Involvement of the Lungs in Tuberous Sclerosis*

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A patient with tuberous sclerosis with involvement of the lungs is presented. The pulmonary involvement appears as a bilateral interstitial (diffuse) fibrosis, which is supported by evidence of reduced membrane permeability and hypoxemia, aggravated by exercise. The pulmonary functional defect is progressive as measured during the last six years, although the patient herself has shown only moderate clinical deterioration since the discovery of the abnormality 19 years ago.

Tubercous sclerosis (Bourneville's disease) may affect the brain, skin, lungs, bones and kidney. The clinical picture in patients with lung changes has been described, but lung function has not been measured. We describe a patient with tuberous sclerosis and lung involvement who has progressive impairment of pulmonary function.

CASE REPORT

This 56-year-old white woman was referred to Firland Sanatorium in 1963 because of a history of exertional dyspnea and pulmonary fibrosis noted on x-ray examination of the chest. The changes were first observed in 1950, at which time she had no symptoms. In 1952-53 she began to notice dyspnea on moderate to heavy exertion. This dyspnea showed little progression before admission to the hospital. There was no history of chest pain, hemoptysis, weight loss, orthopnea or significant cough.

At age four, warty growths appeared on the face, and at age 16 small growths were observed beneath the finger and toe nails. The thumb and toe nails were surgically removed in 1938 because of persistent difficulty from these growths. There was no history of seizures and she had completed ten grades of school without difficulty.

Family history revealed that two living brothers have cutaneous lesions on the face, mental deficiency and seizures. One normal brother has two children with the cutaneous lesions, mental deficiency and seizures.

The patient was a well-developed, well-nourished woman of average intelligence. There were no retinal lesions. The skin over the nose, cheeks and chin showed multiple raised lesions, typical of adenoma sebaeum. The thumb and toenails were absent. Longitudinal striations and periangual fibromata were seen under the free edge of the remaining fingernails. There was no clubbing or cyanosis. The skin elsewhere showed small papular lesions and an early Shagreen's patch in the lumbar area. There was minimal, diffuse enlargement of the thyroid gland. Examination of the chest and heart was unremarkable. The abdomen showed a healed midline surgical scar; the kidneys were not palpable. Pelvic examination demonstrated a cervical stump without palpable uterine body.

X-ray of the chest showed reticular markings toward the bases with "honeycombing" (Fig 1). An intravenous pyelogram revealed hypoplasia of left kidney with some changes suggestive of chronic pyelonephritis; the right pyelogram, including pelvis and ureter, showed normal findings. Skull films showed no abnormal calcifications. Films of the hands revealed sclerotic lesions of the phalanges and metacarpal bones.

Vital capacity was normal (Table 1). The maximal expiratory flow was low as was the maximal voluntary ventilation. The distribution of inspired gas (nitrogen washout) was

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Figure 1. Chest roentgenogram (November 5, 1963) at the beginning of the observation period demonstrating reticulation in the lower lung field.
normal and the membrane permeability (D_m) as measured by a modified steady-state technique (N = 11 l/atmos/min) was low (5.04 l/atmos/min). Her arterial blood had no CO_2 retention, but hypoxemia was present at rest. The walking ventilation index, a measure of dyspnea, was abnormal.

In six years of followup there has been little progression of subjective dyspnea. The patient is active with her own housework and belongs to a bowling league.

She was treated with prednisone for two months in 1963, but this was discontinued by her local physician because there was no subjective improvement or x-ray change and she developed a severe skin rash while on the drug. The last chest film (1969) shows a slight increase in the reticulation at the bases (Fig 2). Her pulmonary function has shown no change in lung volume, a borderline maximal voluntary ventilation relieved by bronchodilators, and a low maximal expiratory flow (Table 1). These values have not changed in six years. Her nitrogen washout continues to be normal and her walking ventilation index shows a high minute ventilation necessary for exercise (2 mph). Membrane permeability (D_m) has deteriorated steadily, and hypoxemia is aggravated more by exercise in recent years.

**DISCUSSION**

Tubercous sclerosis is a familial disease with multiple system involvement. The cerebral lesions commonly present with epilepsy and mental deficiency at an early age, although examples of patients with normal intelligence, have been cited in the literature. Retinal examination may show single or multiple phakoma. The diagnostic skin lesion is an adenoma sebaceum on the face, usually appearing before the age of ten. One or more additional cutaneous lesions may be present, such as periungual fibroma and a Shagreen's patch in the lumbar area. The kidneys may be affected with tumor formation of fat, vascular and connective tissue. Periosteal thickening without cystic changes in the limb bones are often seen. The inheritance has been considered a dominant trait, although in some patients there is no familial history.

Pulmonary involvement in tubercous sclerosis was first described by Berg and later reviewed by Dawson. These patients usually present with spontaneous pneumothorax, hemoptysis, with chest pain or exertional dyspnea. Compared with patients who have more extrapulmonary involvement, those with pulmonary disease are younger, more often women, and of normal intelligence. The common lesions seen on x-ray examination of the chest are motting, reticulation or honeycombing. The differential diagnosis includes other diseases with

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**Table 1—Results of Pulmonary Function Studies**

<table>
<thead>
<tr>
<th>Date</th>
<th>VC % *Pred</th>
<th>MVV % *Pred</th>
<th>MEF L Min (N = 210)</th>
<th>N_2 Washout 7 Min</th>
<th>Permeance</th>
<th>pH arterial blood (rest)</th>
<th>ParO_2 mm Hg (rest)</th>
<th>ParO_2 mm Hg (exercise)</th>
<th>ParCO_2 mm Hg (rest)</th>
<th>ParCO_2 mm Hg (exercise)</th>
<th>SpO_2 % (rest)</th>
<th>SpO_2 % (exercise)</th>
<th>Walking Ventilation Index</th>
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<tbody>
<tr>
<td>11-8-63</td>
<td>110 (129)</td>
<td>74 (101)</td>
<td>100 (160)</td>
<td>1</td>
<td>5.04</td>
<td>7.43</td>
<td>40</td>
<td>39</td>
<td>60</td>
<td>-</td>
<td>90</td>
<td>-</td>
<td>0.46</td>
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<tr>
<td>7-27-64</td>
<td>123 (133)</td>
<td>88 (105)</td>
<td>140 (140)</td>
<td>2</td>
<td>3.82</td>
<td>7.42</td>
<td>38</td>
<td>37</td>
<td>58</td>
<td>53</td>
<td>90</td>
<td>87</td>
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<tr>
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<td>116 (132)</td>
<td>79 (109)</td>
<td>140 (140)</td>
<td>2</td>
<td>3.57</td>
<td>7.44</td>
<td>39</td>
<td>40</td>
<td>54</td>
<td>41</td>
<td>87</td>
<td>73</td>
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<tr>
<td>8-11-67</td>
<td>118 (127)</td>
<td>72 (97)</td>
<td>140 (180)</td>
<td>2</td>
<td>3.76</td>
<td>7.39</td>
<td>41</td>
<td>44</td>
<td>58</td>
<td>36</td>
<td>89</td>
<td>70</td>
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<tr>
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<td>80 (90)</td>
<td>140 (240)</td>
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<td>2.9</td>
<td>7.39</td>
<td>42</td>
<td>44</td>
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<td>88</td>
<td>72</td>
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<tr>
<td>5-23-69</td>
<td>117 (136)</td>
<td>81 (100)</td>
<td>160 (180)</td>
<td>1.8</td>
<td>2.7</td>
<td>7.38</td>
<td>43</td>
<td>45</td>
<td>60</td>
<td>43</td>
<td>89</td>
<td>77</td>
<td>0.37</td>
</tr>
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</table>

*Figures in parentheses indicate response after bronchodilators

*Values for prediction have been derived from the tables given by Baldwin et al*

<table>
<thead>
<tr>
<th>Walking Ventilation Index</th>
<th>(N = 0.05)</th>
</tr>
</thead>
</table>

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**Figure 2.** Roentgenogram of Feb. 12, 1969 showing progression of the fibrosis.
honeycombing such as histiocytosis X and scleroderma. Histopathologic examination of the lungs shows numerous scattered subpleural cysts, which probably cause the recurrent chest pain and pneumothoraces. Microscopically, a characteristic feature has been the formation of new tissue that is rich in smooth muscle, fibrous tissue and blood vessels. The alveolar walls are thickened and the alveoli may be completely obliterated. A reduced arterial blood oxygen saturation at rest and exercise has been reported in one patient with tuberous sclerosis.5

Our patient has the classic cutaneous changes of adenoma sebaceum, subungual warts, a Shagreen patch, the cortical bony defects of the phalanges, a strong family history and x-ray changes in the chest. There is no involvement of the brain or fundi. The renal changes seen on the intravenous pyelograms are suggestive essentially of chronic pyelonephritis and seem to be unrelated. Although tuberous sclerosis is a systemic disease, the organs principally affected differ considerably, even in members of the same family. Other members of this patient's family have a history of seizures and mental deficiency.

The patient reported here has abnormal lung function which has worsened over a period of six years (Table 1). Ventilatory studies have shown a mild and reversible abnormality of expiratory flow without deterioration in this time. The normal nitrogen washout is in keeping with this reversible obstructive syndrome. The principal abnormality has been a membrane defect. The initial value for membrane permeability (Dn) was low (5.04 L/atmos/min) and has fallen progressively each year. This has been accompanied by hypoxemia at rest. Progression of the membrane defect has also been demonstrated by the lower PaO2 with standard exercise seen in recent years. There has been no CO2 retention. The membrane defect is consistent with the pulmonary fibrosis seen on x-ray film and compatible with the histopathology reported by others. In keeping with progression of the alveolar capillary membrane abnormality, radiologic changes in the lung have shown some progression.

The degree of organ involvement determines the course and prognosis in this disease. Patients with pulmonary changes have been reported to do well for periods varying from one to eleven years after the discovery of the chest lesions. Cardiorespiratory failure may supervene in the terminal stages.1 This patient has had known lesions in the lung for 19 years, but is reaching levels of membrane abnormality where she will have more difficulty.

The use of corticosteroids has been recommended in some studies,1 but the results are not impressive. Our patient had prednisone therapy for two months early in our observation period without subjective improvement.

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Secundum Type Atrial Septal Defect with Cleft Mitral Valve*

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A rare case of secundum type atrial septal defect associated with cleft of the anterior leaflet of the mitral valve in a 13-year-old girl is reported. These findings were suspected clinically and proved at operation; the cleft was repaired and the defect closed.

Mitral insufficiency as a result of congenital cleft of the mitral valve is usually associated with the septum primum type atrial septal defect. The

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