Exercise Testing in Pediatric Heart, Heart-Lung, and Lung Transplant Recipients

Patricia A. Nixon, PhD; F. Jay Fricker, MD; Blakeslee E. Noyes, MD; Steven A. Webber, MBChB; David M. Orenstein, MD; and John M. Armitage, MD

Cardiorespiratory responses to progressive exercise were examined in 38 children who had undergone heart (n=16), heart-lung (n=13), or double-lung (n=9) transplantation, and in 41 healthy controls. The four groups were similar in age, but the control subjects and heart transplant recipients were significantly larger than the heart-lung and lung recipients as assessed by body mass index (BMI). Time since transplant was significantly longer in the heart (601 days) compared with heart-lung (146 days) and lung (125 days) transplant groups. Physical work capacity and peak oxygen uptake were significantly reduced (43 to 64% of predicted) in the three transplant groups compared with the control group. Peak heart rate (percent predicted) was significantly higher in the control subjects (94%) compared with the heart (66%), heart-lung (70%), and lung (77%) transplant recipients. Peak minute ventilation was significantly higher in the control group (72.9 L/min) and heart transplant (51.0 L/min) groups than the heart-lung (37.4 L/min) and lung (41.3 L/min) transplant groups. The control group had a higher peak tidal volume than the three transplant groups, and a higher peak respiratory rate than the lung transplant recipients. Correlational analysis revealed that physical work capacity (PWC) was significantly related to heart rate at peak exercise (HRpeak) and minute ventilation at peak exercise (VEpeak) in the heart transplant recipients, BMI, VEpeak, and FEV₁ in the heart-lung transplant recipients, and BMI, HRpeak, VEpeak, FEV₁, and number of days posttransplant in the lung transplant recipients. In addition to these variables, physical deconditioning and factors related to pharmacotherapy, infection, and rejection may also contribute to the decreased PWC observed in the transplant recipients.

(Chest 1995; 107:1328-35)

BMI=body mass index; FEV₁=forced expiratory volume in 1 s; HRpeak=heart rate at peak exercise; MVV=maximum voluntary ventilation; PtCO₂=end-tidal carbon dioxide tension; PWC=physical work capacity; RRpeak=respiratory rate at peak exercise; SaO₂=oxygen saturation; VEpeak=minute ventilation at peak exercise; VE/O₂peak=minute ventilation at peak exercise; VE/MVV=minute ventilation per maximal voluntary ventilation; VE/VCO₂=ventilatory equivalent for carbon dioxide; VE/ht=minute ventilation per height; V̇E/ht=minute ventilation per tidal volume; V̇E/ht=minute ventilation per tidal volume

Key words: children; exercise testing; heart, heart-lung, and lung transplantations

Heart, heart-lung, and lung transplantation have become acceptable treatments for pediatric patients with end-stage cardiac disease, pulmonary disease, or both. Transplantation has prolonged lives and enabled many of the children to resume normal daily activities. Yet, little is known about the effects of heart, heart-lung, or lung transplantations on exercise tolerance in pediatric patients. Significantly reduced exercise capacity and oxygen uptake, heart rate, and minute ventilation have been reported at peak exercise in adolescent heart transplant recipients. Research with adult heart, heart-lung, or lung transplant recipients has shown exercise tolerance (as measured by peak oxygen uptake) to be reduced. The reduced exercise tolerance has, in general, been associated with lower peak heart rates in both heart and lung transplant recipients and with either reduced or normal minute ventilation during exercise in some lung transplant recipients.

The purpose of the present investigation was to examine and compare metabolic, cardiovascular, and ventilatory responses to peak exercise in pediatric heart, heart-lung, and lung transplant recipients, and to examine the interrelationships of these responses with physical work capacity (PWC) within each of the transplant groups.

METHODS

Subjects

Sixteen heart, 13 heart-lung, and 9 double-lung transplant recipients, 20 years or younger, underwent progressive exercise testing on a cycle ergometer. Forty-one normal, healthy children...
were noted for comparison. Only subjects who were 6 years of age or older, and were considered to be in clinically stable condition and able to cooperate sufficiently were tested. Testing was conducted 52 to 2,157 days following transplantation. Written informed consent was obtained from the patient's parent or legal guardian or from patients who were 18 years or older.

**Measurements and Procedures**

Height and weight were measured in centimeters and kilograms, respectively. Body mass index (BMI) was calculated (kg/m²), and BMI percent predicted was determined.11

Progressive exercise testing was conducted on an electronically braked cycle ergometer following the Godfrey protocol.12 Patients began pedaling at “0” W for the first minute, with the work load increasing by 10, 15, or 20 W each minute depending on the height and clinical status of the patient. Subjects were encouraged to give a maximal effort. The PWC was defined as the highest work load (watts) sustained for 1 min, and PWC percent predicted was determined from the equations of Godfrey et al13 based on height and gender.14

Metabolic testing equipment (Medical Graphics 2001) provided on-line, breath-by-breath measurements of oxygen uptake, carbon dioxide production, minute ventilation, respiratory rate, tidal volume, and end-tidal carbon dioxide tension. Values were printed every 15 s, and peak values were determined from the last 15 s of exercise. The ventilatory equivalents for oxygen and carbon dioxide were also calculated to reflect the minute ventilation required for a given level of oxygen uptake and carbon dioxide production, respectively. A 12-lead electrocardiogram was monitored continuously, and heart rate was determined each minute and at peak exercise. Oxyhemoglobin saturation (SaO₂) was monitored continuously using a pulse oximeter (Nellcor N-100) and disposable finger probe, and stable values were recorded during the last 20 s of each minute.

Heart-lung and lung transplant recipients also performed pulmonary function testing within 4 h before the exercise test. Forced expiratory volumes and flow rates were determined by spirometry (according to American Thoracic Society standards14), and values were expressed as percent of predicted.15 Maximal voluntary ventilation was determined by the 12-s sprint method.16 The ratio of minute ventilation at peak exercise (VEpeak) to maximal voluntary ventilation (MVV) was calculated to provide an estimate of the proportion of mechanical ventilatory capacity utilized during peak exercise.

Hemoglobin level (gram percent) was measured on the day following the exercise test as part of the patient’s regular care.

**Data Analysis**

Visual inspection of the data, and the Shapiro-Wilk17 test of normality revealed that several of the dependent measures were not normally distributed. Consequently, the data were analyzed using nonparametric statistics. Subject characteristics and exercise responses were compared among the control, heart, heart-lung, and lung transplant groups using Kruskal-Wallis analysis. Relationships between dependent variables were determined by Spearman rank correlation analysis. Level of significance was defined as p<0.05.

**RESULTS**

Subject characteristics are presented in Table 1. The four groups did not differ significantly in median age or height. Post hoc comparisons also indicated that weight did not differ significantly among the four groups. Body mass index (expressed in kilograms per square meter and percent predicted) was significantly lower in the heart-lung and lung transplant recipients compared with the control subjects and heart transplant recipients. Hemoglobin levels were subnormal in all but eight of the transplant recipients and did not differ significantly among the three patient groups. The number of days since transplant surgery was significantly greater in the heart transplant recipients compared with both the heart-lung and lung transplant recipients.

Forced expiratory volume in 1 s (percent predicted) was measured in the heart-lung and lung transplant recipients. In the heart-lung transplant group, FEV₁ ranged from 31 to 107% predicted, with

---

**Table 1—Subject Characteristics: Median (Range)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n=41)</th>
<th>Heart (n=16)</th>
<th>Heart-Lung (n=13)</th>
<th>Lung (n=9)</th>
<th>p Value</th>
<th>Comparison*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F</td>
<td>21/20</td>
<td>10/6</td>
<td>4/9</td>
<td>4/5</td>
<td>0.813</td>
<td>NS</td>
</tr>
<tr>
<td>Age, y</td>
<td>13 (7-18)</td>
<td>13 (8-19)</td>
<td>13 (6-20)</td>
<td>15 (10-19)</td>
<td>0.039</td>
<td>NS</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>51.0 (22.7-90.0)</td>
<td>40.0 (22.0-92.5)</td>
<td>37.8 (22.0-67.5)</td>
<td>40.2 (21.0-54.8)</td>
<td>0.068</td>
<td>NS</td>
</tr>
<tr>
<td>Height, cm</td>
<td>161.3 (119.4-187.6)</td>
<td>148.3 (116.8-171.5)</td>
<td>146.7 (115.6-172.7)</td>
<td>154.9 (124.5-167.0)</td>
<td>0.008</td>
<td>C,H &gt; HL,L</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>19.3 (13.3-29.4)</td>
<td>19.1 (13.9-31.5)</td>
<td>16.5 (14.6-31.4)</td>
<td>16.4 (13.6-19.7)</td>
<td>&lt;0.001</td>
<td>C,H &gt; HL,L</td>
</tr>
<tr>
<td>BMI, % pred</td>
<td>104 (75-160)</td>
<td>103 (64-150)</td>
<td>88 (66-171)</td>
<td>85 (78-96)</td>
<td>0.110</td>
<td>NS</td>
</tr>
<tr>
<td>FEV₁, % pred</td>
<td>—</td>
<td>—</td>
<td>79 (31-107)</td>
<td>59 (30-107)</td>
<td>0.865</td>
<td>NS</td>
</tr>
<tr>
<td>Hemoglobin, gm/dL</td>
<td>—</td>
<td>12.0 (8.8-14.9)</td>
<td>10.2 (8.2-12.2)</td>
<td>9.9 (7.3-12.7)</td>
<td>0.001</td>
<td>H &gt; HL, L</td>
</tr>
<tr>
<td>Days posttransplant</td>
<td>—</td>
<td>601 (179-2,002)</td>
<td>146 (69-2,157)</td>
<td>125 (52-688)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*NS=not significant; C=control; H=heart; HL=heart-lung; L=lung.
7 of 13 patients having values within normal limits (±2 SDs of predicted). Median FEV₁ was significantly lower in the lung transplant group, with the values of only two of nine patients falling within normal limits.

**Exercise Test Results**

Peak exercise responses are presented in Table 2. Physical work capacity and peak oxygen uptake were significantly reduced in the three transplant groups compared with the control group. The peak heart rates were close to age-predicted maximal values in the control subjects, but were significantly reduced in the three transplant groups. Patients in the lung transplant group tended to have higher peak heart rates than patients in the heart and heart-lung transplant groups, but the difference was not statistically significant.

Peak minute ventilation of the control group was significantly higher than the V̇Epeak of each transplant group. In addition, V̇Epeak in the heart transplant recipients was higher than V̇Epeak in the heart-lung and lung recipients. These differences persisted when V̇Epeak was corrected for height. Minute ventilation expressed per liter O₂ consumed and per liter CO₂ produced was significantly higher in the three transplant groups compared with the control group. Tidal volume at peak exercise was significantly higher in the control subjects than in heart, heart-lung, and lung transplant recipients. Respiratory rate was significantly lower in the lung transplant recipients compared with the control subjects and heart transplant recipients. Respiratory rate of the heart-lung recipients did not differ significantly from the other three groups. Peak minute ventilation expressed as a proportion of MVV varied widely, but in general was close to the normal range of 60 to 70%, and did not differ between heart-lung and lung transplant groups. Oxyhemoglobin saturation was significantly higher in the control group compared with three transplant groups. However, only two heart, one heart-lung, and two lung transplant recipients had values below 93% at peak exercise. End-tidal CO₂ tension at peak exercise did not differ significantly among the control, heart, heart-lung, and lung transplant groups.

**Correlational Analyses**

The relationships between PWC (percent predicted) and subjects' characteristics and exercise re-
Table 3—Spearman Rank-Order Correlations With PWC Percent Predicted

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Heart</th>
<th>Heart-Lung</th>
<th>Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>0.04</td>
<td>-0.08</td>
<td>-0.29</td>
<td>0.06</td>
</tr>
<tr>
<td>BMI, % pred</td>
<td>0.23</td>
<td>-0.21</td>
<td>0.56*</td>
<td>0.75*</td>
</tr>
<tr>
<td>FEV1, % pred</td>
<td>—</td>
<td>—</td>
<td>0.80*</td>
<td>0.84*</td>
</tr>
<tr>
<td>Heart rate, % pred</td>
<td>0.31*</td>
<td>0.66*</td>
<td>0.24</td>
<td>0.81*</td>
</tr>
<tr>
<td>V̇Epeak, L/min/cm²</td>
<td>0.45*</td>
<td>0.86*</td>
<td>0.82*</td>
<td>0.82*</td>
</tr>
<tr>
<td>V̇E/MVV, %</td>
<td>—</td>
<td>—</td>
<td>-0.07</td>
<td>0.20</td>
</tr>
<tr>
<td>V̇̇peak, mL</td>
<td>0.23</td>
<td>0.84*</td>
<td>0.23</td>
<td>0.56</td>
</tr>
<tr>
<td>RRpeak, breaths/min</td>
<td>-0.02</td>
<td>-0.23</td>
<td>0.22</td>
<td>0.00</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>0.19</td>
<td>0.19</td>
<td>-0.26</td>
<td>-0.33</td>
</tr>
<tr>
<td>PETCO₂, mm Hg</td>
<td>-0.03</td>
<td>-0.62*</td>
<td>-0.36</td>
<td>0.15</td>
</tr>
<tr>
<td>Hemoglobin, g %</td>
<td>—</td>
<td>-0.27</td>
<td>-0.39</td>
<td>-0.05</td>
</tr>
<tr>
<td>Days posttransplant</td>
<td>—</td>
<td>-0.02</td>
<td>0.03</td>
<td>0.73*</td>
</tr>
</tbody>
</table>

*p<0.05.

Responses were determined separately for each group using Spearman rank-order correlational analysis (Table 3). As demonstrated in Figure 1, BMI was significantly related to PWC in the heart-lung and lung transplant groups, but not in the heart or control groups. In the control group (Fig 1, top left), all but one patient had a BMI >80% predicted, and all but one patient had a PWC ≥80% of predicted. In
the heart-lung and lung recipients (Fig 1, right), a higher BMI was associated with a higher PWC. However, despite most of the patients having a BMI $\geq 80\%$ of predicted, all of the patients had a PWC $<80\%$ of predicted. In the heart recipients (Fig 1, bottom left), the correlation between PWC and BMI was not significant. All of the patients had a PWC $<100\%$ predicted, and patients with a BMI $>140\%$ or $<80\%$ tended to have lower PWCs.

The correlations between PWC (percent predicted) and heart rate at peak exercise (percent predicted) were significant in the heart, lung, and control groups, but not in the heart-lung group. As is evident in Figure 2, none of the heart, heart-lung, or lung transplant recipients had peak heart rates that exceeded 90% of predicted, while more than 50% of the control subjects' heart rates exceeded 90% predicted. Correspondingly, the PWCs of the transplant recipients were all below 90%, with nearly half the control subjects having a PWC $\geq 100\%$ of predicted. In the lung transplant group, only one patient had a peak heart rate below 73%, while more than half of the patients who had undergone heart or heart-lung transplantation had peak heart rates below this value. The lower peak heart rates corresponded with lower PWCs in the heart and lung transplant recipients, but not in the heart-lung recipients.

Peak minute ventilation (corrected for height) was highly related to PWC in the control and three transplant groups. Fifty percent of the control subjects had a $V_{E\text{peak}} \geq 0.47 \text{ L/min/cm}_\text{height}$. Only two heart recipients, one heart-lung recipient, and none of the lung patients had $V_{E\text{peak}} \geq 0.47 \text{ L/min/cm}_\text{height}$. In all of the groups, a higher $V_{E\text{peak}}$ was associated with a higher PWC (percent predicted).

The relationship between PWC and pulmonary...
function (as measured by FEV₁) was examined in the heart-lung and lung recipients. Significant positive correlations between FEV₁ and PWC were apparent for both the heart-lung (r=0.80, p=0.002) and lung (r=0.84, p=0.005) transplant groups. In the heart-lung group, two patients had an FEV₁ >100% predicted, and their PWCs were the highest (>60% predicted). The remaining 11 patients had FEV₁ <100% predicted, including 3 patients with FEV₁ >80% predicted, and all of their PWCs were <60% predicted. In the lung transplant group, two patients had an FEV₁ >80% predicted and their PWCs were >60% predicted. The remaining seven patients had an FEV₁ <50% predicted and had PWCs <60% predicted. The VE/MVV was also examined in these patients to provide a measure of ventilatory reserve, and was found not to correlate significantly with PWC percent predicted in either the heart-lung or the lung transplant groups (r=-0.07 and r=0.20, respectively).

The number of days posttransplant was significantly related to PWC in the lung transplant group, but not in the heart or heart-lung transplant groups. End-tidal CO₂ at peak exercise was inversely related to PWC in the heart transplant group, but the correlation was not significant in the control, heart-lung, or lung transplant groups. Oxyhemoglobin saturation, hemoglobin level, and age were not significant correlates of PWC in any of the four groups.

**DISCUSSION**

The results of this study indicate that exercise tolerance is diminished in pediatric patients who have undergone heart, heart-lung, or lung transplantation. Specifically, peak work capacity was 64, 48, and 43% of predicted values in the heart, heart-lung, and lung transplant groups, respectively. These values are consistent with those reported for adolescent heart transplant and adult heart and lung transplant recipients.¹⁻¹⁰

There are multiple factors that may have contributed to the reduced work capacities observed in the pediatric transplant recipients.

First, the reduced work capacities were accompanied by peak heart rates that were substantially below age-predicted maximal levels. In the heart and heart-lung transplant recipients, the reduced peak heart rates may be attributed to cardiac denervation associated with heart transplantation.¹⁸ The lung transplant recipients also had lower peak heart rates, although their heart rates tended to reach higher values than those of the heart and heart-lung recipients. There is evidence that cardiac innervation may be interrupted during lung transplant surgery as well,¹⁹ which may account for the lung transplant recipients’ subnormal heart rates at peak exercise. Exercise capacity may subsequently be limited by lower peak heart rate, which would contribute to a lower cardiac output²⁰ and a diminished oxygen supply to the exercising muscles.

Ventilatory factors may also contribute to the reduced exercise tolerance observed in the transplant recipients. The heart, heart-lung, and lung transplant groups had significantly diminished VEpeak compared with the control subjects, and the heart-lung and lung groups had significantly lower VEpeak than the heart transplant group. Despite the lower VEpeak, the VE/VO₂ and VE/VCO₂ were higher in the three transplant groups compared with the control group. The higher VE may be needed to compensate for increased dead space during peak exercise in the transplant recipients or it may reflect greater lactic acidosis.²¹ In the present investigation PaCO₂ was not measured, and consequently, dead space could not be determined. The relatively normal SaO₂ and end-tidal CO₂ values suggest that the minute ventilation was sufficient for adequate gas exchange in most of the patients.

It has been speculated that the pattern of ventilation may be altered in lung transplant recipients by pulmonary afferent denervation. Sciriha et al⁶ reported that adult lung transplant recipients utilized a greater VT to compensate for a reduced respiratory rate. In the present study, respiratory rate was lower in the lung transplant recipients but not in the heart-lung transplant recipients, and there was considerable variability within the two groups. In fact, there were several heart-lung and lung transplant recipients who had high respiratory rates at peak exercise. These patients may have utilized a higher respiratory rate to compensate for a lower tidal volume consistent with a pulmonary restrictive defect in the first few months following transplantation.¹⁰

We also examined the ratio of peak minute ventilation to maximal voluntary ventilation (VE/MVV) as a measure of ventilatory reserve in the heart-lung and lung transplant recipients. In healthy subjects, VE/MVV is usually in the range of 60 to 70%,²² indicating that approximately 60 to 70% of the mechanical ventilatory capacity is used at peak exercise. Despite being somewhat elevated in several patients, VE/MVV was less than 100% in all but one lung transplant recipient. This finding suggests that maximal mechanical ventilatory capacity was not reached, and that factors other than ventilatory mechanics may be limiting exercise in these patients.

Airway obstruction may also contribute to reduced exercise capacity in the heart-lung and lung recipients. Correlational analysis indicated that FEV₁ percent predicted and PWC were highly correlated.
in the heart-lung and lung transplant groups. The contribution of FEV\textsubscript{1} to PWC in these patients may reflect abnormal mucus clearance, infection, or rejection of the lung allograft.

Peripheral factors may also contribute to exercise tolerance in these patients. It was interesting to note that most patients reported that leg fatigue, not dyspnea, caused them to terminate exercise. In our experience, and that of others,\textsuperscript{23} it is not uncommon for patients with lung disease to terminate exercise because of leg fatigue. Leg fatigue is consistent with peripheral limitations that may reduce exercise tolerance, particularly in patients who were extremely inactive prior to transplantation, and who report limited physical activity following transplantation. Physical inactivity and deconditioning are associated with changes in skeletal muscle tissue such as reduced oxidative enzymes, \textit{etc.}, in healthy persons.\textsuperscript{24} Reduced skeletal muscle glycogen and a low percentage of type I (oxidative) skeletal muscle fibers have been reported in adult patients with COPD in chronic respiratory failure.\textsuperscript{25} Furthermore, skeletal muscle structural and functional abnormalities have been reported in adult heart transplant recipients both prior to and 6 weeks following heart transplantation.\textsuperscript{26} Consequently, the low oxidative capacity of the working muscles related to physical deconditioning or the preexisting condition (congestive heart failure, chronic respiratory failure) may have played a major role in limiting our patients' exercise capacity following transplantation.

Exercise tolerance may also be affected indirectly by pharmacologic agents. All patients were taking either cyclosporine or FK 506 (tacrolimus) for immunosuppression. Both drugs have been shown to have hemolytic effects,\textsuperscript{27,28} and cyclosporine has been shown to inhibit erythropoietin production,\textsuperscript{29} which may contribute to the lower serum hemoglobin levels in transplant recipients. Although our sample sizes may be too small to yield significant relationships between PWC and hemoglobin level, anemia may be a factor that contributes to the reduced exercise capacities observed in the transplant recipients. In addition, cyclosporine has been shown to alter muscle metabolism.\textsuperscript{30} Most of the patients were also taking or had taken corticosteroids for immunosuppression. Corticosteroids have been shown to induce myopathy of skeletal muscles, including respiratory muscles, which may in turn diminish exercise capacity.\textsuperscript{31} Finally, the results of our study are somewhat biased in that only patients who were in clinically stable conditions were tested. No patient had evidence of chronic rejection. Rejection and infection were not controlled for in the statistical analyses, and their effects on exercise tolerance have yet to be determined.

It is also possible that the time since transplant surgery may have a significant effect on exercise tolerance. However, Hsu et al\textsuperscript{5} reported no significant differences in exercise capacity, \(V_{O2peak}\), and peak heart rate in pediatric heart transplant recipients tested 1 year and 3 years after transplantation. In contrast, our finding of a significant correlation between PWC and number of days posttransplant in the lung transplant group suggests that exercise tolerance may improve with time posttransplant, supporting the need for standardization of testing posttransplant, particularly in the first year after surgery.

**Conclusion**

The results of our study have shown that children and adolescents who have undergone heart, heart-lung, or lung transplantations have significantly reduced exercise tolerance as reflected in reduced peak work capacity and peak oxygen uptake. The reduced exercise tolerance may be associated with reduced cardiovascular and ventilatory responses, as well as subnormal nutritional status. Furthermore, exercise capacity may be diminished because of peripheral limitations associated with physical deconditioning, preexisting abnormal muscle structure and function, pharmacologic side effects, or a combination of these factors. The effects of infection and allograft rejection on exercise tolerance have yet to be determined. Future research is warranted to determine if exercise tolerance changes over time and if the changes are associated with cardiovascular, ventilatory, or peripheral factors, or a combination of these factors.

**Acknowledgments:** We are indebted to Debbie Cassinelli and Mary Kay Margolis for their assistance with the acquisition and management of data essential to this project.

**References**

12 Godfrey S. Exercise testing in children. Philadelphia: WB Saunders, 1974; 30
15 Schoenberg JB, Beck GJ, Bouhuys A. Growth and decay of pulmonary function in healthy blacks and whites. Respir Physiol 1978; 33:367-93
22 Godfrey S, Mears M. Pulmonary function and response to exercise in cystic fibrosis. Arch Dis Child 1971; 46:144-51
31 Decramer M, Stas JK. Corticosteroid-induced myopathy involving respiratory muscles in patients with chronic obstructive pulmonary disease or asthma. Am Rev Respir Dis 1992; 146:800-02