one had an elevated hemidiaphragm.

Chest Radiograph Findings in Asymptomatic Sicklers

Of the 28 patients whose records were reviewed, one had evidence of pulmonary hypertension on chest radiograph indicated by prominence of the main pulmonary artery and redistribution of blood flow to the upper lung zones. This patient, a 28 year old woman, had had a severe course of sickle cell anemia with a history of 26 episodes of hospitalization for crisis and five hospitalizations for acute pulmonary disease. She declined to be studied. One other patient, a 22 year old woman, had a borderline increase in the prominence of the main pulmonary artery on chest radiograph, which was suggestive of possible pulmonary hypertension, but not diagnostically definite.

Pulmonary Function Studies: Ten Patients with Sickle Cell Disease (Tables VII to XI)

The mean age of the ten patients studied was 26. Nine of those studied have been followed for a total of 122 patient-years--48 pediatric and 74 adult. One patient was followed primarily at another hospital and

Table VII —Ten subjects of pulmonary function studies.

Patient	sex	age	Hemoglobin	%F	#Months Followed	Hospitalizations** Crisis	Pulm.Disease	Pulm. Dis. & Crisis	Outpt. Pulm.Dis.	Outpt. Pulm.Dis. & Crisis
S.B.	F	28	SS	10.5	201	1	1	1	3	0
J.C.	F	24	SThal	10.6	152	8	0	0	0	0
E.D.	M	25	SThal	6.1	30	3	2	2	0	1
S.E.	F	29	SS	5.2	340	4	2	1	0	0
D.H.	F	23	SS	-	180	8	6	5	0	0
E.T.	F	21	SS	18.0	115	0	0	0	0	0
B.K.	F	28	SC	3.0	174	0	0	0	2	0
H.S.	F	38	SC	2.2	123	0	2	0	4	0
S.Si.	F	27	SThal	4.9	147	4	1	0	0	0
F.M.	F	25	SS	11.2	*	*	*	*	*	*

Outpt.=outpatient. Pulm.Dis.=episodes of acute pulmonary disease.

* Patient followed at another hospital, figures not available.

** Hospitalizations for crisis, hospitalizations for acute pulmonary disease, and hospitalizations for acute pulmonary disease with concurrent crisis.

is not included here. During the period they were followed at Yale-New Haven Hospital these patients were hospitalized 28 times for crises and had 23 episodes of acute pulmonary disease (pneumonia, pulmonary infarction, and bronchitis as discharge diagnosis). Fourteen of these episodes necessitated hospitalization. Three patients including both with SC disease and one with SS and 18% F hemoglobin had never been hospitalized for crisis. Two patients had never had an episode of pulmonary disease.

All patients were asymptomatic and denied cough or dyspnea. There was no history of occupational exposure to known pulmonary toxins in any of the patients. Eight of the ten patients were smokers; seven smoked one-half pack of cigarettes per day or less. All patients were free of acute pulmonary disease at the time of the study. Physical examinations were unremarkable except for the presence of soft (grade I to II on a scale of VI) systolic ejection murmurs, which were heard at the lower left sternal border and were nonradiating, in six patients.

The mean hemoglobin of the ten patients was 10.1 +/-2.2 mg% (see Table VII). The mean percentage of F hemoglobin was 9.1%. Chest radiographs were normal except for cardiomegaly in four of the patients.

Lung volume measurements (see Table IX) demonstrated a reduced functional residual capacity (FRC) in four of

Table VIII — Flow-Volume Studies

Patient	Hgb/Hct	Smoking History	FEV_1	%Pred.	FVC	%Pred.	FEV_1/FVC	%Pred.	MEF_{50}	%Pred.
S.B.	10.4/31.6	1 pack-year	2.16	86	2.72	93	79	91	2.4	72
S.E.	7.6/21.9	None	3.05	121	3.83	131	80	93	4.0	122
D.H.	7.8/23	4 pack-years	2.30	88	3.30	94	87	124	1.9	58
F.M.	8.9/28	2.5 pack-years	2.50	96	2.84	95	88	101	2.9	86
E.T.	11.0/31.4	2.5 pack-years	3.10	118	3.48	99	89	101	5.1	126
S.Bi.	13.5/40.5	7.5 pack-years	2.42	89	2.90	92	83	95	3.1	90
J.C.	7.8/23.5	None	2.40	107	2.95	100	81	91	3.1	96
B.K.	13.2/39.6	5.5 pack-years	2.15	93	2.70	102	80	90	2.4	76
H.S.	11.1/33.7	16 pack-years	1.72	74	2.48	91	69	81	1.5	64
E.D.	10.4/30.4	less than 0.5 pack-year	3.42	80	3.80	63	90	108	6.1	130

All measurements are in liters.
%Pred. = % predicted calculated as outlined in materials and methods.

Table IX — Lung volumes.

Patient	FRC	%Pred.	TLC	%Pred.	RV	%Pred.	RV/TLC	%Pred.
S.B.	1.92	78	3.91	83	0.77	55	20	69
S.E.	2.33	93	4.93	104	1.10	77	22	74
F.M.	2.50	100	4.36	91	1.23	88	28	97
E.T.	2.27	93	4.95	105	1.19	91	24	85
S.Bl.	1.48	54	3.26	63	0.62	39	19	63
J.C.	1.98	106	3.56	94	0.86	91	24	97
B.K.	3.10	147	5.08	123	2.19	192	43	160
N.S.	1.87	77	3.96	88	1.34	93	34	106
E.D.	2.92	62	5.28	61	1.48	79	28	108

All measurements are in liters.
%Pred.= % predicted calculated as outlined in materials and methods.

nine patients and increased in one patient. The residual volume was reduced in four subjects and elevated in one.

Forced vital capacity (FVC) and FEV_1 were normal in nine out of ten patients. One patient had a decrease in FVC. The FEV_1/FVC ratio was normal for all subjects. MEF_{50} (air) was decreased in four patients.

Three of nine patients had a $\Delta MEF_{50}He$ of less than 20%, values for the remaining six patients were normal.

Measurements of the diffusing capacity for carbon monoxide showed the corrected DLCO (see Table X) to be normal in all but one subject.

Sixty percent (six of ten) of the subjects had an arterial PO_2 while breathing room air which was less than 85% the predicted value (Table XI). The (A-a) O_2 gradient was increased in all patients. The mean value for the 20 to 29 age group (nine of 10 subjects) was 31.86 +/-9.61. The tenth subject who was in her late thirties also had an abnormally increased gradient of 19.75 (see Table X).

Six patients were tested for the presence of shunting. A normal physiologic shunt is considered to be five percent or less (West, 1977). An abnormal degree of intrapulmonary shunting was present in all six of these patients with a mean calculated shunt of 10.8 +/-1.5% (Table X).

Table X — Helium Flow Studies and DLCO.

Patient	Δ $Vmax_{50}He$ *	DLCO**	% Predicted
S.E.	21	18.4	95
S.E.	22	27.2	140
D.H.	39	—	—
F.M.	17	23.6	162
E.T.	32	23.9	116
S.Bl.	8	14.9	73
J.C.	22	26.5	141
B.K.	1.67	22.1	102
H.S.	32	21.6	133
E.D.	—	34.9	100

* A $\Delta Vmax_{50}$ of 20% or more is considered normal (see text).

** This represents corrected DLCO, as outlined in materials and methods, and takes patient's anemia into account.

Table XI — Pulmonary Function

Patient	Arterial PO_2 (room air)	PO_2 (100% O_2)	Aa Gradient	Predicted*	Calculated Shunt
S.B.	76 (79%)**	—	34.0	8.3 S.D. 6.2	—
S.E.	64 (66%)	450	48.5	"	12.59%
D.H.	91 (93%)	530	17.8	"	8.42%
F.M.	89 (91%)	—	23.5	"	—
E.T.	77 (78%)	460	33.0	"	12.28%
S.Bi.	90 (93%)	—	25.0	"	—
J.C.	80 (83%)	—	28.8	"	—
B.K.	82 (84%)	490	33.0	"	10.23%
H.S.	99 (105%)	490	19.8	11.1 S.D. 6.3	10.71%
E.D.	63 (65%)	483	43.2	8.3 S.D. 6.2	10.55%

*Based on Mellemgaard, 1966.

**Percent predicted based on Bates et al., 1971.

Discussion

Clinical Data

This review of the Yale-New Haven Hospital population of sickle cell patients establishes for the first time the incidence and characteristics of acute pulmonary disease in an adult population of sicklers. The characteristics of acute pulmonary disease in our overall population differ somewhat from those reported in the literature. During the period they (both as adults and as children) were followed, our patients were hospitalized 103 times for crises and only 37 times for acute pulmonary episodes. In contrast, in Barrett-Connor's population acute pulmonary disease was the most frequent cause for hospitalization. Even if all episodes of acute pulmonary disease are included, emergency room treated as well as those necessitating hospitalization, the incidence of pulmonary disease remains less than the incidence of crisis necessitating hospitalization.

The overall incidence of pneumonia was less in our population than in Barrett-Connor's population (1971-a),

but greater than that in Henderson's population (1950). Barrett-Connor (1971-a) found 169 episodes of pneumonia requiring hospitalization over a period of 864 patient-years,--or one case every 5.1 patient-years. In contrast in our population there were only 21 hospitalizations with a diagnosis of pneumonia over 339 patient-years, or one case every 16.1 patient-years. Even if we include all cases of pneumonia, hospitalized as well as those treated as outpatients the figure only rises to one episode every 10.2 patient-years. One reason for this difference is the age of the populations. The mean age of Barrett-Connor's population was 12 years with a range of seven weeks to 47 years, while the mean age of our population was 28 with a range of 17 to 65. Looking at adults alone, we find an incidence of hospitalization for pneumonia of once every 12.5 patient-years. We might explain the difference then on the basis of different age groups. However, the incidence of pneumonia in our patients during the periods of their childhoods when they were followed here (a total of 113 patient-years) is only one episode of hospitalization for pneumonia every 37.8 years. A key to the difference in frequency may lie in Barrett-Connor's population having a greater proportion of young children. She has found that the incidence of pneumonia under five years of age in this population is significant, and that pneumonia before age

five makes later episodes more likely. Only two of our patients are known to have had pneumonia before age five, and these two patients combined have had a total of ten episodes of acute pulmonary disease over a follow-up period of 36.4 patient-years.

Another factor influencing the frequency of pulmonary disease in our population is that it is a somewhat transient population with a certain degree of movement between Connecticut and the South. Where possible, the total follow-up period was adjusted to not include periods where it was clearly indicated in the chart that the patient had been residing in the South. Since it was not always possible to determine from the chart if a patient was continuously present in the New Haven area, this may have made the figures for the years of follow-up falsely high and also have made the incidence of acute pulmonary disease falsely low. There is no way of determining if a patient was well for a one or two year period or if he was living in another area at that time, and perhaps even having episodes of pulmonary disease. Thus, our figures may underestimate the incidence of acute pulmonary disease.

The frequency of crises accompanying pneumonia (42%) is less than that of Henderson (1950) who observed it in 13 of 14 cases, and greater than that of Barrett-Connor (1971-a) who observed crisis in only one quarter of the patients with pneumonia. Crisis in our population

more frequently accompanied pulmonary infarction, but the presence of crisis does not rule out the possibility of pneumonia.

The most reliable factors in distinguishing pneumonia from infarction in our population were productive cough, onset chill, and multi-lobe involvement on chest radiograph. Pleural effusion favored pulmonary infarction. Of note, the absence of fever on presentation is not a reliable sign of the absence of infection, for 48% of our patients with pneumonia were afebrile on presentation. On the other hand, one third of those with infarction were febrile.

The white blood cell count and its differential cannot be relied upon alone to distinguish between infection and infarction. The wide range of white blood cell counts observed in our population concurs with the findings of others (Petch et al., 1970). There is much overlap between the white blood cell counts found in infection and infarction. Patients with pulmonary infarction can present with high white blood cell counts and "left shifts." Rather it is the clinical picture as a whole, not any one single aspect, which must be examined in order to make the difficult diagnostic distinction between pneumonia and pulmonary infarction in the sickle cell patient. Furthermore, the possibility that the two entities can co-exist and that <u>in situ</u> sickling in the

lungs can potentially complicate the picture, must be kept in mind.

In contrast to other investigators (Petch and Serjeant, 1970; Petch et al., 1970; Henderson, 1950), we found a prolonged fever course to be uncommon with the mean in our patients with pneumonia being five days with treatment. Cultures were very frequently negative, even in the presence of a clinical setting strongly favoring the diagnosis of pneumonia.

Barrett-Connor observed that jaundice and the elevation of bilirubin above five occurred in four of five of her patients with pulmonary infarction. In our population only two of nine patients with pulmonary infarction had a bilirubin above five mg%, while two of ten with pneumonia for whom values are available had elevations of bilirubin above five mg%. Bilirubin levels in our patients were not reliable in distinguishing pneumonia from pulmonary infarction.

Pulmonary Function Studies

The pulmonary function studies demonstrate that pulmonary dysfunction is common in sickle cell patients even in the absence of symptoms, and even in the presence of clinically mild sickle cell disease. All of the patients tested had abnormalities in pulmonary function.

Impaired oxygenation of the blood was present in all patients.

Arterial PO_2 was decreased in 60% of the patients studied. The $(A-a)O_2$ gradient was found to be markedly increased in all subjects, which confirms the findings of other investigators (Bromberg and Jensen, 1967). The $(A-a)O_2$ gradient was more consistently increased in our population than in the patients studied by Bromberg and Jensen. This increase in the $(A-a)O_2$ gradient with a normal DLCO may be due to a reduction in the pulmonary vascular bed and consequent decrease in the transit time across the pulmonary capillary bed and/or a V/Q mismatch.

A number of earlier investigators found DLCO to be consistently low (Bromberg and Jensen, 1967; Young et al., 1976; Femi-Pearse et al., 1970). However, none of these investigators corrected their measurements for their subjects' anemia. Corrected DLCO was normal to increased in all our subjects except one.

Of interest is the marked abnormality of the $(A-a)O_2$ gradient in the three patients in the study who have milder sickle cell disease, never having been hospitalized for crisis, and one of whom never had any known pulmonary disease.

In the six patients in which the determination of intrapulmonary shunting was done after breathing 100%

oxygen, the mean shunt in these patients was 10.8% which is markedly abnormal. This supports the finding of Bromberg and Jensen of a nonphysiologic degree of shunting in a number of their patients (1967).

One third of our patients had evidence of small airway disease. This is in contrast to Young et al. (1976) who using a different technique (closing volumes) found the small airways to be normal in the subjects they tested. However, most of the subjects in our study were smokers, and smokers have been shown to have small airway disease.

The pulmonary function studies demonstrated no consistent abnormality in lung volumes or in flow-volume parameters. TLC was normal in two-thirds of the patients. FVC was normal in 80% of the subjects studied. These results differ from those found by other investigators. FVC was found to be abnormally low by both Young et al. (1976) and by Miller and Serjeant (1971). These investigators along with others also found TLC to be reduced (Diggs, 1969; Femi-Pearse et al., 1970; Bromberg and Jensen, 1967). While we found RV/TLC to be reduced in one-third of our subjects, Miller and Serjeant found it to be increased (1971).

Flow-volume studies showed FEV_1 to be normal in all but one subject. Miller and Serjeant had found FEV_1 to be normal in females, which most of our subject group were, and reduced in males. FEV_1/FVC was normal in all

subjects studied. This agrees with the findings of Young et al. (1976) and Miller and Serjeant (1971). MEF_{50} was reduced in four of the subjects we studied.

A key factor in determining whether a subject has normal pulmonary function is defining what normal is for that individual. In determining the predicted normal for a subject in addition to taking into account the variable of age, height, and sex, it is critical to correct for race. Pulmonary function tests for blacks and caucasians matched for the usual variables are not identical, and could be corrected by a factor of 0.85 (Binder et al, 1976). Miller and Serjeant in their study used Jamaicans of African descent as controls for their patients who were of the same racial origin. Some of the difference between their observations and those reported here may be related to differences between the population of American blacks with sickle cell anemia and Jamaicans with sickle cell anemia.

The consistent pulmonary abnormalities we found were a reduced arterial PO_2, an increased $(A\text{-}a)O_2$ gradient, and a nonphysiologic degree of intrapulmonary shunting. There is a possibility of small airway disease, but this needs to be confirmed with studies in nonsmoking sickle cell patients. We did not find any consistent abnormality in lung volumes or in flow rates. In a minority of individuals lung volume and flow-volume tests were suggestive of a

restrictive ventilatory defect. The majority of these parameters, though, were normal in the patients studied, in contrast to earlier studies.

The population studied was relatively young with a mean age of 26. Our subjects had a high percentage of F hemoglobin (mean 9.1%). Their young age and their high percentage of F hemoglobin both may contribute to making this population less likely to have severe pulmonary disease. However, that there is definite evidence of impaired gas exchange in these patients who are healthier than the overall sickle cell population at Yale-New Haven Hospital, argues that an even greater degree of pulmonary disease may be present in the sickle cell population as a whole.

The impairment of gas exchange demonstrated in these studies may be due to the hypothesized multiple insults occurring in the lungs as a result of embolization of sickled cells, fat, and marrow during crises, of <u>in situ</u> sicking in the lungs both as a manifestation of crisis and as a potential complication of infection.

One of the patients in the total population of 28 has evidence of pulmonary hypertension on chest radiograph, and a second has changes suggestive of pulmonary hypertension. The long term course in the development of pulmonary hypertension and impairment of pulmonary function needs to be further evaluated. Our results indicate that arterial

blood gases and/or the $(A-a)O_2$ gradient, and the degree of intrapulmonary shunting are the lung function tests that are useful to follow in these patients.

Conclusions

The pulmonary function studies demonstrate an impairment of gas exchange indicated by an increased $(A-a)O_2$ gradient and reduced arterial oxygen tension at rest. These results support the hypothesized chronic series of insults to the lung in the form of emboli accompanying crisis and of *in situ* sickling. More studies are needed to better elucidate whether scarring of the alveolar-capillary membrane (less likely with a normal DLCO) or obliteration of the pulmonary vascular bed secondary to chronic embolization and sickling, or some other mechanism is responsible for the abnormal gas exchange seen in these patients.

Pulmonary function studies show intrapulmonary shunting and small airway disease, though the latter could be due to cigarette smoking. Some evidence of restrictive disease was present in the lung volume studies, but this was far from conclusive and more studies are needed on more patients to clarify whether restrictive disease develops in these patients.

The clinical review presented here demonstrates that there is a high incidence of acute pulmonary disease and of pneumonia alone in the sickle cell population. Our findings indicate that the rate of pneumonia in the adult with sickle cell disease is high, but lower than the incidence in children with sickle cell disease.

Parameters which can help distinguish between pneumonia and pulmonary infarction have been outlined. No single sign or symptom is pathognomonic for either entity in the patient with sickle cell disease. The definitive study in the diagnosis of pulmonary infarction and embolism is pulmonary angiography, but in a population already at risk for sickling, where this risk will be potentiated by the use of hypertonic contrast material, one is reluctant to increase the risk of sickling in the lungs without definite, tangible benefit to the patient. An alternative is the use of the gallium scan, and its use will be discussed below.

The diagnosis and management of the pulmonary infiltrate in the patient with sickle cell disease is clearly not straightforward. The differential diagnosis is between pulmonary infarction and pneumonia. All sickle cell patients with pulmonary infiltrates and/or lower respiratory tract symptoms (e.g. cough) if sick enough to be admitted to the hospital, should have arterial blood gases drawn (on room air) and sputum obtained for gram

stain and culture. Sickle cell crisis should be treated vigorously in the usual manner with oxygen, hydration, analgesics, and transfusion and/or exchange transfusion as the clinical situation dictates. With their funtional asplenia and impaired white blood cell function sicklers can potentially have overwhelming infections. That pulmonary infection and infarction can coexist in the lungs must be kept in mind. The initiation of antibiotic treatment will depend on the clinical history, physical findings, and laboratory studies including sputum gram stains and cultures.

At the present time we are conducting further studies to delineate whether the pulmonary infiltrate is due to an inflammatory process such as pneumonia or to pulmonary infarction. This can be done with a gallium scan of the lungs followed by a V/Q scan (Nider et al., 1977). The infiltrate of a pneumonia will be positive with a gallium scan, while a V/Q mismatch should be seen with pulmonary infarction. These two tests are relatively noninvasive and avoid the risk of pulmonary angiography. Better elucidation of the underlying pathophysiology in the acute pulmonary episode in the patient with sickle cell disease will facilitate a more rational approach to diagnosis and management of pulmonary disease in these patients.

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Addendum

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