Indicator-Dilution Curves in Acyanotic Congenital Heart Disease

By James C. Broadbent and Earl H. Wood

Dye dilution and cardiac catheterization techniques were used to study 36 patients with a central left-to-right shunt due to patent ductus arteriosus, atrial septal defect or ventricular septal defect. The configuration of dilution curves following injection of dye into an antecubital vein was similar in all instances. Principal abnormalities of the curve were a prolongation of its disappearance slope and a relative reduction in the peak concentration of dye. Quantitatively expressed, these abnormalities could be correlated with the magnitude of the left-to-right shunt. Curves of normal contour were observed following surgical closure of the ductus arteriosus, and in patients with isolated pulmonary stenosis.

The dilution of an indicator substance by the blood stream during its initial passage through the central circulation proceeds in a manner determined by several hemodynamic variables. These include, among other things, the velocity, volume and pathway of the circulating blood. Stewart, Hamilton and associates and others have derived methods for determining the cardiac output and the circulating central blood volume from dye dilution curves recorded in persons with normal circulations. More recently, Nicholson and associates in a study of patients with abnormal conditions of the circulation, observed unusual and distinctive patterns of the dye curve associated with central left-to-right and right-to-left shunts and with congestive heart failure. These observations indicated that the dye dilution curve might provide information of significant clinical value in patients with suspected or demonstrated abnormalities of the central circulatory pathway.

In order to explore this possibility, a systematic study of dye dilution curves in patients with demonstrated abnormalities of the central circulatory pathway was undertaken, employing dye injection and cardiac catheterization techniques. Swan and associates have reported on the characteristics of the dye curve in cyanotic forms of congenital heart disease. It is the purpose of this paper to describe the significant abnormalities of the dye dilution curve observed in a study of 26 patients with a known left-to-right shunt, and to demonstrate the correlation between the magnitude of the shunt and the degree of abnormality of the dye curve.

Methods and Materials

Indicator-dilution curves employing the blue dye T-1824 (Evans blue) were recorded in 36 patients with acyanotic congenital heart disease. There were sixteen patients with patent ductus arteriosus, six with a defect of the atrial septum, four with a ventricular septal defect and ten with isolated pulmonic stenosis. With the exception of eight patients who had patent ductus arteriosus, the diagnosis and the magnitude of the shunt were determined by cardiac catheterization performed concurrently with the dye injection procedure. Seven of the group with patent ductus arteriosus were also studied following surgical closure of the ductus.

In all instances the injection of dye was made as rapidly as possible into an antecubital or forearm vein, followed immediately by 5 cc. of isotonic saline solution, also injected very rapidly. The amount of dye injected was 10 to 40 mg. in 1 to 2 cc. of a sterile aqueous solution, or approximately 0.5 mg. per kilogram of body weight. The varying concentration of dye in arterial blood following the injection was recorded simultaneously at the ear and radial artery, using a simultaneous single and
double scale ear oximeter and a cuvette oximeter for whole blood, respectively. The operation of these and other instruments employed in this study was recorded continuously on 18-inch photographic paper by means of a photokymographic recording assembly described previously. A typical recording is shown in figure 1.

Measurements of dye curves were made directly from the photographic record. The several time components of the curve which were measured routinely are shown in figure 2. Values for the peak of concentration of dye in whole arterial blood were determined from the curve recorded by cuvette oximeter, after the method of Nicholson and co-workers.

The technic of cardiac catheterization as performed in this laboratory and the calculations made from data so obtained have been described previously. 

**Results**

1. Abnormalities of Dye Curves in Central Left-to-Right Shunts

A centrally located left-to-right shunt, when of sufficient magnitude, produces an alteration in the dye dilution pattern which is highly characteristic of this circulatory disturbance.
(fig. 1, "preoperative"). In its typical form, this pattern is characterized by: (1) an appearance time and a build-up time of normal duration; (2) an initial peak of concentration of dye which is lower than would be anticipated in a normal person for the amount of dye injected; (3) a prolongation of the disappearance slope of the curve; and (4) the absence of the normal secondary peak of dye concentration due to systemic recirculation of dyed blood.

One or more of these abnormal features was present in varying degree in curves from each of the 26 patients with left-to-right shunts included in this study. In some patients believed to have shunts of relatively small magnitude, the dye curve was nearly normal in configuration; in others, with evidence of a larger shunt, the curve was grossly abnormal, presenting the typical left-to-right shunt pattern. This pattern was not observed in curves from 16 normal subjects, from 10 patients with isolated pulmonary stenosis, or from seven patients with patent ductus arteriosus following surgical closure of the ductus (fig. 1, "postoperative").

Similar dilution patterns were observed in patients with patent ductus arteriosus, atrial septal defect, and ventricular septal defect. No special feature of the dye curve was observed which would permit an anatomic localization of the site of the shunt. It was of interest that the dye curve from a patient with partial anomalous pulmonary venous drainage presented the typical left-to-right shunt pattern.\(^{13}\)

**II. Dimensions of Dye Curves in Patients With A Central Left-to-Right Shunt**

**A. Time Components.** Table 1 presents the average and range of values of the several time components of the dye curve recorded by

| Table 1.—Comparison of Average Circulation Times (in Seconds) from Dye Dilution Curves Recorded Simultaneously at Ear and Radial Artery after Injection of Evans Blue into an Antecubital Vein |
|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Normal subjects | Oximeter | Subjects | AT* | BT | DT | CLT | PT | DT/BT |
| Ear | 16 | 14±1† | 9±1 | 15±1 | 24±2 | 24±1 | 1.6±0.1 |
| | | (10-27) | (6-14) | (9-26) | (15-40) | (16-35) | (1.2-2.0) |
| | Radial | 16 | 15±1 | 9±1 | 14±1 | 22±2 | 23±1 | 1.6±0.1 |
| | | (10-21) | (6-14) | (7-29) | (11-43) | (15-33) | (1.2-2.1) |
| Patent ductus arteriosus | Ear | 16 | 11±1 | 8±1 | 22±6 | 29±7 | 19±2† | 2.4±0.2 |
| | | (7-18) | (4-20) | (6-102) | (10-122) | (12-38) | (1.4-5.1) |
| | Radial | 13 | 13±1 | 8±1 | 26±7 | 34±8 | 21±2 | 2.8±0.3 |
| | | (8-21) | (4-20) | (8-99) | (12-119) | (13-41) | (1.4-4.9) |
| Atrial septal defect | Ear | 6 | 10±1 | 11±2 | 48±3 | 61±5 | 22±3 | 4.8±0.7 |
| | | (8-12) | (6-20) | (35-57) | (44-76) | (14-29) | (2.4-7.3) |
| | Radial | 6 | 12±1 | 9±1 | 52±5 | 62±6 | 21±2 | 6.1±0.9 |
| | | (8-16) | (5-14) | (38-71) | (46-85) | (13-28) | (4.5-10.2) |
| Ventricular septal defect | Ear | 4 | 9±3 | 12±2 | 46±11 | 57±12 | 21±4 | 3.8±0.5 |
| | | (4-17) | (9-16) | (27-70) | (36-86) | (14-32) | (3.0-4.6) |
| | Radial | 3 | 12±4 | 11±3 | 70±28 | 80±29 | 23±7 | 7.1±3.5 |
| | | (4-19) | (8-16) | (21-118) | (28-126) | (13-35) | (2.7-14.0) |

* AT = appearance time; BT = build-up time; DT = disappearance time; CLT = clearance time; PT = peak time; DT/BT = ratio of disappearance time to build-up time; see figure 2 for diagrammatic definition of these terms.

† Figures after ± signs are standard errors of the mean. Figures in parentheses are extreme values.

† In 15 patients only, since moment of dye injection was not indicated in one patient.
Fig. 3. Variation in the contour of dye dilution curves with physiologic status of normal subjects; dye curves simultaneously recorded from ear and radial artery in three normal adult men, ages 31 to 38 years, with individual values for metabolic rate, heart rate, and cardiac index (cardiac output in liters per minute per square meter of body surface). For the sake of clarity and simplicity these curves are traced from photographic recordings of multiple physiologic variables similar to those shown in figure 1. The cuvette oximeter (radial artery) curves were moved to the left on the record a distance equivalent to the time required for blood to flow from the radial artery to the midpoint of the cuvette. This time was calculated by dividing the volume in cubic centimeters from needle point to midcuvette by the rate of blood flow through the cuvette in cubic centimeters per second. Note that in these subjects the degree of steepness or rapidity of the dye curves apparently varies in the same direction as the cardiac output, heart rate and metabolic rate.

Ear and cuvette oximeters in 16 normal subjects and in 16 patients with patent ductus arteriosus, six with atrial septal defect, and four with ventricular septal defect. The disappearance time (DT) of curves from patients with a central left-to-right shunt tends to be increased as compared with the normal average value. However, there is a considerable variability of disappearance time in normal subjects (mean 15 ± 1 seconds; range 9–26 seconds), limiting the reliability of this comparison. This variability of disappearance time in normal subjects is related in part to cardiac output, as shown in figure 3, which compares dye curves recorded from 3 of the 16 normal subjects. The disappearance time of the curve from one subject was 26 seconds when the cardiac index was 2.0 liters per minute per square meter of body surface, and in another the disappearance time was 9 seconds when the cardiac index was 5.6.

This variation of the disappearance time of the dye curve with cardiac output in the absence of a shunt is better shown in figure 4.

Fig. 4. Relationship of disappearance time and of ratio of disappearance time to build-up time of arterial dye dilution curves to the cardiac output in 16 normal subjects and 32 patients with mitral stenosis. The curved solid line was drawn as the visual best fit for the points (circles) representing the disappearance times. The straight solid line is the calculated linear regression line for the points (squares) representing the ratios of disappearance time to build-up time. The slope of this line (−0.088) was slightly but significantly less than zero (p value: <0.02). The double-ended dashed arrow on the left was drawn through the mean cardiac index value of the group falling below 3.0 liters per minute per square meter. This arrow covers a range of ± twice the standard deviation of the disappearance time–build up time (DT/BT) ratios of this group of subjects. The double-ended dashed arrow on the right covers a similar range for the group of subjects with cardiac indexes above 3.0 liters per minute per square meter. All injections of dye were made into a peripheral (ante cubital) vein. The cardiac index values for the normal subjects were calculated from the dye dilution curves recorded from a radial artery. The cardiac indexes for the patients with mitral disease were obtained by the direct Fick method almost simultaneously with the recording of the dye dilution curves during cardiac catheterization. Note that the disappearance time–build-up time ratio values are much more nearly independent of the level of cardiac output and much less variable than are the disappearance time values for the same dye curves. The disappearance time–build-up time ratio is therefore a much more useful measurement for the detection of asymmetry in the disappearance limb of a dye curve than is the disappearance time alone.
TABLE 2.—Relationship of Peak Concentration of Dye Curve Recorded at Radial Artery (in Milligrams per Liter of Blood) to Amount of Dye Injected (in Milligrams per Kilogram of Body Weight) in Normal Subjects and in Patients With Left-to-right Shunts

<table>
<thead>
<tr>
<th></th>
<th>Amount of dye injected, mg./Kg.</th>
<th>Peak concentration of dilution curve, mg./L.</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>B/A</td>
</tr>
<tr>
<td>16 normal subjects</td>
<td>0.5±0.0* (0.4-0.7)</td>
<td>33±3 (21-62)</td>
<td>61±5 (34-103)</td>
</tr>
<tr>
<td>12 patients with patent ductus arteriosus</td>
<td>0.7±0.1 (0.5-1.6)</td>
<td>28±4 (9-50)</td>
<td>42±6 (18-84)</td>
</tr>
<tr>
<td>6 patients with atrial septal defect</td>
<td>0.6±0.0 (0.5-0.8)</td>
<td>16±2 (12-24)</td>
<td>26±3 (16-35)</td>
</tr>
<tr>
<td>3 patients with ventricular septal defect</td>
<td>0.7±0.1 (0.5-0.9)</td>
<td>17±5 (11-26)</td>
<td>25±6 (14-37)</td>
</tr>
<tr>
<td>4 patients after closure of a patent ductus arteriosus</td>
<td>0.6±0.0 (0.5-0.7)</td>
<td>39±7 (22-56)</td>
<td>63±10 (43-88)</td>
</tr>
</tbody>
</table>

* Figures after ± signs are standard errors of the mean. Figures in parentheses indicate the range of values.

The disappearance times of curves from 16 normal subjects and 32 patients with mitral stenosis were plotted against cardiac index. In the normal subjects, cardiac output was calculated from the contour of the dye curve recorded by cuvette oximeter by the replot method of Hamilton; in patients with mitral stenosis cardiac output was calculated by the Fick method from data obtained at cardiac catheterization.

Figure 4 demonstrates that the disappearance time of the dye curve in persons without a shunt is inversely related to cardiac output, that at any level of cardiac output there is a wide range of values for the disappearance time, and that the variability of the disappearance time is greater at the lower levels of cardiac output than at the higher levels.

Thus it is apparent that the disappearance time of the curve may be increased in patients with a central left-to-right shunt, in patients with low cardiac output without a shunt, and in certain normal subjects. This fact limits the value of the disappearance time, per se, as a guide to the presence and magnitude of a central left-to-right shunt. Accordingly, it became desirable to find some characteristic of the curve or an index which would be independent of cardiac output and yet permit a determination of that degree of prolongation of the disappearance slope of the curve which was due to cardiopulmonary recirculation in patients with a central left-to-right shunt.

Owing to the internal consistency of indicator-dilution curves it was anticipated that variation of the disappearance time with cardiac output could be nearly eliminated if a correction was made for the steepness or the rapidity of the curve. It was found that this correction was most simply made by calculating the ratio of the disappearance time of the curve to its build-up time (DT/BT ratio). The effectiveness of this correction is shown at the top of figure 4 where the disappearance time—build-up time (DT/BT) ratio of dye curves in the same normal subjects and patients is plotted against cardiac output. Note that the disappearance time—build-up time ratio is nearly independent of cardiac output, and that at any level of cardiac output, the disappearance time—build-up time ratio is less variable than the disappearance time alone.

B. The Peak of Concentration of Dye. The peak of concentration of the dye curve recorded by cuvette oximeter was determined in 16 normal subjects and in 21 patients with a central circulatory shunt of left-to-right type. The peak of concentration was expressed as the ratio of the maximal concentration of the dye curve (in milligrams of dye per liter of whole arterial blood) to the amount of dye injected (in milligrams of dye per kilogram of body weight). Table 2 presents the average and range of values for this ratio in normal subjects and patients. A comparison of average values reveals that the peak concentration of dye curves from patients with a left-to-right shunt tends to be reduced below the normal range.
TABLE 3.—Cardiac Catheterization and Dye Curve Data From 15 Patients with a Left-to-right Shunt Compared to Values Obtained in Normal Subjects

<table>
<thead>
<tr>
<th>Case</th>
<th>Diagnosis</th>
<th>Age, years</th>
<th>Sex</th>
<th>Cardiac output, L./min.</th>
<th>Cardiac index, L./min./M²</th>
<th>Pulmonary artery flow, L./min.</th>
<th>Left-to-right shunt</th>
<th>Data from dye curves</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>P.D.A.†</td>
<td>45</td>
<td>F</td>
<td>6.7</td>
<td>4.7</td>
<td>9.1</td>
<td>2.4</td>
<td>1.5</td>
</tr>
<tr>
<td>11</td>
<td>P.D.A.</td>
<td>16</td>
<td>M</td>
<td>7.4</td>
<td>3.5</td>
<td>10.0</td>
<td>3.5</td>
<td>32</td>
</tr>
<tr>
<td>12</td>
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<td>26</td>
<td>F</td>
<td>6.5</td>
<td>4.4</td>
<td>10.2</td>
<td>3.7</td>
<td>36</td>
</tr>
<tr>
<td>15</td>
<td>P.D.A.</td>
<td>22</td>
<td>F</td>
<td>6.1</td>
<td>3.6</td>
<td>9.9</td>
<td>3.8</td>
<td>38</td>
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<td>1</td>
<td>P.D.A.</td>
<td>38</td>
<td>M</td>
<td>6.6</td>
<td>2.9</td>
<td>11.2</td>
<td>4.6</td>
<td>41</td>
</tr>
<tr>
<td>9</td>
<td>P.D.A.</td>
<td>46</td>
<td>F</td>
<td>4.3</td>
<td>2.6</td>
<td>14.0</td>
<td>9.7</td>
<td>69</td>
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<td>19</td>
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<td>45</td>
<td>M</td>
<td>4.6</td>
<td>2.8</td>
<td>6.1</td>
<td>1.5</td>
<td>25</td>
</tr>
<tr>
<td>22</td>
<td>A.S.D.</td>
<td>15</td>
<td>M</td>
<td>5.2</td>
<td>3.8</td>
<td>10.0</td>
<td>4.8</td>
<td>48</td>
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<td>20</td>
<td>A.S.D.</td>
<td>24</td>
<td>M</td>
<td>6.7</td>
<td>3.9</td>
<td>14.1</td>
<td>7.4</td>
<td>53</td>
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<tr>
<td>18</td>
<td>A.S.D.</td>
<td>20</td>
<td>F</td>
<td>6.7</td>
<td>4.4</td>
<td>22.1</td>
<td>15.4</td>
<td>70</td>
</tr>
<tr>
<td>21</td>
<td>A.S.D.</td>
<td>24</td>
<td>F</td>
<td>4.1</td>
<td>2.5</td>
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<td>25</td>
<td>V.S.D.</td>
<td>9</td>
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<td>26</td>
<td>V.S.D.</td>
<td>5</td>
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<td>4.6</td>
<td>6.0</td>
<td>2.7</td>
<td>45</td>
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<tr>
<td>24</td>
<td>V.S.D.</td>
<td>18</td>
<td>M</td>
<td>4.9</td>
<td>3.3</td>
<td>9.1</td>
<td>4.2</td>
<td>46</td>
</tr>
<tr>
<td>23</td>
<td>V.S.D.</td>
<td>29</td>
<td>M</td>
<td>4.6</td>
<td>2.3</td>
<td>8.6</td>
<td>4.0</td>
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</tr>
</tbody>
</table>

Average values in normal subjects

<table>
<thead>
<tr>
<th></th>
<th>3.4§</th>
<th>6.7§</th>
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<tr>
<td>(2.2–4.5)</td>
<td>(4.1–8.3)</td>
<td></td>
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</table>

* See table 2 for exact definition.
† P.D.A. = patent ductus arteriosus; A.S.D. = atrial septal defect; V.S.D. = ventricular septal defect.
§ Average and range of values in 5 normal adult male subjects.
∥ Average values in 16 normal subjects (see table 1).
¶ Average value in 16 normal subjects (see table 2).

III. The Correlation of Dye Curve Abnormalities With Shunt Magnitude

A. The Correlation of Shunt Magnitude with Disappearance Time–Build-up Time Ratio of Dye Curve. The magnitude of the central left-to-right shunt was calculated by the Fick method from data obtained at cardiac catheterization in six patients with a patent ductus arteriosus, in five with an atrial septal defect, in four with a ventricular septal defect (table 3), and in one additional patient with partial anomalous pulmonary venous drainage. From the dye curves recorded by ear oximeter, the disappearance time–build-up time ratio was calculated and plotted against the magnitude of the left-to-right shunt, expressed as percentage of the total pulmonary arterial blood flow (fig. 5). A positive correlation was demonstrated between the magnitude of the shunt and the disappearance time–build-up time ratio of the dye curve. It is evident from this figure that the magnitude of the shunt must usually be greater than about 35 per cent of the pulmonary artery flow in order to produce a significant abnormality in this aspect of the dye curve. This conclusion is illustrated in figure 6 in which dye curves from six patients with a patent ductus arteriosus were arranged in order of increasing magnitude of the shunt. In two of three patients with patent ductus arteriosus whose shunts were 36 per cent or less of the total pulmonary arterial flow, the contour of the curve presented only minor abnormalities. However, with increasing magnitude of the shunt the contour became increasingly abnormal, with a progressive reduction in the peak of concentration of the dye curve, and an increase in the disappearance time–build-up time ratio.

B. The Correlation of Shunt Magnitude with the Peak Concentration of the Dye Curve. Dye dilution curves were recorded by cuvette (and ear) oximeter in 14 of the 16 patients who were catheterized at the time of the dye
Fig. 5. Relation of magnitude of central left-to-right shunt to the disappearance–build-up time ratio of arterial dye dilution curves recorded by ear oximeters. All injections of dye were made into a peripheral (antecubital) vein. The magnitude of the arteriovenous shunts was determined at cardiac catheterization. The average (heavy bar) and range of the disappearance–build-up time (DT/BT) ratios obtained in 16 normal subjects are shown on the ordinate of the zero shunt line. Note that there is a positive correlation between the magnitude of the shunt and the disappearance–build-up time ratio of the dye dilution curve. However, dye curves from patients with shunts amounting to 35 per cent of the pulmonary arterial flow may have disappearance time–build-up time ratios within the range of normal subjects. P.D.A. indicates patent ductus arteriosus, A.S.D. indicates atrial septal defect, V.S.D. indicates ventricular septal defect and A.P.V. indicates anomalous pulmonary venous drainage.

Injection study (table 3). In each of these 14 patients, the peak of concentration of dye was calculated from the curve recorded by cuvette oximeter and plotted against the magnitude of the left-to-right shunt, expressed as percentage of the total pulmonary arterial blood flow (fig. 7). An inverse correlation was demonstrated between the magnitude of the shunt and the peak of concentration of dye attained in these 14 patients (six with patent ductus arteriosus, five with atrial septal defect, and three with ventricular septal defect). The peak of concentration of dye was less than the lower limit of normal in seven of nine patients whose shunts were 40 per cent or more of the pulmonary arterial blood flow and was within the normal range in all of the five patients whose shunts were less than 40 per cent of the pulmonary arterial blood flow. In other words, the magnitude of the shunt was 40 per cent or more of pulmonary arterial flow before a significant reduction occurred in the peak of concentration of dye.

Comment

It was observed by Nicholson and associates, and confirmed during this study, that dye curves are of the same general configuration (Nicholson’s left-to-right shunt pattern) when patients have an atrial or ventricular septal defect, a patent ductus arteriosus, or partial anomalous pulmonary venous drainage (into the right atrium). The explanation of this phenomenon is the fact that each of these anatomic defects results in a similar functional disturbance, that is, cardiopulmonary recirculation of blood via the abnormal circulatory pathway.

A typical left-to-right shunt pattern of the dye curve has not been observed in the absence of such a shunt.* For example, this pattern was not observed in curves from seven patients following closure of a patent ductus arteriosus. Moreover, dye curves were of normal contour in 10 patients with pulmonary stenosis who had no demonstrable shunt by cardiac catheterization, and a left-to-right shunt pattern was not recorded from any of 16 normal subjects.

However, contours of dye curves which were nearly normal in their configuration have been recorded from patients with proved left-to-right shunts of relatively small magnitude. Thus, although dye curves have yielded no “false positive” results, contours representing a “false negative” result at low values of shunt have been observed. On the basis of this study in which dye was injected peripherally, it appears that the magnitude of a left-to-right shunt must be greater than about 35 per cent of the pulmonary artery flow in order to produce gross abnormality of the dye curve. A probable explanation for the apparent failure of the dye curve to detect left-to-right shunts of small magnitude is that with small shunts the

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* Dye curves similar in some respects to those observed in patients with a central circulatory shunt have been recorded from patients with a peripheral arteriovenous fistula (unpublished data).
Fig. 6. Variation in the contour of dye dilution curves with magnitude of shunt in six patients with patent ductus arteriosus. The dye dilution curves were recorded simultaneously from the ear (ear oximeter) and radial artery (cuvette oximeter). They are arranged in order of increasing magnitude of the shunt. For increased clarity and simplicity these curves were traced from photokymographic records of multiple physiologic variables similar to those shown in figure 1. The time delay in the radial artery (cuvette oximeter) curve has been corrected; see legend of figure 3. Note that as the magnitude of the shunt increases from 26 to 69 per cent of the pulmonary artery flow the prolongation of the disappearance limb and decrease in peak concentration of the dye curve become evident.

percentage of injected dye recirculated is insufficient to produce an alteration of the initial rate of disappearance of dye from the heart and lungs which falls outside the range obtained in normal subjects. Recent results indicate that abnormalities in the disappearance slope are more definite for low values of shunt when central injections of dye are used.¹³, ¹⁶, ¹⁷

It has been abundantly demonstrated that the abnormalities of the dye curve which are characteristically associated with central left-to-right shunts are the result of such shunts. The alterations of circulatory dynamics produced by such a shunt, and the manner in which these alterations bring about dye curve abnormalities, can be postulated. It is well known that a central left-to-right shunt results in an increase in pulmonary blood flow; that systemic blood flow remains normal and adequate unless there is a very large pulmonary blood flow, as in certain instances of atrial septal defect; and that with large increases in pulmonary blood flow, pulmonary blood volume is increased, as indicated by the roentgenologic appearance of engorged pulmonary vessels. There may be significant enlargement of individual cardiac chambers depending on the site and magnitude of the left-to-right shunt. From a consideration of these several factors, it may be postulated that one or more of the following mechanisms may operate to produce the dye curve abnormalities characteristic of the left-to-right shunt. Prolongation of the time required for the initial passage of dye through the heart and lungs may be due to: (1) cardiopulmonary recirculation of dyed blood; (2) an increase in cardiac and pulmonary
Fig. 7. Relation of magnitude of central left-to-right shunt to peak concentration of arterial dye dilution curve. The maximal concentration of T-1824 in arterial blood was determined from the curve recorded by cuvette oximeter at the radial artery. All injections of dye were made into a peripheral (antecubital) vein. The magnitude of the arteriovenous shunt was determined at cardiac catheterization. The average (heavy bar) and range of the peak concentration obtained in 16 normal subjects are shown on the ordinate of the zero shunt line. Note that there is an inverse correlation between the magnitude of the shunt and the peak concentration of the dye dilution curve. However, dye curves from patients with shunts ranging from 20 to 45 per cent of the pulmonary blood flow may have peak concentration values within the range of normal subjects. P.D.A. indicates patent ductus arteriosus, A.S.D. indicates atrial septal defect and V.S.D. indicates ventricular septal defect.

blood volume. Reduction in the maximal concentrations of dye attained could result from: (1) the dilution of dyed venous blood with shunted but still undyed arterial blood; (2) an increase in cardiac and pulmonary blood volume.

This study has introduced the concept of the disappearance time–build-up time (DT/BT) ratio of the dye curve as an aid in demonstrating the presence or absence of a central left-to-right shunt, and as an index of the relative volume of blood flow through such a shunt, when present. Accordingly, further comments regarding this concept seem indicated.

It has been demonstrated that a prolongation of the disappearance time of the curve characterizes the left-to-right shunt pattern. However, the disappearance times of curves from certain normal subjects, and from patients with congestive failure and low cardiac output are also prolonged. Thus, the duration of the disappearance time, per se, is not a reliable indication of the presence of cardio-pulmonary recirculation. Accordingly, it became desirable to find some measurement or index which would be independent of cardiac output and yet permit a determination of that degree of prolongation of the disappearance slope of the curve which is due to cardio-pulmonary recirculation. It was found that dividing the disappearance time of the curve by its build-up time in effect corrects the disappearance time for the over-all degree of steepness of the curve related to the individual level of cardiac output and other factors. It has been demonstrated that (1) the disappearance time–build-up time ratio is nearly independent of cardiac output over a wide range, and (2) the disappearance time–build-up time ratio can be correlated with the magnitude of the left-to-right shunt, as determined by cardiac catheterization.

The concept of the disappearance time–build-
Fig. 9. Portions of the photokymographic record of arterial dye dilution curves and other physiologic variables from a boy aged 14 years, with a peripheral (femoral) arteriovenous fistula. The dye dilution curves were recorded simultaneously from both ears (ear oximeters) and the right radial artery (cuvette oximeter) when the fistula was open (top panel), and during manual occlusion of the fistula (bottom panel). The injections of dye were made into a peripheral (antecubital) vein. The patient breathed 100 per cent oxygen throughout the procedure to insure complete and constant saturation of arterial blood with oxygen. When the fistula was open, the peak of concentration of the radial dye curve was 8.8 mg. per liter, the mean systemic recirculation time (R.T.) was 10 seconds, and the cardiac output was 10.7 liters per minute per square meter of body surface. Closure of the fistula resulted in (1) a prompt and sustained increase in the levels of systolic and diastolic pressure within the right radial artery; (2) a reduction in heart rate; (3) an increase in the peak concentration of the dye curve (to 14.1 mg. per liter); (4) an increase in the mean systemic recirculation time (R.T. equals 17 seconds); and (5) a decrease in cardiac output to 8.2 liters per minute per square meter of body surface. Reopening of the fistula resulted in a lowering of radial artery pressure, and an increase in heart rate. In the top panel, the deflections of the 3 traces labeled "single scale oximeter" are calibrated in terms of percentage oxygen saturation of blood; these calibration scales reveal that the oximeter attached to the right ear was operated at a sensitivity somewhat greater than that of the other oximeters and therefore that the greater deflection of the curve recorded by this instrument is more apparent than real and not due to a greater concentration of dye in the blood of this ear.

The up time ratio of the dye curve has been of considerable practical value, since it has, in many instances, permitted the distinction between normal curves of low output type, and curves associated with a central left-to-right shunt. In fact, the disappearance time-build-up time ratio was of value in recognizing the presence of a left-to-right shunt due to a patent ductus arteriosus in three patients with this anomaly who were also in congestive failure (fig. 8).

The dye injection method is of value in the differential diagnosis of acyanotic congenital heart disease since it provides a simple and
fairly reliable means of determining the presence or absence of a central circulatory shunt, of the magnitude usually associated with acyanotic congenital cardiac defects. It has been of greatest value in the study of patients with a systolic murmur in the pulmonic area, that is, in distinguishing isolated pulmonary stenosis from those forms of acyanotic congenital heart disease which are associated with a left-to-right shunt. Thus, in 10 patients with pulmonary stenosis who had no demonstrable defect of atrial or ventricular septum, the contour of the curve was entirely normal. Conversely, a completely normal contour of the dye curve was not observed in any of 26 patients with a central circulatory shunt of left-to-right type.

However, like all specialized examinations, the dye injection method is subject to certain limitations, and the interpretation of data provided by it must be integrated with other available clinical data. In particular, the dye injection method, as it is applied to the study of acyanotic congenital heart disease, is subject to the following limitations: (1) A wide variability in the contour of the curve from normal subjects makes difficult the distinction between certain normal and certain slightly abnormal contours. (2) The contour of the dye curve from patients with left-to-right central circulatory shunts of small magnitude may present only minor and perhaps hardly recognizable abnormalities. (3) It has not been possible from the contour of a peripheral dye curve to predict the anatomic location of a central circulatory shunt. Localization of shunts can frequently be accomplished by central injections of dye.\(^{17, 18}\)

The following advantages of the dye injection method seem to give it a place among other laboratory technics as a valuable tool in the study of patients with acyanotic congenital heart disease: (1) in certain situations, by establishing a definite diagnosis, this method may make cardiac catheterization unnecessary; (2) the dye injection method is a safe, relatively simple technic suitable for the study of all age groups, and may even be used in those situations in which cardiac catheterization would be hazardous, or would entail the use of a general anesthetic, or perhaps would be unavailable.

Theoretic considerations, as well as our own observations and those of others,\(^{18}\) indicate that dye curves in patients with a peripheral arteriovenous fistula would be similar in some respects to those recorded from patients with a patent ductus arteriosus. Thus, it was of interest to observe incidentally, in the course of this study, the configuration of the dye curves from a series of patients with femoral arteriovenous fistula. Dye dilution curves and other physiologic variables were recorded before and after temporary (manual) interruption of blood flow through the communication (fig. 9). The dye curve recorded when the fistula was open was normal except for (1) a relatively low peak of concentration of dye, and (2) an abnormally short systemic recirculation time. Closure of the fistula resulted in an increase in the peak of concentration of dye, and a prolongation of the recirculation time to the normal range.

**Summary and Conclusions**

1. Dye dilution curves were recorded from 16 normal subjects and from 36 patients with acyanotic congenital heart disease due to a single uncomplicated cardiac abnormality.

2. Dye curves associated with central left-to-right shunts were of similar configuration, presenting, in varying degree, two principal abnormalities of contour: (a) a maximal concentration of dye which was less than would be anticipated in a normal person for the amount of dye injected; and (b) a disproportionately increase in the disappearance time of the curve, resulting in an increase in the ratio of the disappearance time to the build-up time of the curve.

3. When quantitatively expressed, each of these abnormalities could be correlated with the magnitude of the left-to-right shunt. It was found that the magnitude of the shunt was related inversely to the peak of concentration of dye, and positively to the disappearance time–build-up time (DT/BT) ratio of dye curves in 14 and 16 patients respectively, with central left-to-right shunts.

4. Dye curves associated with central left-
to-right shunts were consistently abnormal when the magnitude of the shunt was greater than about 40 per cent of the pulmonary artery blood flow; only minimal abnormalities of contour were noted when the magnitude of the shunt was less than about 40 per cent of the pulmonary artery blood flow.

5. Abnormalities of contour specifically related to the anatomic location of a given left-to-right shunt were not observed.

6. The left-to-right shunt pattern of the dye curve was not observed in seven patients following surgical closure of a patent ductus arteriosus, in 10 patients with isolated pulmonary stenosis, or in 16 normal subjects.

**SUMARIO ESPAÑOL**

1. Curvas de dilución de tinte fueron registradas en 16 sujetos normales y en 26 pacientes con enfermedad cardiaca congénita acianótica producida por una sola anormalidad sin complicaciones.

2. Curvas de tinte asociadas con shunts centrales de izquierda a derecha fueron de similar configuración, presentando, en grado variable, dos principales anormalidades de contorno: (a) una concentración máxima de tinte que fue menor que lo que se anticipó en la persona normal para la cantidad de tinte inyectada; y (b) un incremento desproporcionado en el tiempo de desaparición de la curva, resultando en un incremento en la proporción de tiempo de desaparición al tiempo de formación de la curva.

3. Cuando estas anormalidades fueron expresadas cuantitativamente pudieron ser correlacionadas a la magnitud del shunt de izquierda a derecha. Se encontró que la magnitud del shunt estaba relacionada inversamente al vértice de la concentración del tinte y positivamente al tiempo de desaparición tiempo de formación (TD/TF) proporciona curva de tinte en 14 y 16 pacientes respectivamente con shunts centrales de izquierda a derecha.

4. Curvas de tinte asociadas a shunts centrales de izquierda a derecha fueron consistentemente anormales cuando la magnitud del shunt fue mayor que 40 por ciento de la circulación en la arteria pulmonar; solamente anormalidades mínimas de contorno fueron observadas cuando la magnitud del shunt fue menos que 40 por ciento de la circulación en la arteria pulmonar.

5. Anormalidades de contorno específicamente relacionadas a la localización anatómica de un shunt de izquierda a derecha dado no fueron observadas.

6. El patrón de curva de tinte de shunts de izquierda a derecha no se observó en siete pacientes luego de cierre quirúrgico de un ducto arterioso, en 10 pacientes con estenosis pulmonar aislada, o en 16 sujetos normales.

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INDICATOR-DILUTION CURVES IN ACYANOTIC CONGENITAL HEART DISEASE


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