STUDIES IN PULMONARY HYPERTENSION IN CONGENITAL HEART DISEASE*

BY

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I feel honoured to have been asked this year to deliver the St. Cyres Lecture. I am burdened with the double responsibility of attempting to attain the high standards set by the preceding lecturers and of giving this lecture in the first year of the second century of the life of the National Heart Hospital, which sponsors it. I feel that tribute should be paid to the late Viscountess St. Cyres, who established this lectureship in 1926, the year of the death of her husband. The present Viscount St. Cyres has written me that in 1918 "both the late Lord and Lady St. Cyres contracted very severe influenza which apparently affected their hearts." From what I have heard in conversations it would be fitting to pay tribute to the first lecturer also, Dr. Strickland Goodall, who had some influence in the bequest. I understand that one of the stipulations in the trust for the lectureship was that it was to be on the subject of the myocardium, and one wonders whether there might be a particular relationship of this subject to the illness of Viscount St. Cyres or to the interests and medical convictions of the unconventional Australian-born descendant of a long line of English physicians, a stimulating teacher of physiology and cardiology, Dr. Strickland Goodall.

The material that I shall present today deals mainly with the hæmodynamics of the pulmonary circulation, but it is proper to keep always in the background of our minds an awareness of the driving force that creates the pulmonary hypertension with which we shall deal. This force originates in the myocardium. By stressing this point I can justify this presentation as fulfilling in a broad sense the stipulation of the donor of the lectureship. While Dr. Strickland Goodall properly emphasized the myocardium as the important factor in the maintenance of an adequate circulation, I would like to quote the following statement from a 1927 lecture given by him (Strickland Goodall, 1927): "I would also point out that the efficiency of the circulation as a whole depends, not only on the myocardium, and valves of the heart . . . but also upon [other factors] together with the musculature of the arterioles."

In classifying pulmonary hypertension associated with congenital heart disease, one can separate the cases into those in which the venous outflow is impeded and those in which it is not impeded. I shall not discuss today the type of pulmonary hypertension associated with pulmonary venous obstruction such as is exemplified by stricture of the pulmonary veins, by narrowing of a common vein draining anomalously the total pulmonary venous system, or by cor triatriatum. Rather, I shall concentrate on the pulmonary hypertension occurring with ventricular and atrial septal defects and I shall make added references at times to pertinent data from cases of patent ductus arteriosus. Our clinic has previously reported on the incidence of pulmonary hypertension in these three conditions. For equivalent pulmonary blood flows, pulmonary hypertension is most common in ventricular septal defect and least common in atrial septal defect (Swan *et al.*, 1954).

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VENTRICULAR SEPTAL DEFECT

For the maintenance of life a minimal systemic pressure is necessary. In cases of large ventricular septal defect this systemic pressure must be maintained by an adequate stroke volume of the joint ventricular system delivered to an arterial reservoir from which the run-off is neatly regulated. The actual pressure existing in the pulmonary artery will be similar to that in the aorta and will be set by those factors that determine systemic blood pressure in the mammalian organism. If the pulmonary resistance were to be inadequate it is evident that systemic flow could not be maintained and heart failure with engorged lungs would result. This is the explanation that my colleagues and I offer for the high mortality rate in infants who have an uncomplicated ventricular septal defect. If the pulmonary vascular resistance is maintained at a level that is adequate to support a normal systemic flow, the child survives and usually does not get into serious difficulty until the second or third decade of life.

Studies by Civin and Edwards (1951) on fetal lungs have demonstrated the normal thick-walled small arteries; it is believed likely that these arteries may maintain their thick walls and never undergo the involution necessary to become normal pulmonary vascular structures in patients whose hearts exhibit what Edwards has termed a "common ejectile force." To what degree, in any single patient, there may be partial involution of these vessels allowing greatly increased pulmonary flow in the early postnatal state, and then redevelopment of thick-walled vessels, is controversial. I believe that varied patterns may occur, but with involution being common, in the wide spectrum of pulmonary vascular changes in the postnatal state when a large ventricular septal defect is present. Pertaining to this problem are the observations of Heath *et al.* on the pulmonary vasculature of two infants who died on the second day of life with a widely patent ductus. The ratio of the diameter of the lumen to the thickness of the arterial wall in the small pulmonary arteries was found to be abnormally high. It was suggested that, in the newborn, unduly rapid transition from the fetal thick-walled pulmonary arteries to the thin-walled adult type of vessel might result in fatal pulmonary oedema as a complication of left ventricular failure from a large left-to-right shunt. It should be emphasized that the morphological differences in the pulmonary vasculature in infants are primarily medial. It is only later that intimal obstructive changes develop in patients with a ventricular septal defect, and these may indeed be very late in appearing in some instances.

It has long been recognized that the size of the ventricular septal defect is an important determinant in the clinical picture and that small ventricular septal defects may be associated with a functionally normal circulation in both the systemic and the pulmonary circuits. The relationship that usually has been employed as an index of circulatory difficulty is that between the area of the aortic orifice and the area of the ventricular septal defect. This is a proper comparison; however, it is not possible from post-mortem examination of the size of the defect to determine the quantities of blood that would pass from the right ventricle into the aorta across the defect. This will depend upon the resistance offered by the defect itself and the resistances of the pulmonary and systemic circulations. From recent observations made at the time of the surgical closure of ventricular septal defects and observations of angiocardiograms, it seems possible that the systolic, or dynamic, size of the ventricular septal defect may not be equivalent to what is measured at the time of necropsy and one must give a word of caution regarding the significance of analyses of the sizes of ventricular septal defects measured in the dead heart. Let me not suggest to you that there is necessarily a gross difference between the size of the "dynamic defect" and the size of the "anatomical defect" but rather that there could be, in occasional instances, a significant difference. If one examines the size of the defect as described by the surgeon at the time of his repair or the size described by the anatomist, and relates it to the pulmonary pressure, one finds that there is apparently a critical size beyond which pressure in the pulmonary artery is equivalent to aortic pressure. To make comparisons at different ages possible, the size of the ventricular defect per square metre of body area may be plotted against the ratio of pulmonary to systemic pressures. The critical area of the defect at which the pulmonary and systemic pressures equalize comes out to be one sq. cm. per sq. m.

of body area. These observations by Savard and co-workers at our clinic include measurements of either surgeon or anatomist and support in general the conclusions of Paul Wood *et al.* (1954) who, largely on a theoretical basis utilizing the hydraulic formula of Gorlin, stated that a defect 1 cm. in diameter is of critical size in relation to the presence of severe pulmonary hypertension. Actually, for adult patients, the calculated critical area is in excess of 1 sq. cm. if one considers our data given in relation to body area; thus Wood's critical area is too small; an orifice in adults closer to a diameter of 1.5 cm. would be one that roughly fitted our data. The size of the ventricular septal defect may determine not only the clinical pattern of the disease at the time of observation but also the life history of the disease. As illustrated by the studies of Brotmacher and Campbell (1958) and our data, a population afflicted with a large ventricular septal defect and pulmonary hypertension shows increments of the pulmonary pressure for each added decade of age. It is logical to assume from charts such as theirs that, when in the presence of a ventricular septal defect pulmonary hypertension is found, it will increase in time, and this assumption is all the more likely to represent a sound conclusion in view of the fact that pulmonary vascular resistance also increased with age. Our data are in essential agreement with theirs. It seems hardly necessary to mention that such graphs of a population do not reflect necessarily what an individual with a ventricular septal defect may do in his lifetime.

In years past, there was much emphasis upon the relationship of the aortic root to the ventricular septum, that is, upon whether the aorta "overrode" the ventricular septal defect and appeared to originate from the right ventricle. There is no question that anatomically there is considerable variation in the relationship of the aortic root to the ventricular septal defect and its so-called dextral position, but position *per se* plays no significant role in the altered haemodynamics; with this conclusion, the majority of present-day investigators are, I believe, in agreement.

Let us examine further the situation existing in the circulation when a large ventricular septal defect is present, or indeed when there is a single ventricle. When the right and left cardiac pumps are not separate units but communicate with each other through a large ventricular septal defect, it may seem unnecessary and even pretentious to mention the inescapable fact that there is a common source of power, the equivalent of a single pump. But at the risk of extolling the obvious I would mention that in this situation the distribution of the flow of blood to the two great vessels will depend upon the relative resistances in the systemic and the pulmonary arterioles. One of the early interests of my colleagues and myself was assessment of the two vascular beds (Burchell *et al.*, 1950), particularly as to whether resistances changed in parallel or possibly reciprocally. Very early in our experience it was noted that under some circumstances there might be reciprocal change in the respective resistances. Marked changes in this respect were rare and not predictable for any individual patient. There were three situations wherein a differential effect on the systemic and pulmonary vascular control was observed. In the order noted these were: (1) exercise, (2) the breathing of mixtures containing low and high concentrations of oxygen, and (3) the use of certain drugs that were known to raise or lower systemic blood pressure in the normal subject.

As to the effect of exercise, certain subjects with severe pulmonary vascular obstruction and pulmonary hypertension were observed in whom exercise increased the peripheral systemic flow but reduced the pulmonary flow, with the net result of an increase in the right-to-left shunt and the cyanosis. In one adult studied during exercise the lungs became so nearly excluded from the circulation that the oxygen saturation of the arterial blood closely approached that of mixed systemic blood. A detailed analysis of the effect of exercise on the *left-to-right* shunt in patients with a central defect between the two circulations and with pulmonary hypertension has been made by Swan *et al.* (1958) in our clinic. Exercise regularly caused a decrease in the left-to-right shunt, with a decrease in systemic resistance and usually an increase in pulmonary resistance. The pulmonary flow remained relatively constant, and as would be expected, the pressure in both circuits rose. These observations are in accord with those of Scebat *et al.* (1957) who reported mainly on patients with low pulmonary vascular resistance. Contrary results in a limited number of patients exercising in the upright position have been reported by Bruce and John (1957).

It is generally known and accepted at this time that breathing of low oxygen mixtures will cause an increase in pulmonary vascular resistance, and breathing of high oxygen mixtures (particularly 100 per cent oxygen) will cause a decrease in pulmonary vascular resistance. No satisfactory explanation for this phenomenon is as yet known. We believe that there is danger in subjecting a patient to the breathing of a low oxygen mixture when there is severe pulmonary vascular obstruction, though no accidents resulted from our investigations in this area about ten years ago. To illustrate the phenomenon of breathing a low oxygen mixture, in one subject with pulmonary hypertension and a patent ductus the arterial saturation dropped precipitously to a very low level, approaching that of the venous systemic blood, and the lungs apparently were practically excluded from the circulation just as they were nearly excluded in the previously mentioned patient who was subjected to exercise.

Interest in the effect of the breathing of 100 per cent oxygen on pulmonary vascular resistance has not waned over the past ten years. One of the first communications (Burchell *et al.*, 1953) from our laboratories to deal with the differential effect of breathing various oxygen mixtures on the systemic and pulmonary circulations pertained to studies in patients who had a patent ductus arteriosus and equivalent pressures in the aorta and the pulmonary artery. There existed here a natural biological state wherein one could readily measure the differential effect of breathing varying oxygen mixtures by means of the variation of the right-to-left shunt through the ductus, in that blood from the proximal part of the aorta as sampled from the right brachial artery was of different saturation from that in the descending aorta as sampled from the femoral artery. With the breathing of 100 per cent oxygen, one consistently saw a decrease in the right-to-left shunt; this could be demonstrated not only by the respective saturations in the samples from the two blood vessels mentioned, but also from dye-dilution curves obtained at the two respective sampling sites, the right brachial (or radial) and the femoral arteries, following the injection of dye into the right ventricle or pulmonary artery. With the breathing of air or a low oxygen mixture, one often saw early-appearing dye in the femoral dye curve, but this might completely disappear or at least decrease when pure oxygen was breathed.

In all types, but not in all cases, of pulmonary hypertension studied in our laboratory, the breathing of 100 per cent oxygen has been observed (Marshall *et al.*, 1957) to cause a lowering of pulmonary vascular resistance as manifested by an increase in pulmonary flow concomitantly with a varying decrease in pressure. Exceptions have occurred; these have been noted particularly in primary pulmonary hypertension and in some cases of pulmonary hypertension associated with ventricular septal defect. Of exceptional interest to me is the fact that the effect of breathing oxygen instead of air in lowering the pulmonary vascular resistance gave early promise of correlating with the degree or grade of the morphological changes in the lungs as reported by the pathologists. In particular, those extensive pulmonary vascular changes, wherein not only medial thickening and intimal proliferation and fibrosis, but also the vasodilatation lesions so characteristic of late stages of pulmonary vascular obstruction are present, might predict that the response of the pulmonary vascular resistance to oxygen might be decreased or absent.

The first drugs we used to modify the situation, which guardedly we may label as the "Eisenmenger syndrome," were those that were known to produce systemic vasoconstriction or vasodilatation. The two drugs initially investigated were the pressor amine, "vasoxyl," and the ganglion-blocking agent, tetraethylammonium bromide (or chloride). The early efforts in this pharmacological field were desultory in that it was particularly difficult to differentiate pulmonary and systemic effects. It appeared, however, in at least certain cases that when systemic pressure was increased with vasoxyl there was some shift of blood flow into the pulmonary circulation, and that when systemic pressure was lowered with tetraethylammonium ion there was a shift of flow toward the systemic side. In other words, raising the systemic blood pressure decreased the right-to-left shunt, while lowering the systemic blood pressure increased the right-to-left shunt.

Recently, along with many others throughout the world, Shepherd (1958) of our laboratories has become interested in the effect of acetylcholine, particularly because of the fact that one can

produce a local effect within the lungs, owing to rapid destruction of the drug by the circulating blood before it reaches the left side of the heart and the peripheral circulation.

Studies of acetylcholine have been carried out in nine cases of pulmonary hypertension associated with atrial or ventricular septal defects. In all the six cases with atrial septal defect the pulmonary vascular resistance decreased to some degree, but in three cases of ventricular septal defect slight decrease occurred in only one. The records indicating the decrease in pulmonary resistance are those of a reduction in right ventricular pressure and a simultaneous rise in the oxygen saturation of the pulmonary blood, both of these factors being monitored constantly during the studies. My original impression concerning the effect of breathing 100 per cent oxygen was that probably maximal dilatation of the pulmonary vasculature might be obtained, this impression having been based on the great changes in the calculated resistance values in some instances. However, the injection of acetylcholine in occasional patients, following maximal decrease of pressure in the pulmonary artery from the breathing of 100 per cent oxygen, has resulted in a further decrement in the pulmonary pressure, indicating that the two mechanisms possibly could be dissimilar and additive in their effect.

PATHOLOGICAL CHANGES OF MAIN PULMONARY ARTERY

The contributions of Donald Heath, who has been working with Edwards *et al.* (unpublished data) in our clinic the past year, have been outstanding, in my opinion, in the field of pulmonary vascular change. I believe that his observations on the histological architecture of the great vessels, namely the aorta and pulmonary trunk, in relation to the presence of congenital or acquired pulmonary hypertension are of sufficient interest to mention here. At birth the structure of the media is similar in the aorta and in the pulmonary artery, with characteristic long uniform strands of elastic tissue. In the normal infant there is a fairly rapid involutionary process in the pulmonary arterial structure and the elastic tissue breaks up and becomes irregularly disposed through a thinned media. In the presence of a large ventricular septal defect or of other lesions such as a single ventricle or tricuspid atresia with an open pulmonary artery, the wall of the main pulmonary artery apparently never goes through the involutionary process and the media shows a histological structure similar to the normal adult aortic media. On the other hand, if the media of the pulmonary artery has undergone involution and later pulmonary hypertension develops, for example in cases of atrial septal defect or acquired heart disease, the thickness of the media increases but the elastica does not form the even stratified strands characteristic of the wall of the pulmonary artery in cases in which it is believed that there is congenital pulmonary hypertension. These differences are so dramatic that I believe that one could teach a medical student to make the differentiation within a few minutes; indeed, letting one's imagination run wild, it would seem possible to make the diagnosis of congenital pulmonary hypertension in persons dead for centuries if a piece of pulmonary artery were available and in reasonable condition.

At this juncture one can return to a discussion of the myocardium again, since in those cases of ventricular septal defect in which there is a high pulmonary resistance the chambers may stay small, the walls of the two ventricles may be of equal thickness, and clinically the heart is quiet as compared with the tumultuous action observed in the cases characterized by a very large shunt from left to right and a high pulmonary flow. In the latter cases, in which the flow is high, the pulmonary hypertension may equal that observed in cases in which the pulmonary flow is small, but obviously the calculated value for pulmonary resistance is much lower than that for systemic resistance. In this situation, a high pulmonary flow may be said to help maintain the pressure in both the systemic and the pulmonary circuits, a hyperkinetic pulmonary hypertensive factor already alluded to.

ATRIAL SEPTAL DEFECT

Pulmonary hypertension in association with atrial septal defect is relatively uncommon, usually developing in early adult life and being practically unknown in young children.

Forty-two patients in whom pulmonary systolic pressure was in excess of 60 mm. of mercury have

been seen in our clinic. The factors responsible for the pulmonary vascular obstruction with resultant pulmonary hypertension are unknown, and there are individual cases that would seem to rebut any universal theory. That there is probably a cause-and-effect relationship between the atrial septal defect and the greatly increased pulmonary blood flow is accepted by me, and the early histological lesions have been demonstrated by Edwards to occur at the thin arteriolar junction to the small arteries. He believes that the small arteries just proximal to these stenotic areas hypertrophy and that the condition may gradually spread in an erratic way throughout the whole pulmonary vasculature. I share in Edward's opinion that thrombosis is not a primary mechanism in the development of pulmonary vascular obstruction in patients with atrial septal defect. It is known that serotonin, or 5-hydroxytryptamine, is a potent vasoconstrictor in the pulmonary circuit, and it has been postulated that there may be degeneration of platelets that is related to the high turbulent flow through the defect and the main pulmonary arteries and that causes the release of this vasoconstrictor agent. This suggestion was offered years ago to explain the pulmonary constriction thought possibly by Comroe *et al.* (1953) to occur with pulmonary embolism, and last year it was discussed by Rudolph and Paul (1957) in relation to intracardiac defects. This must remain only a theory and is not helpful in explaining why certain patients become the subjects of the complicating pulmonary vascular disease and the majority do not. While I know of no exceptions to the generalization that it is only in those subjects with a high pulmonary flow in atrial septal defect that pulmonary hypertension may develop, it is of more than casual interest that one cannot predict the exact size of the atrial septal defect with any accuracy prior to surgical repair. Some patients may have pulmonary hypertension when the atrial septal defect is relatively small, for instance 2.5 cm. in diameter, and it is a curious coincidence perhaps that we have seen a series of patients with severe pulmonary hypertension who had that type of rather small atrial septal defect located in the superior part of the atrial septum just below the opening of the superior vena cava. If this experience is more than coincidence, we can offer no explanation for a causal relationship.

While undoubtedly many patients with atrial septal defect maintain high pulmonary blood flows into late adult life without clinical evidence of significant pulmonary vascular obstruction, we have had an enlarging experience with patients who have been followed for 5 to 10 years in whom there has been progressive increase in pulmonary resistance and in some of whom there has been eventual reversing of the shunt. We have also had the opportunity of studying some patients in whom for some reason an accelerated change in vascular resistance and pulmonary hypertension and a reduction of pulmonary flow have taken place in an interval of one to two years.

POSSIBILITIES OF REGRESSION IN PULMONARY HYPERTENSION AND PULMONARY VASCULAR CHANGES

The data concerning regression of the abnormal hæmodynamic patterns in the lung when such are associated with a large ventricular septal defect or a patent ductus are quite scanty. In regard to patent ductus, for which operations have been performed for many years, the most extensive follow-up to my knowledge has been at Mexico City where Limon-Lason (1958) has collected data that would indicate that there is little regression in pulmonary vascular resistance. When adult patients are considered, this would coincide with our more limited experience. Our longest follow-up is on a patient who was operated on in 1950, at which time the pressure in the pulmonary artery was equivalent to the aortic pressure and there was a left-to-right shunt of only 30 per cent. Following operation the patient's physical status markedly improved and he has been able to be gainfully occupied over the past 8 years. Post-operative catheterization at a year and at 7½ years after operation showed a cardiac output of 3.1 litres a minute, a moderate pulmonary hypertension, and moderately high values for pulmonary vascular resistance. Several children have shown some evidence of regression and one adult rather good evidence of regression of the pulmonary vascular resistance since the report from the clinic of Silver *et al.* (1954).

When patients with a ventricular septal defect are operated on, it is found that the pulmonary pressure, particularly the diastolic level, is somewhat lower than the pressure observed at cardiac

catheterization before operation. In addition, the left atrial pressures may be quite high before the repair is commenced. Following the repair and a return of the heart to the circulation, there is usually a drop in pulmonary arterial pressure if there has been a prior left-to-right shunt, but it is doubtful if this post-operative drop will necessarily predict what will happen over the next few years. However, if the pressure does not drop, one can expect a small chance of survival, or at best a resistant pulmonary hypertension that probably will be clinically significant and a regression potential that probably is a scant one.

The results of repair of atrial septal defects when associated with moderate pulmonary hypertension have been excellent in our clinic, and in my opinion the response of the pressure in the pulmonary artery to the breathing of 100 per cent oxygen may give a clue as to whether the post-operative period will be smooth and uneventful or the reverse. Perhaps it is needless to say that operations are performed only on patients with a left-to-right shunt and some increase in pulmonary blood flow. It is of interest that in an occasional patient the hæmodynamic calculations following closure of the defect may show an increase in pulmonary vascular resistance. The suggested explanation is that the pulmonary hypertension has kept the pulmonary vasculature slightly distended, the assumption being made that there is still compliance in the "resistance vessels" in the lungs. Late post-operative studies on patients with atrial septal defect indicate that the pulmonary vascular system appears to be changing very slowly, if at all. Persistence of the increased pulmonary vascular resistance is often clearly demonstrated only if the patient is exercised; in such instances there are two types of response—the type in which the pulmonary flow and the mean pulmonary pressure have the same percentage increment, and the type in which the percentage increase in the pulmonary pressure was much more than the pulmonary flow.

While there is enthusiasm about the clinical and limited hæmodynamic results in surgical cure of ventricular or atrial septal defects when associated with severe pulmonary hypertension and pulmonary vascular changes, it seems premature to predict return to complete normality. In this regard it is encouraging to the clinician and surgeon to read the statement of Lillehei (1958) that "the majority of children that have advanced pulmonary arteriolar intimal proliferation, proved by lung biopsy, have had normal or near normal pulmonary artery pressures when recatheterized one to two years after successful closure of their ventricular septal defects," but he does not give data on pressure and flow on which to evaluate critically the regression in resistance.

The experimental work of Ferguson (1958) wherein aortopulmonary shunts and pulmonary hypertension have been produced in animals, and later the shunt has been removed and the pulmonary artery reconstituted, shows that regression of the pulmonary vascular lesions occurs.

No discussion of anatomical regressive change in the pulmonary circuit would be complete without reference to an important integral part of the circuit, namely the right ventricular mass or thickness. Direct observations on expected involutionary changes in the right ventricular wall following surgical cure of ventricular septal defect are obviously unavailable as yet and one is dependent upon indirect evidence, primarily the electrocardiogram. The interpretation of post-operative electrocardiographic changes are fraught with difficulty because of variations in intraventricular conduction existing before and persisting after operation, and because of the fact that not infrequently in the surgical procedure right bundle-branch block may be produced. Suffice it to say that records are accumulating to indicate that regression of the right ventricular hypertrophy occurs, but no adequate correlation of post-operative electrocardiographic findings and hæmodynamic data can yet be presented.

SUMMARY

The problem of pulmonary hypertension occurring in the presence of free communication between the systemic and pulmonary circuits remains a challenging one with every indication that in the next few years exciting observations will be forthcoming to explain phenomena so far unexplained. The pulmonary hypertension occurring with atrial septal defect must be regarded as having a different genesis and pattern than that occurring with a large ventricular septal defect. In

the former it is an acquired complication, in the latter an integral part of the hæmodynamic state allowing survival, but at the cost of an increased cardiac load. Over the past ten years the confidence of investigators regarding a good correlation between the fine anatomy of the pulmonary vasculature and calculations of pulmonary resistance has varied, but the relationship is being more firmly established with emphasis on the varied qualitative as well as the quantitative aberrations in the pulmonary vasculature in the presence of pulmonary hypertension. Patients may be predicted to have nearly identical pressures in the "lesser" and "greater" circulations in the presence of a ventricular defect, when the size of the orifice exceeds 1 sq. cm. per sq. m. of body area. Such patients distribute the stroke volumes of the two ventricles in relation to the resistance in the pulmonary and systemic vascular beds. While evidence seems conclusive that the limitation of pulmonary flow by a high pulmonary vascular resistance may be necessary for survival in the neonatal period, the physiological process usually is supplanted by a pathological one, the pulmonary small arteries and the arterioles developing a diseased state with, in some instances, an apparently irreversible vascular obstruction.

A corollary to these concepts is that the amount of shunting across the defect is related to the respective resistances of the two circuits. It is evident that these resistances may operate reciprocally (and perhaps independently): the situations wherein such reciprocal changes may be regarded as established are exercise and the breathing of varied percentages of oxygen. The mechanisms underlying these effects are not known. While a teleological explanation such as that offered by Scebato whereby the shunt is regulated by the need of the tissues for oxygen is interesting, there is no clue to my knowledge as to what the mythical somatic substance might be. It is of interest that the concept does fit most of the observed facts regarding the changes in the central shunt and in pulmonary vascular resistance under both the condition of exercise and the conditions of breathing 100 per cent oxygen and low percentages of oxygen.

The hæmodynamic and structural regression to normal in the patient with pulmonary hypertension related to an intracardiac shunt, following repair of the defect, may be slow and incomplete even after some years. Clinically, one may emphasize that results of surgical repair of intracardiac defects may be most satisfactory and gratifying even when a persistent hæmodynamic fault, that is, an increased pulmonary vascular resistance, may be demonstrated with data obtained by cardiac catheterization. However, it is reasonable to expect the brilliant long-term results to be in those patients with a high pulmonary flow and normal or only moderately raised pulmonary resistance.

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