Transposition of the Great Vessels
Pathophysiologic Considerations Based upon
a Study of the Lungs

By Charlotte Ferencz, M.D., C.M.

The introduction of the Mustard operation\(^1\) for the physiologic correction of transposition of the great vessels has made the year 1964 a turning point in the history of this malformation. As with tetralogy of Fallot, 20 years ago,\(^2\) there has been a sudden change from a grave to a hopeful outlook for patients suffering from transposition of the great vessels. With this there is also a new and urgent necessity for an understanding of the anatomic and physiologic variations of the malformation as well as of the alterations in the pulmonary vascular bed, which may affect the timing and the outcome of surgical therapy. The histologic evaluation of the lungs of patients with transposition of the great vessels, projected earlier,\(^3\) has therefore assumed practical importance.

Methods

A microscopic study of the lungs of 106 patients with transposition of the great vessels forms the subject of this report. Patients were included only if, apart from the origin of the arterial trunks, the basic design of the heart was normal and only a simple intracardiac defect or a patent ductus permitted cross-shunting of blood. Patients in whom the transposition of the great vessels was associated with other malformations, i.e., pulmonic stenosis, aortic stenosis, coarctation of the aorta, single ventricle, ventricular inversion (corrected transposition), hypoplasia of the right or left heart, atrioventricular canal defect, were excluded. This limitation of the case material was made in order to evaluate as accurately as possible the impact upon the pulmonary vascular bed of the hemodynamic effects of transposition in its uncomplicated form. Cases of the Taussig-Bing syndrome were included, since the physiologic alterations of this malformation are essentially identical to those of transposition with large ventricular septal defect.\(^4,5\) Lung tissue was obtained at autopsy in 105 instances and by biopsy in one. In each case one or two blocks of lung were available. Sections were stained with hematoxylin and eosin and with Verhoeff's elastic-tissue stain counterstained with van Giessen's stain. All components of the pulmonary vascular bed were examined.

Age

This was a very young group of patients. Although the age range extended from 4 days to 21 years, the mean age of the group was only 14 weeks. This age distribution does not reflect the true proportion of deaths in infancy to survival into childhood, since the cases for this study were not selected at random. Every effort was made to find material on patients who lived beyond 1 year of age, but not all of the younger patients were included, once an adequate representation of each age group had been obtained.

Associated Defects

The period of survival was clearly related to the presence of a large ventricular septal defect. Among 29 infants who died under 6 weeks of age none had a large ventricular septal defect, while a third of the remaining patients under 6 months and nearly two thirds of those over this age had a large defect. In a few instances the size of the ventricular septal defect was not recorded.

<p>| Table 1 |</p>
<table>
<thead>
<tr>
<th>Transposition of the Great Vessels—Cumulative Age Incidence of 106 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Under 6 months</td>
</tr>
<tr>
<td>Under 1 year</td>
</tr>
<tr>
<td>Under 2 years</td>
</tr>
<tr>
<td>Under 21 years</td>
</tr>
</tbody>
</table>

From the Department of Pediatrics, State University of New York at Buffalo and the Edward J. Meyer Memorial Hospital, Buffalo, New York.

Supported by the Heart Associations of Maryland and of Erie County and by the United Health Foundation of Western New York.

Presented in part before the Seventh Inter-American Congress of Cardiology, June 14-19, 1964, Montreal, Quebec, Canada.
Table 2

Transposition of the Great Vessels—With Ventricular Septal Defect

<table>
<thead>
<tr>
<th>Age</th>
<th>Total number</th>
<th>Large VSD Number</th>
<th>% of total</th>
<th>VSD Size unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 6 weeks</td>
<td>29</td>
<td>0</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>7 Weeks to 6 months</td>
<td>41</td>
<td>14</td>
<td>34</td>
<td>7</td>
</tr>
<tr>
<td>Over 6 months</td>
<td>36</td>
<td>21</td>
<td>58</td>
<td>4</td>
</tr>
<tr>
<td>Totals</td>
<td>106</td>
<td>35</td>
<td>33</td>
<td>13</td>
</tr>
</tbody>
</table>

Results

Pulmonary Arteries

The pulmonary arterial tree was the site of early and severe hypertensive arterial disease. The progression of increasing severity of lesions followed the typical stages described by Heath and Edwards,6 and the findings have been classified according to the grading of these authors.

Normal Arteries

The pulmonary arteries of nine patients were considered to be definitely normal. In these a well-defined muscular media was present, but it was thin and the arterial lumen was wide. These patients varied in age from 1 to 7 months.

Medial Hypertrophy (Grade 1)

A thick muscular media was present in 97 patients. In 47 patients this was the only finding and in 50 patients it was associated with intimal changes.

In young infants in whom the small pulmonary arteries have a thick muscular media and a narrow lumen a clear-cut line cannot be drawn between the degree of muscular hypertrophy normally present in the fetal state and one which is abnormal. It was therefore decided to classify all patients, regardless of age, as showing medial hypertrophy (grade 1) if in the majority of muscular arteries the thickness of the media exceeded 15 to 20 per cent of the external diameter (measured from the external elastic laminae) of the vessel.7

Intimal Fibrosis (Grade 2)

Mild to moderate intimal fibrosis in the small elastic and in the muscular pulmonary arteries was observed in 26 patients. These patients varied in age from 2 weeks to 3 years. Intimal fibrosis usually had its onset around the mouths of arteriolar branches and extended from there proximally and peripherally into the arterial tree.

Occlusive Intimal Fibrosis (Grade 3)

Vascular occlusion as the most severe lesion was found in only 5 instances, while in 19 others who also had these changes, evidence of greater vascular damage was already apparent.

Occlusive Intimal Fibrosis with Beginning Dilatation (Plexiform Lesions) (Grade 4)

Plexiform lesions mark the beginning of dilatation in the hypertensive pulmonary arterial bed6,8 and represent the hallmark of grade 4 in the classification of Heath and Edwards. In this group of young individuals nearly one fifth of the patients were found to have these lesions. The youngest patient in whom they were found was 6 weeks of age. Nine more instances occurred under 2 years of age and in patients older than this their presence was almost uniform.

The appearance of plexiform lesions is usually followed by the development of other dilatation lesions and the gradual destruction of the normal arterial architecture of the lung with elastosclerosis, hyalinization, and the destruction of the lungs in the younger patients. No effort was made to separate the vascular lesions seen in this series beyond grade 4 severity, but there was no instance of necrotizing arteritis (grade 6).

Pulmonary Veins

In contrast to the dramatic changes in the pulmonary arteries, the pulmonary veins appeared normal in almost all instances. A thin layer of a cellular intimal thickening of the
TRANPOSITION OF THE GREAT VESSELS

PULMONARY VASCULAR CHANGES

106 PATIENTS

* LARGE V.S.D.

AGE

YEARS

1 YEAR

MONTHS

NORMAL
(WIDE LUMENS)

GRADE 1
(MEDIAL)
(HYPERTROPHY)

GRADE 2
(MILD INTIMAL)
(FIBROSIS)

GRADE 3
(OCCLUSIVE INTIMAL)
(FIBROSIS)

GRADE 4
(PLEXIFORM)
(LESIONS AND)
(DILATATION)

PULMONARY ARTERIES

Figure 1

Increasing grades of severity of pulmonary arterial lesions plotted in relation to the age of the patient. Stars indicate the presence of a large ventricular septal defect and their distribution shows the relatively longer survival of these patients.

larger veins was present in the lungs of three patients and four others showed slight thickening of the venous walls. In a single instance severe intimal fibrosis of the pulmonary veins was found. This was a 12½-year-old girl in whom transposition of the great vessels was associated with a large atrial septal defect as the only site of communication between the two circulations.

Bronchial Collateral Circulation

Dilatation and tortuosity of the bronchial arteries was noted in the majority of sections. Although the bronchial circulation cannot be evaluated by histologic sections taken at random, the bulging arteries which surrounded the larger bronchi attracted attention and were noted in the lungs of small infants as well as older children. In this sole respect

Table 3

Transposition of the Great Vessels—Arterial Changes in Relation to Associated Defect

<table>
<thead>
<tr>
<th>Pulmonary arteries</th>
<th>Total no.</th>
<th>No VSD</th>
<th>Small</th>
<th>Large</th>
<th>? Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (wide lumens)</td>
<td>9</td>
<td>1</td>
<td>5</td>
<td>—</td>
<td>3</td>
</tr>
<tr>
<td>Medial hypertrophy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone (grade 1)</td>
<td>47</td>
<td>20</td>
<td>9</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>With intimal fibrosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild fibrosis (grade 2)</td>
<td>26</td>
<td>12</td>
<td>5</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Occlusive fibrosis (grade 3)</td>
<td>4</td>
<td>2</td>
<td>—</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Occlusive fibrosis with plexiform lesions (grade 4)</td>
<td>20</td>
<td>3</td>
<td>1</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Totals</td>
<td>106</td>
<td>38</td>
<td>20</td>
<td>35</td>
<td>13</td>
</tr>
</tbody>
</table>
did the lungs of patients with transposition of the great vessels resemble those of patients with tetralogy of Fallot.

**Intravascular Thrombosis**

Thrombotic lesions were rare. In two patients there was evidence of thrombosis within some of theplexiform lesions. In three other patients a few arteries showed the "multilumened" appearance suggestive of re-canalized thrombi, although in each instance the medial muscle was well defined and the intimal lesion may have originated as fibrous proliferation.

**Arterial Changes in Relation to the Associated Septal Defect**

An examination of the relationship of arterial changes to the presence and size of a ventricular septal defect revealed no definite correlation. Intimal lesions were present at an early age in almost one third of the patients in whom a significant ventricular septal defect was not present. These were the patients in whom death occurred early. Among the patients with ventricular septal defect severe intimal damage was almost the rule, but these were the children who lived longer. Thus, the significant disparity in the ages of the patients does not permit a simple comparison of the incidence of abnormal findings in these two groups.

**Discussion**

The presence of severe hypertensive pulmonary arterial disease in infants and children with transposition of the great vessels has been noted by previous workers and suggests that the forces that act upon the lungs in this malformation differ from those present in other forms of congenital heart disease.

The morphologic alterations observed in the pulmonary vascular bed of these patients, without regard to any other information, permit only one conclusion: a state of high pulmonary vascular resistance existed in these individuals. Intimal fibrosis appeared within the first month of life and progressed so rapidly that destruction of the normal pulmonary arterial architecture could occur in babies under 2 months of life and was almost the rule in patients over 2 years of age. These are the findings, not only of severe, but of malignant pulmonary hypertension.

The presence of a thick muscular media is a normal characteristic of the pulmonary arteries of the newborn. Abnormal forces acting upon the lung from birth tend to delay or prevent the normal evolution toward the thin-walled adult state. Such arteries, similar in appearance to those of the systemic circulation, can effectively control the pulmonary resistance by contraction and relaxation of their walls. Thus, the persistence of the fetal structure can be considered as an adaptive mechanism and as a benign and useful feature of the pulmonary circulation.

In contrast to medial hypertrophy, intimal fibrosis must be regarded as evidence of arterial injury. Its effects are always detrimental, never adaptive, and, once initiated, progressive vascular damage is the rule. Fibrosis leads to occlusion and in time to dilatation and destruction of the vessels.

The appearance of plexiform lesions heralds the onset of this malignant process. Plexiform lesions are characteristically associated with long-standing hypertension of the lesser circulation. It was therefore suprising to find them in nearly one fifth of this young group of patients. Their almost uniform occurrence together with vascular occlusion (grade 3) suggests that in the patients under discussion the onset of patchy intimal fibrosis (grade 2) was very rapidly followed both by vascular occlusion and by the development of plexiform lesions (grade 4). It has been noted that the development of plexiform lesions is related to the speed with which pulmonary hypertension develops. They are less frequent in patients in whom pulmonary vascular resistance rises slowly, as in mitral stenosis, than in patients in whom the onset of pulmonary hypertension is abrupt, as in idiopathic pulmonary hypertension or in the sudden onset of pulmonary vascular disease of adult patients with an atrial septal defect. Since in these latter examples evidence favors a vaso-
Figure 2

The course of the circulation in transposition of the great vessels (A) compared to the normal crossing of the circulation (B). Reproduced from Taussig, H. B. Congenital malformations of the heart. Commonwealth Fund and Harvard University Press, Cambridge, Mass. 1960 with the permission of the author and the publishers.

must be returned in equal amounts or one or other of the circulations would be depleted. On the other hand, the systemic and pulmonary flows can vary independently, depending upon the magnitude of the shunts. To understand the circulatory state that results from an anatomic transposition of the great vessels it is necessary to consider the physiologic events also in a "transposed" manner. It is an error, which has considerably impeded the physiologic evaluation of this malformation, to consider the blood that crosses defective cardiac septa as a "shunt," that is, as useless blood which is added to one or the other circulation.

The application of the standard physiologic concepts leads to the definition of two criteria which characterize the transposition circulation: the effective flow is reduced; the systemic and pulmonary flows vary in inverse proportion to the effective flow and there is always a bidirectional shunt.

The existence of certain anatomic pathways between the two sides of the heart fixes the magnitude of the effective circulation of a particular patient. The location of the pathways, which permit this essential exchange of blood, has relatively less importance than their size.

The most extreme form of the transposition circulation occurs when the anatomic communication between the two circulations is small. With increasing size of communications the effective circulation improves and the flow relationships gradually approach normal until the free exchange of the two circulations, as seen with a single ventricle, makes the relative positions of the arterial trunks physiologically insignificant.

Thus, the physiologic spectrum leads from the transposition circulation to that of the single ventricle and depends upon an increasing size of the intracardiac defects. This progression is beneficial at first, but leads at the other extreme to the detrimental effects of a common circulation.

The various physiologic states seen in patients with transposition of the great vessels are diagrammatically represented in figure 3.
II. WITH LARGE VENTRICULAR SEPTAL DEFECT

\[ \text{Figure 3} \]

Schematic representation of various physiologic states in transposition of the great vessels by modification of the diagrams of Taussig. PR, pulmonary resistance; SR, systemic resistance; VC, venae cavae; RA, right atrium; RV, right ventricle; Ao, aorta; PV, pulmonary veins; LA, left atrium; LV, left ventricle; PA, pulmonary artery.

and examined with regard to the validity of the above concepts.

In infants with transposition of the great vessels and an intact ventricular septum, life is maintained by the small effective flow that crosses a persistently patent foramen ovale or a patent ductus (fig. 3, Ia). Thus, the blood in the pulmonary artery will be highly saturated and the aortic blood markedly unsaturated. The oxygen needed for life is therefore taken up by a very greatly increased pulmonary flow and delivered by an increased systemic flow.

An increase in systemic and pulmonary blood flows was demonstrated in the earliest reports of Bing and associates. In the studies of Noonan et al. these alterations are strikingly demonstrated. In the very cyanotic infants with intact ventricular septum, in whom the effective flow was very small, the left ven-

tricular and hence the pulmonary arterial blood was virtually fully saturated and the pulmonary flow must have been of torrential magnitude. This vast flow could not be expected to pass through the pulmonary vascular bed without an increase in the perfusion pressure and, indeed, the left ventricular, hence the pulmonary artery pressure was elevated in almost every instance.

A larger size of the intracardiac communication and thus of the magnitude of the effective flow will obviously ameliorate this paradoxical situation (fig. 3, Ib). Relatively free mixing of the two circulations will result in more nearly equal saturations of the aortic and pulmonary arterial bloods, and, hence, more modest systemic and pulmonary blood flows. This hemodynamic arrangement may be possible without a significant elevation of the pulmonary arterial pressure. Such adequate intercommunication, however, is probably seldom achieved in the absence of a ventricular septal defect.

A large ventricular septal defect ensures an adequate effective flow and thus acts as a vent which prevents the excessive flows seen in the first group of patients. It, however, introduces an additional and unfavorable factor, since it unites the ventricles in a common systolic ejectile force. Thus, pulmonary hypertension, which in patients with intact ventricular septum resulted from the need to force a torrential flow through the lungs, will in patients with a large ventricular septal defect be present irrespective of the size of the pulmonary blood flow. Indeed, in these patients, as in all others in whom there is a common systemic ejectile force, the pulmonary vascular resistance comes to play a decisive role in the distribution of blood into the two circulations (fig. 3 IIa, b, c). The physiologic state may be that of a predominantly left-to-right shunt, a balanced shunt, or as the pulmonary resistance rises, a predominantly right-to-left shunt.

Support for the existence of this spectrum of hemodynamic alterations is also found in the data of Noonan et al. Some of their patients had a calculated pulmonary blood flow
several times the magnitude of the systemic flow, but in the group designated as having "pulmonary vascular obstruction," the pulmonary flow exceeded the systemic flow in some, was similar to it in others, and was less in the remainder.

Thus, it seems clear that the significance of the ventricular septal defect in transposition of the great vessels differs fundamentally from that in the normal circulation, because in this malformation the presence of a ventricular septal defect does not add blood to the pulmonary circulation but rather lessens the excessive pulmonary blood flow characteristic of the transposition circulation. On the other hand, the damaging effect upon the lung of a common systolic ejectile force is equally felt in the normal and in the transposition circulation.

The impact upon the pulmonary vascular bed of the torrential blood flow or of a common systolic ejectile force does not explain fully the gravity of pulmonary arterial disease noted in patients with transposition of the great vessels. Both of these effects can be present in patients with other malformations in whom the pulmonary arterial changes remain, nevertheless, more benign. It appears likely, therefore, that in transposition of the great vessels the impact of these influences is aggravated by pulmonary arterial vasoconstriction. This possibility is not purely theoretical, since in these patients at least two mechanisms are present that are known to raise the pulmonary vascular resistance: anoxia and an elevated pulmonary venous pressure.

Anoxia as a cause of pulmonary arterial vasoconstriction is well recognized. The recent work of Enson and co-workers suggests that the vasomotor response is affected by an increase in hydrogen ion concentration and that the sensitivity of the pulmonary arterial pressure to arterial unsaturation is enhanced at low pH levels. This observation is of special interest in the problem of transposition of the great vessels because Gootman et al. demonstrated the presence of metabolic acidosis in very cyanotic infants. Respiratory compensation fails in these babies because of the low effective flow.

Pulmonary venous obstruction is also recognized as a cause of pulmonary arterial hypertension both in congenital and in acquired heart disease. In patients with transposition of the great vessels elevation of the pulmonary venous pressure due to an excessive pulmonary blood flow occurs in exactly those patients in whom systemic anoxia is greatest, that is, in whom the effective circulation is smallest.

Thus, two mechanisms that enhance pulmonary arterial tone are present together in patients with transposition of the great vessels and might be expected to be additive. However, the normal appearance of the pulmonary veins of these patients suggests that pulmonary venous obstruction either is not a major factor in the genesis of the elevated arterial resistance or that death has occurred before anatomic alterations of the veins could have developed.

Clinical Correlations

On the basis of the anatomic and physiologic considerations outlined above, the sequence of hemodynamic events in transposition of the great vessels can be reconstructed as follows:

At birth the ductus and the foramen ovale are patent and allow a fairly adequate effective blood flow. As pulmonary vascular resistance begins to fall, the pulmonary blood flow increases. The left atrial inflow of pulmonary venous blood closes the foramen ovale and the ductus also begins to obliterate. Thus, a rapid diminution of the effective flow and an increase in the systemic and pulmonary flows results. Vasoconstrictive impulses initiated by anoxia and an increasing pulmonary venous pressure combine with the rapid and excessive pulmonary blood flow and cause early damage to the pulmonary arteries. The heart is faced with large and rising flows and with high pressures and begins to fail. A vicious cycle is established and leads to early demise. Creation of an atrial septal defect in such an infant can effect...
a significant improvement in the effective circulation and hence a reduction of the pulmonary blood flow, of anoxia, and of pulmonary arterial vasoconstriction.

Patients with transposition of the great vessels and a ventricular septal defect are not affected significantly by the closure of the fetal communications. An effective flow of a certain magnitude is ensured and correspondingly the occurrence of severe anoxia and of an exceedingly high pulmonary blood flow is prevented. The malformation is more benign and pulmonary arterial injury is less severe. In patients with a large ventricular septal defect, however, pulmonary hypertension is inevitable, if the size of the ventricular septal defect is great enough to unite the ventricles in a common systolic ejectile force. In these patients, in spite of an adequate effective circulation and, therefore, a lesser pulmonary flow and a lesser degree of anoxia, hypertensive pulmonary arterial disease is present independently of these factors. It is progressive, but it can be consistent with survival for a considerable period of time. Severe pulmonary arterial disease was indeed found in all of the older patients in this series, but it is hardly credible that these patients could have lived as long as they did if they had already had such severe arterial changes in infancy as were found in some of the young babies with intact ventricular septum.

The Bronchial Circulation

The prominence of bronchial arteries in the lungs of patients with transposition of the great vessels leads to speculation concerning the possible adaptive value of an expanded collateral circulation in the presence of an excessive pulmonary blood flow. Normally the bronchial arterial flow is drained into the pulmonary veins and a significant enlargement of the bronchial arterial circulation in transposition of the great vessels would disturb the circulatory balance unless the venous drainage were returned in equal amount to the systemic circulation. This could occur through an intracardiac communication (fig. 4, I) but could occur also through the azygos venous system (fig. 4, II). If the latter is indeed the case, the bronchial arterial-venous flow could act as an accessory pulmonary circulation and could augment the effective flow without having to pass through the intracardiac communications. The demonstration of an increased bronchial venous-azygos drainage system would represent important supportive evidence for this supposition.

Summary

A microscopic study of the lungs of 106 patients with transposition of the great vessels has revealed early and severe hypertensive alterations in the pulmonary arteries. These striking changes, associated in almost all instances with normal pulmonary veins, indicate a state of high resistance of the arterial bed.

Pulmonary arterial damage was, in general, most advanced in the patients with a large ventricular septal defect, but in spite of this these were the patients who lived longest. It seemed obvious, therefore, that their relatively favorable course was due to a greater beneficial than damaging effect of the ventricular septal defect.

Consideration of these findings in the light of known physiologic data has led to a clarification of the physiologic variations of the transposition circulation. Using the recognized physiologic definitions of flows and shunts the transposition circulation is characterized by a diminished effective flow and a bidirectional but predominantly left-to-right shunt. The effect of a large intracardiac communication is to increase the effective flow and to
lessen the shunts. With increasing size of the intracardiac communication the spectrum is completed when the circulatory characteristics of a single ventricle are reached in which the anatomic position of the great vessels becomes physiologically insignificant.

The effect of a common systolic ejection force in patients with a large ventricular septal defect will be similar in the transposition circulation and in the normal circulation. Three physiologic states are possible which depend upon the relative magnitude of the systemic and pulmonary resistances.

The early appearance and malignant nature of the hypertensive alterations in the pulmonary arteries of patients with transposition of the great vessels suggest that the impact upon the lungs of high blood flow and pressure is aggravated by arterial vasoconstriction. This may be initiated by anoxia and a lowered blood pH. Elevation of pulmonary venous pressure and the increased viscosity of the blood due to polycythemia may add to the damage.

Prominence of the bronchial arteries noted in the lung sections suggests that an expanded bronchial circulation augments the effective flow in these patients. If the bronchial venous drainage leads to systemic veins, the bronchial circulation could act as an accessory pulmonary circulation and could improve the effective flow without having to cross the already overloaded intracardiac communications.

The anatomic findings and physiologic considerations reported in this study reveal several aspects of the early and severely damaging cardiopulmonary effect of transposition of the great vessels and indicate an urgent necessity of surgical therapy in early life.

Acknowledgment

I acknowledge with gratitude the help and advice of Drs. J. F. Dammann, John D. Keith, William T. Mustard, John Groves, F. W. Wiglesworth, F. Ger- muth, and Norman B. Thomson.

References


Circulation, Volume XXXIII, February 1966
My conception of experimental medicine is summed up above. As I have often repeated, it is nothing but the consequence of the wholly natural evolution of scientific medicine. In this respect, medicine does not differ from other sciences which have all passed through empiricism before reaching their final experimental stage. In chemistry and in physics, practical methods of extracting metals, making magnifying glasses, etc., were known before the scientific theory evolved.

Empiricism, then, also guided these sciences through their nebulous days; but only since the advent of experimental theories have physics and chemistry taken such brilliant flights as applied sciences, for we must be careful to avoid confusing empiricism with applied science. Applied science always implies pure science as its support. Medicine will doubtless pass through empiricism much more slowly and laboriously than the physico-chemical sciences; not only because the organic phenomena with which it is concerned are much more complex, but also because the requirements of medical practice, which I need not study here, help to keep medicine in the personal realm, and thus oppose the experimental development.—CLAUDE BERNARD: An Introduction to the Study of Experimental Medicine. New York, The Macmillan Company, 1927, p. 215. Centenary of the First Publication, 1865.

Circulation, Volume XXXIII, February 1966
Transposition of the Great Vessels: Pathophysiologic Considerations Based upon a Study of the Lungs
CHARLOTTE FERENCZ

Circulation. 1966;33:232-241
doi: 10.1161/01.CIR.33.2.232

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/33/2/232

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/