A Comparison of the Pulmonary Blood Flow between Left and Right Lungs in Normal Subjects and Patients with Congenital Heart Disease

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Carbon dioxide labeled with oxygen-15 can be used to compare the blood flow in different regions of the lung. The subject takes a quick breath of a known volume of air containing a minute proportion of labeled carbon dioxide and then holds his breath for about 10 seconds. The gamma rays emitted by the isotope penetrate the chest wall and can be detected by pairs of crystal scintillation counters arranged opposite each other, front and back, over the chest. The rate of fall of counting rate during the period of apnea is used as a measure of the regional blood flow through the cylinder of lung tissue between the counters.

Various factors, including posture, exercise, total pulmonary blood flow, and changes in pulmonary artery and venous pressures, influence the regional partition of blood flow through the lungs. Normal subjects sitting upright at rest have a low flow at the apex of the lung and a progressive increase toward the base; when they lie flat, the flow in the two regions becomes equal. When normal subjects sitting upright do leg exercise, the flow increases at both apex and base but the difference between the two becomes less.

Patients with cardiac shunts and high pulmonary blood flow have a regional perfusion similar to normal subjects on exercise. Patients with cardiac shunts and pulmonary hypertension have equal flow at the apex and base of the lung. All these results can be explained by supposing that hydrostatic pressure due to gravity influences the regional blood flow in the resting normal subject and that this factor is less important when the total pulmonary flow or the pulmonary artery pressure is high. Patients with very severe mitral stenosis have a higher blood flow through the apical regions of the lung than the basal, and it is possible that this change is related to the rise in pulmonary venous pressure in this disease.

Patients with obstruction of the pulmonary outflow tract present another opportunity for assessing the effect of hydrostatic pressure, for they often have a low pulmonary artery pressure and low pulmonary blood flow. During a study of a group of patients with this condition we found unequal flow through the left and right upper zones, so comparisons of flow in the upper zones were made in normal subjects and in patients with atrial septal defects, ventricular septal defects, and patent ductus arteriosus.

Methods

Production of the Radioactive Carbon Dioxide

The method was that used in previous investigations. Oxygen-15, which has a half life of 2 minutes, was produced by deuteron bombardment of nitrogen in the Medical Research Council cyclotron at Hammersmith Hospital. The target gas consisted of pure nitrogen with 4 per cent of oxygen to act as carrier for the oxygen-15. This gas mixture flowed continuously through the target box during the investigations. The labeled gas was piped to the chemical laboratory, where it was first passed over hot charcoal at 450 C. and then over copper oxide at 900 C. The charcoal converted most of the oxygen to carbon dioxide, and the small amount of carbon monoxide formed was converted to carbon dioxide by the copper oxide. The completion of chemical conversion was checked by analyzing the exit gases from the fur-
The clearance rates of radioactive carbon dioxide at the left second rib (U) and 4 inches (10 cm.) lower on the right side (L). Each line connects the upper and lower zone clearance rates of an individual patient. Section A shows results in five normal subjects; section B, seven patients with isolated pulmonary stenosis; and section C, seven patients with the tetralogy of Fallot.

The patient breathed through a respiratory valve box with a low deadspace, and at the end of a normal expiration took a rapid inspiration from a plastic bag containing 900 ml. of air containing a small quantity of carbon dioxide of which a minute proportion was labeled with oxygen-15. As soon as the bag was empty, the patient held his breath for about 10 seconds and then resumed normal breathing.

Analysis of Records

The records show a rapid increase in counting rate as the patient breathes in and draws the radioactive gas into the lung within the counting field (figs. 2 and 3). During the period of apnea the counting rate falls exponentially for the first few seconds, until recirculation takes place. The curves were plotted on a semilogarithmic scale after allowance for background radiation and radioactive decay. The slope of the semilogarithmic plot was then expressed as the carbon dioxide clearance rate in per cent per second of the instantaneous activity.

Carbon dioxide labeled with oxygen-15 is removed from the alveoli extremely rapidly because carbon dioxide is very diffusible, and the exchange of the oxygen-15 from bicarbonate ions with hydroxyl ions in water ensures that there is no significant back pressure.4 The curves therefore record the rate of removal of the labeled pulmonary capillary blood from the counting field; this has been used as a measure of regional blood flow.

Normal Values

With the use of this technic values of carbon dioxide clearance rate in different regions of the lung were obtained from some normal subjects. In an earlier investigation measurements were made in normal subjects in a basal state, at the level of the left second rib, and 10 cm. lower over the right lung. The mean clearance rate at the second rib was 4.8 per cent per second (S.E. 2.1) and 10 cm. lower 25.9 per cent per second (S.E. 1.7).

During the present study a total of 20 paired observations of the upper zone clearance rate was made in six young normal members of the hospital staff. The mean left upper zone clearance rate was 12.2 per cent per second (S.D. 5.9) and the mean right upper zone clearance rate 10.5 per cent per second (S.D. 4.7). The difference between the left and right upper zone clearance rates of each individual divided by the mean of the left and right upper zone clearance rates of that individual was used for statistical analysis. The difference between the individual paired values of left and right upper zone clearance rates was significant (p < 0.001), despite the small separation of the group means for the left and right sides because

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the difference was consistent. The values of upper zone clearance obtained in this study were higher than the previous normal values but on this occasion no special precautions were taken to ensure that the normal subjects were in a basal state. The upper zone values are very sensitive to anxiety and exercise.

Patients with Pulmonary Stenosis

Fourteen patients with obstruction of right ventricular outflow tract and reduced pulmonary artery pressure and flow were studied. There were seven with lone pulmonary stenosis (five valvular, two infundibular) and seven with the tetralogy of Fallot. The diagnoses were made on clinical evidence including electrocardiography and radiography, and verified in all cases by routine right heart catheterization. In the seven patients with the tetralogy of Fallot angiocardiography provided additional confirmation of the diagnosis.

Relevant hemodynamic data are listed in table 1. Of the patients who had only pulmonary stenosis two were mild, having pressure gradients of 26 and 44 mm. Hg across the valve (cases 1 and 2); two were moderately severe with gradients of 80 and 90 mm. Hg (cases 3 and 4); and three more severe with gradients of over 100 mm. Hg (cases 5, 6, and 7). The arterial saturation was normal in all these patients, and none gave a history of cyanosis on effort. In the patients with the tetralogy of Fallot the resting arterial oxygen saturation was regarded as an index of severity of the

**Table 1**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Case no.</th>
<th>Age (yr.)</th>
<th>Right ventricle</th>
<th>Pulmonary artery</th>
<th>Arterial saturation (%)</th>
<th>Measured simultaneously Left upper zone</th>
<th>Measured simultaneously Right upper zone</th>
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<td>1</td>
<td>14</td>
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<td>94</td>
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<td>10</td>
<td>65/0</td>
<td>21/10</td>
<td>93</td>
<td>9.5</td>
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<tr>
<td></td>
<td>3</td>
<td>8</td>
<td>80/0</td>
<td>31/18</td>
<td>94</td>
<td>25.1</td>
<td>5.7</td>
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<tr>
<td></td>
<td>4</td>
<td>14</td>
<td>90/5</td>
<td>10/5</td>
<td>94</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>16</td>
<td>110/30</td>
<td>15/5</td>
<td>94</td>
<td>7.8</td>
<td>2.1</td>
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<tr>
<td></td>
<td>6</td>
<td>20</td>
<td>112/0</td>
<td>—</td>
<td>94</td>
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<td></td>
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<td>13</td>
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<td>95</td>
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<td>85</td>
<td>10.6</td>
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<td>84</td>
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<td></td>
<td>11</td>
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<td>120/2</td>
<td>7/0</td>
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<td>1.1</td>
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<td>0</td>
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<td></td>
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<td>—</td>
<td>79</td>
<td>5.2</td>
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<td></td>
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<td>15</td>
<td>104/0</td>
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**Table 2**

<table>
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<tr>
<th>Case no.</th>
<th>Age (yr.)</th>
<th>Pulmonary to systemic flow ratio</th>
<th>Pulmonary artery pressure (mm. Hg)</th>
<th>Total resistance units</th>
<th>CO₂ clearances %/second</th>
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<td>29/9</td>
<td>1</td>
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<td>7</td>
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<td>15/8</td>
<td>2</td>
<td>26</td>
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<tr>
<td>17</td>
<td>13</td>
<td>3:1</td>
<td>28/4</td>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td>18</td>
<td>36</td>
<td>1.7:1</td>
<td>45/0 (RV)</td>
<td>—</td>
<td>30</td>
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<td>3.5:1</td>
<td>28/9</td>
<td>1</td>
<td>40</td>
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<tr>
<td>20</td>
<td>44</td>
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<td>34/14</td>
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<td>32</td>
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<td>19</td>
<td>2.8:1</td>
<td>35/10</td>
<td>3</td>
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</tr>
<tr>
<td>22</td>
<td>34</td>
<td>2:1</td>
<td>74/32</td>
<td>5</td>
<td>11</td>
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<tr>
<td>23</td>
<td>13</td>
<td>2:1</td>
<td>10/5</td>
<td>1</td>
<td>40</td>
</tr>
<tr>
<td>24</td>
<td>33</td>
<td>3.5:1</td>
<td>40/10</td>
<td>1</td>
<td>26</td>
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</tbody>
</table>
The chest x-ray of a patient (case 7) with isolated pulmonary stenosis, to show the oligemic lungs.

outflow tract obstruction. This varied between 91 per cent and 74 per cent.

Patients with Left-to-Right Shunts

A group of patients with left-to-right shunts was also studied and the findings were compared with the data obtained from patients with pulmonary outflow tract obstruction. There were 10 patients with atrial septal defect, eight with ventricular septal defect, and four with patent ductus arteriosus. In all but two patients with patent ductus arteriosus the diagnosis was confirmed by cardiac catheterization. All the patients with ventricular septal defects and the majority with atrial septal defects were studied by angiocardiography. Hemodynamic data on the patients with atrial septal defects are in table 2.

Results

Pulmonary Stenosis and Tetralogy of Fallot

The hemodynamic data and the carbon dioxide clearance rates of the patients with pulmonary stenosis have been brought together in table 1. The patients fall naturally into two groups, those with pulmonary stenosis and those with Fallot's tetralogy.

The clearance rates in patients with isolated pulmonary stenosis were not significantly different from normal values in any zone. The mean clearance rate from the two upper zones was 8.3 per cent per second (S.D. 6.5) and the mean from the two upper zones in normal subjects was 11.4 per cent per second (S.D. 5.3). Three patients (cases 2, 3, and 4) had high clearance rates from both zones that are unexplained. The mean clearance rate from the right lower zone was 25.9 per cent per second (S.D. 6.5) and the normal value was 23.5 per cent per second (S.D. 1.7). Clearance rate measurements from the left upper zone appear twice in table 1 and the values often differ. The lower values were obtained later in the recording session and it is thought that this is an effect of rest with reduction in cardiac output. To minimize the effects of this kind of varia-
tation the order of regional measurements was randomized. Despite these changes the ratio of clearance rates in the two upper zones maintained a similar relationship throughout the time of measurement.

Patients with the tetralogy of Fallot had lower carbon dioxide clearance rates than normal subjects in both upper and lower zones. The mean upper zone clearance rate was 2.1 (S.D. 1.7) and the mean lower zone clearance rate was 16.7 per cent per second (S.D. 6.3). These results are in accord with the low pulmonary blood flow associated with the right-to-left cardiac shunt in this disease.

The upper and lower zone comparisons for individual patients are shown graphically in figure 1. Measurements were also made at a level 5 cm. below the second rib in three patients with Fallot’s tetralogy in whom the upper zone clearance rates were zero. These results are shown in table 3.

An interesting point arose when comparisons were made of the carbon dioxide clearance rates from the two upper zones in both pulmonary stenosis and the tetralogy of Fallot. There was a significant difference (p < 0.01) between the individual paired clearance rates, the left side showing the faster clearance. Normal subjects also had a higher clearance rate at the left upper zone (12.2 per cent per second) than the right (10.5 per cent per second) and the difference between the individual paired values was significant (p < 0.001). The preponderance of flow through the left upper zone in normal subjects was proportionately less than in patients with pulmonary stenosis and the tetralogy of Fallot, the difference between the groups being highly significant (p < 0.001). The results are illustrated by the following two case reports.

Case Reports

Case 7

The patient was a boy aged 13. Pulmonary stenosis had been diagnosed at the age of 5, but he had been asymptomatic until recently when his parents noticed that he was tiring more easily during exertion. He continued to take part in all school activities. There was no history of cyanosis or chest pain.

The jugular venous pulse showed an “a” wave 5 cm. above the sternal angle. There were a strong left parasternal lift over the right ventricle and a long systolic thrill and murmur maximal in the second left intercostal space. The pulmonary element of the second sound was soft and delayed and occurred 0.08 second after the aortic element. On the electrocardiogram there was a tall R wave and no “S” wave in lead V3 with inverted T waves extending across to lead V5. Cardiac catheterization confirmed the diagnosis. A systolic pressure gradient of 115 mm. Hg was found at valve level: the pulmonary artery pressure was 15/10 mm. Hg. The arterial saturation was normal and no shunts were detected. Radioactive carbon dioxide clearance curves and the chest x-ray are shown in figure 2. The chest radiograph shows oligemia of the lung.
The angiocardiogram of a patient (case 14) with Fallot's tetralogy, showing simultaneous filling of the aorta and pulmonary artery. The filling of the pulmonary arteries in the lung fields is greater on the left than on the right.

**Figure 3A**

The carbon dioxide clearance rate was 3.9 per cent per second from the upper zone and 13.3 per cent per second from the lower zone; both values are low.

**Figure 3B**

Comparison of the two upper zones showed a clearance rate of 6.6 per cent per second on the left and only 0.3 per cent per second on the right.

**Figure 3C**

The patient, a boy of 15, had the tetralogy of Fallot. He was first noticed to be blue at the age of 3. There was no history of syncopal attacks but he used frequently to squat when breathless. He had dyspnea when climbing stairs or walking rapidly on a flat surface.

There was central cyanosis at rest. He was polycythemic, and the fingers and toes were clubbed. The venous and arterial pulses were normal. The cardiac impulse was right ventricular in type and there was a long ejection-type systolic murmur maximal over the left second interspace. No thrill was felt, and on auscultation the second sound was
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single. The electrocardiogram showed right ventricular hypertrophy. The pressure gradient between the body of the right ventricle and the pulmonary artery at cardiac catheterization was 95 mm. Hg. There was obstruction at both valve and infundibular levels. The pulmonary artery pressure was 9/2 mm. Hg and the resting arterial saturation was 74 per cent. Selective angiography demonstrated early filling of the aorta and confirmed that the obstruction was mainly valvular (fig. 3A). The carbon dioxide results show that the clearance rate at the left second rib was 3.9 per cent per second, and 4 inches (10 cm.) lower on the right it was 13.3 per cent per second (fig. 3B). Simultaneous measurements in the two upper zones (fig. 3C) showed a clearance rate of 6.6 per cent per second on the left and 0.3 per cent per second on the right.

Atrial Septal Defect

There were 10 patients with this diagnosis. The hemodynamic data and the measurements of carbon dioxide clearance rate have been summarized in table 2. The measured carbon dioxide clearance rates were high, in keeping with the high pulmonary blood flow. The relevance of these results to the present paper concerns the comparison of the two upper zones. The mean left upper zone clearance rate was 28.4 per cent per second (S.D. 9.2) and the right upper zone 31.1 per cent per second (S.D. 7.1). The difference between the upper zones was small but that between the individual paired values was significant ($p < 0.02$). Normal subjects have a slightly higher flow through the left upper zone than the right in contrast to patients with atrial septal defects who had the higher flow on the right side: a significant difference ($p < 0.01$) between the groups.

Ventricular Septal Defect and Patent Ductus Arteriosus

There were eight patients with ventricular septal defects. The mean left upper zone clearance rate was 32.6 per cent per second (S.D. 9.0) and the right upper zone 32.2 per cent per second (S.D. 9.6). There was no significant difference between the individual paired upper zone clearance rates in this group. There were only four patients with patent ductus arteriosus. The paired upper zone clearance rates in these four patients were closely similar.

![Table 3](https://example.com/table.png)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Clearance rate 5 cm. below second rib %/second</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Left: 1.7 Right: 3.5</td>
</tr>
<tr>
<td>10</td>
<td>Left: 1.7 Right: 1.1</td>
</tr>
<tr>
<td>12</td>
<td>Left: 3.8 Right: 2.6</td>
</tr>
</tbody>
</table>

Discussion

The carbon dioxide clearance rates have been used as a measure of regional blood flow in this study. Several factors probably affect the clearance rate of the labeled pulmonary capillary blood from the counting field. These include the volume flow rate, the degree of mixing, and the pulmonary venous and capillary blood volumes in the counting field. Since the clearance curves are affected by all these factors, they can most safely be used to compare blood flow through different regions of the lung of the same patient, or, as in the present investigation, to compare the blood flow through similar areas of a patient's left and right lung. The regional clearance rates of the upper zones are particularly sensitive to excitement, presumably because of changes in cardiac output.

The observed differences between the flow in the left and right upper zones in patients with pulmonary stenosis, atrial septal defects, and normal subjects were usually only moderate but they were consistent. The most striking finding was the preponderance of blood flow through the left upper zone in some patients with pulmonary stenosis, both with and without a closed ventricular septum. It was surprising to find that normal subjects also showed a higher flow in the left upper zone than the right, although the difference between the two zones was proportionately smaller than in the patients with pulmonary stenosis. A similar difference appeared in previous measurements on normal subjects but numbers were small. By contrast patients with atrial septal defects showed a small but significant preponderance of flow through the
right upper zone. The patients with ventricular septal defect and patent ductus arteriosus had almost identical flows through the two upper zones.

The difference in clearance between left and right upper zones in normal subjects may be because the main pulmonary artery is directed toward the left lung, and the momentum of the blood partly determines its distribution. If this is a factor, the difference between the two lungs should be more marked when the velocity of the blood ejected into the pulmonary artery is higher, and the greater left-to-right difference found in patients with pulmonary stenosis supports this suggestion. In pulmonary stenosis the blood moves through the narrow valve as a fast jet.

The higher right upper zone clearance rates in patients with atrial septal defects are consistent with the findings of Fleming,6 who found a much higher oxygen uptake in the right lung than the left, by bronchospirometry. If the heart is enlarged, radioactive blood in it may interfere with clearance curves recorded from the left lower zone; so it is unwise to compare the flow through the two lower zones by our method. It is therefore impractical to determine whether or not a preponderance of flow through one apex reflects a similar situation throughout the whole lung.

The patients with isolated pulmonary stenosis had relatively normal flow rates in both the upper and lower zones, but the patients with the tetralogy of Fallot had low values in both zones. This presumably reflects the low total pulmonary blood flow in these patients. Three patients with the tetralogy of Fallot who had no clearance at the level of the second rib had low clearance rates 5 cm. lower. These patients had oligemia of the upper one third of the lung.

In 1946 Dock,6 using the data of Cournand and his co-workers,7 calculated that the effective pulmonary artery pressure near the lung apices in an erect man would be close to zero. He suggested that this explained the apical localization of pulmonary tuberculosis, and that the higher incidence of the disease at the right apex than the left might be the result of higher blood flow at the left apex as the blood gushed from the conus straight into the left pulmonary artery. Dock pointed out that patients with pulmonary stenosis, particularly those with the tetralogy of Fallot, have a high incidence of apical pulmonary tuberculosis. It is interesting that the predictions that Dock made about the apical pulmonary blood flow, from the localization of pulmonary tuberculosis in patients with a normal cardiovascular system, are exactly those found experimentally in this study.

Summary

Carbon dioxide labeled with oxygen-15 has been used to study the regional blood flow in the lungs of patients with pulmonary stenosis. The upper and lower zone flows were normal in patients with isolated pulmonary stenosis, but both were low in patients with the tetralogy of Fallot. A comparison of the two upper zones showed a significantly higher blood flow through the left upper zone in patients with both isolated pulmonary stenosis and the tetralogy of Fallot.

A significantly higher flow was also found through the left upper zone than the right of normal subjects. By contrast, patients with atrial septal defect had a higher flow through the right upper zone than the left. Neither difference was as large as in the patients with right ventricular outflow tract obstruction.

Patients with ventricular septal defect and those with patent ductus arteriosus had almost identical flow through the two upper zones.

Acknowledgment

We thank the staff of the Medical Research Council cyclotron and Radiotherapy Research Unit for the use of their facilities, Mr. G. Forse, for valuable technical assistance, and Dr. J. F. Goodwin, for his assistance and willing cooperation in these studies of patients under his care.

References

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There is certain evidence in the history of research for the belief that some discoveries could not have been made until some other discovery had been made. This fact underlies an aspect of research that has nothing to do with our roulette or chance. But it does have to do with the imagination and creativeness of a good researcher. It underlies, too, what are called “good leads,” for when knowledge in one field reaches a given stage, men in other fields may see how to incorporate that new knowledge or method in fruitful ways. And sometimes they may not: witness the lapse of time between the synthesis of one of the sulfa drugs in 1908 and its successful use in bacterial infections in the thirties. This dependence of some discoveries on antecedent discoveries furnishes the main reason for saying, “You can’t just go out and buy the discoveries you want.” Some discoveries have cost a good deal of money. But one can’t infer from that fact that spending a good deal of money will buy whatever you want. In Professor V. R. Khanolkar’s laboratory in Bombay I saw an excellent statement: “Il faut chercher pour trouver mais pas pour trouver ce qu’on cherche”—you must search to find but not to find what you are searching for.—ALAN GREGG, M.D., Challenges to Contemporary Medicine. New York, Columbia University Press, 1956, p. 71.
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