Effect of Flow and Pressure on Pulmonary Vessels

A Semiquantitative Study Based on Lung Biopsies

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SUMMARY
Of a total of over 1,000 lung biopsies, carried out over a 3½-year period on patients, the great majority of whom were operated on for various acquired or congenital cardiac diseases, 86 were on patients operated upon for atrial septal defect, 99 on patients with a ventricular septal defect, and 82 on patients with patent ductus arteriosus. The morphological data, particularly with regard to the lung vessels, were correlated with hemodynamic findings in these patients. In atrial septal defect the pulmonary vessels did not differ significantly from those in normal controls of the same ages. Notably there were no differences between patients with relatively low pulmonary arterial flow and those with high flow. In patent ductus arteriosus the only difference was an increase in intimal fibrosis of the pulmonary arteries as compared to normals. In ventricular septal defect, on the other hand, there was an increase in thickness of both media and intima and also in incidence of hemosiderosis. These changes did show a correlation with increased pulmonary arterial pressure but not with pulmonary arterial flow. It is concluded that pulmonary hypertension may provoke these vascular lesions and conversely may be maintained or increased by these lesions, while an increased flow in itself has little or no effect with regard to the morphological alterations, if it is not accompanied by pulmonary hypertension.

Additional Indexing Words:
Pulmonary vascular disease Atrial septal defect Congenital heart disease Lung biopsy Patent ductus arteriosus Ventricular septal defect

EXTENSIVE qualitative and quantitative studies of pulmonary vascular lesions in cases of acquired and congenital heart disease have been carried out to correlate these morphological findings with the clinical and hemodynamic data in the patients. Almost all information in this respect has been obtained from autopsy material. Obviously, this implies that the more severe or complicated cases were available for such investigations.

We have felt the need for a systematic study of lung biopsies from patients with cardiac disease, who came to operation. Such an approach has one definite disadvantage in that the available lung tissue is limited and may not always be representative for the lung as a whole, whereas in autopsy cases larger blocks of tissue and blocks from different areas of the lung may be studied microscopically. The surgical approach, on the other hand, has the advantage, in that material from many more patients is available, including those with the less severe forms of the disease. Although there is a selection for operability, it is likely that our material better reflects the spectrum of cardiac disease in its various stages.

Moreover, by taking lung biopsies regularly over a prolonged period, as we did, it is possible in some cases to compare these with a later biopsy or eventually with autopsy.
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material of a later date. In this way some insight may be gained into the natural history of the pulmonary vascular alterations and their underlying diseases.

Among the lung biopsies, thus collected, a relatively large number was obtained from cases of atrial septal defect, ventricular septal defect, and patent ductus arteriosus. In this paper we will present the histological findings in the lung tissue from these cases in correlation with the clinical and hemodynamic data.

Methods

Over a 3½-year period (October 1962 to May 1966) we have collected, in all, more than 1,000 lung biopsies from a continuous series of patients, the great majority of whom were operated on for various acquired or congenital cardiac diseases. The biopsies were taken at operation from the middle parts of the lung, that is, from the middle lobe or the lingula, from the base of the upper lobe, or from the top of the lower lobe, and more often from the left than from the right lung. The size of the specimen varied from approximately 0.5 to 1 cm³; those from young infants, however, were somewhat smaller. In this group of over 1,000 patients on whom biopsy was performed, no complications due to the biopsy were encountered.

There were among this number 86 patients in whom the predominant cardiac abnormality was an atrial septal defect; in 99 patients it was a ventricular septal defect, and in 82, a patent ductus arteriosus. These 267 biopsies form the subject of the present study. The cases were divided into isolated and complicated malformations.

Among the 86 patients with an atrial septal defect the first group was formed by 77 patients in whom a dorsal atrial septal defect (secundum type) was the only cardiac abnormality. In seven patients there were minor complications, that is, slight pulmonic stenosis (four patients), slight mitral insufficiency (two patients), or slight tricuspid insufficiency (one patient). Two other patients had a ventral atrial septal defect (primium type).

Of the 99 patients with a ventricular septal defect, 44 had this defect as an isolated lesion. In 55 the defect, although the main cardiac abnormality, was complicated by an anatomic deformity of a different nature. In eight of these cases this complication was slight pulmonic stenosis, that is, with a pressure gradient between right ventricle and pulmonary artery of more than 15 mm Hg systolic, but with an increased flow to the lungs. The remainder of the group, 47 cases in all, was formed by cases of ventricular septal defect complicated by patent ductus arteriosus (19 cases), atrial septal defect (six cases), shunt from left ventricle to right atrium (four cases), aortic stenosis (three cases), mitral stenosis (two cases), aortic insufficiency (one case), coarctation (one case) or combined lesions (11 cases).

In 74 of the 82 cases of patent ductus arteriosus, this was an isolated lesion. In eight cases it was complicated by other, though minor, malformations, that is, coarctation (four cases), a small or doubtful ventricular septal defect (three cases), or aortic stenosis (one case).

Cardiac catheterization was performed before operation in nearly all patients with septal defects but only in a minority of those with patent ductus. The clinical and hemodynamic data were recorded.

The lung tissue from the biopsies was embedded in paraffin, and histological sections were cut and stained with hematoxylin and eosin, elastic-van Gieson stain, and Perls' iron stain. All sections were judged by one of us (C.A.W.) and always without advance knowledge of the age, sex, and clinical diagnosis of the patient. The lesions observed in these biopsies were evaluated according to a grading system as normal (−), slight (+), moderate (++), and severe (+++). In this way also the pulmonary arteries and veins were judged as to the presence of medial hypertrophy or atrophy, intimal fibrosis, thrombi, and so on; the lung tissue itself was viewed for interstitial fibrosis, hemosiderosis, lymphocyte infiltration and the presence of collateral arteries, and the pleura, for dilated lymph vessels.

As is well known, in young infants the media of pulmonary arteries is thicker than it is in later life. Although a "blind" observation was indicated to avoid bias, this meant that in these infants media that was normal for the age was often graded as medial hypertrophy. This necessitated a later correction in the few instances wherein the age was less than 1 year. The sections from these patients were reexamined this time with knowledge of the age of the patient, and reevaluated.

A major problem was the collection of control material. Initially it was thought that biopsies in cases of pulmonary tuberculosis and bronchial carcinoma could be used for this purpose, as long as these specimens were not taken from the lobe with the lesion. It appeared, however, that biopsies in these cases by no means represented the picture that we expected on the basis of previous experience. In the meantime we have
shown in autopsy cases of bronchial carcinoma that a marked degree of medial hypertrophy and intimal fibrosis of the pulmonary arteries is commonly found.2 As a control group for the present study, therefore, we had to resort to autopsy material from a continuous series of noncardiac cases without major pulmonary pathology. This control group was so composed that it contained 77 cases, the same number as in our series of uncomplicated atrial septal defects, with the same representation of the different age groups since, although in older children and adults the media of muscular pulmonary arteries is not affected by age, intimal fibrosis occurs as an age change.3 We used the same grading system as we did for the biopsies; a single section of lung tissue was taken from each control lung from a site comparable to that used in the lung biopsies in the cases studied.

Results

For the correlation of morphological with clinical and hemodynamic data we have been particularly interested in the uncomplicated cases of atrial septal defect, ventricular septal defect, and patent ductus arteriosus as it seemed especially likely that in these groups lesions eventually to be found in the lung vessels could be attributed to the presence of these malformations. The complicated cases, therefore, will only be briefly considered.

Normal Controls

The 77 individuals without heart or lung disease varied in age from 2 to 54 years with an average of 22.2 years. The division in age groups together with the most important data with regard to the muscular pulmonary arteries are indicated in figures 1 to 4. The pulmonary veins showed only insignificant alterations, mostly slight intimal fibrosis, especially in the older age groups. In seven of the 77 cases we found slight, and in one case moderate, hemosiderosis of the lung tissue. Thrombi, known to occur regularly in lungs of random autopsy cases, were rare in our material, probably since it was based on single sections in each case, and since the average age of our patients was low. We found only two recent and one organized thrombi in our sections.

Atrial Septal Defect

Of the patients with isolated atrial septal defect of the dorsal type, 44 were male and 33 female. Their ages varied from 3½ to 55 years with an average of 21.8 years. These 77 patients were divided according to their age into three groups. These, together with the data on the muscular pulmonary arteries, are given in figures 1 to 4.

In 65 out of the 77 cases, data about flow, and in 75 cases data about pressure in the pulmonary artery or in the right ventricle were known. In 20 of the 65 cases in which the pulmonary arterial flow was known, it was only moderately increased, that is, it was calculated to be twice that in the systemic circulation or less. In 45 patients, constituting the large flow group, this ratio was more than 2. The pressure in the pulmonary artery or in the right ventricle in these cases was almost always less than 60 mm Hg systolic. For this reason it was not possible to divide the patients into a low pressure and a high pressure group. A division was therefore made between a low pressure (30 mm Hg systolic or less) group with 35 individuals and a moderate pressure group (more than 30 mm Hg systolic) with 42 individuals.

With regard to the morphological data we have been concerned primarily with eventual changes in lung vessels.

Media of Muscular Pulmonary Arteries

This was normal in 39 out of 77 cases; in 15 cases there was slight, and in seven cases moderate, medial hypertrophy. In no instance was there severe medial hypertrophy. Atrophy is much more difficult to judge than hypertrophy since the media of normal muscular pulmonary arteries is already relatively thin. According to our evaluation there were seven cases of slight, six of moderate, and three of severe, medial atrophy. As shown in figure 1, the medial thickness in uncomplicated cases of atrial septal defect does not differ from that in normal individuals.

When a division was made between low and moderate pulmonary arterial or right ventricular pressure, it turned out that there
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Normal - A.S.D. V.S.D.*%XXX' P.D.

Hypertrophy

Figure 1

Incidence of degrees of thickness of pulmonary arteries in cases of atrial septal defect (A.S.D.), ventricular septal defect (V.S.D.) and patent ductus arteriosus (P.D.A.) compared with normal controls. Only in cases of ventricular septal defect is the media significantly thicker than it is in controls.

was no difference in medial thickness between these groups. Nor were such differences found when the division was made according to low and high flow-ratio groups (fig. 2).

Intima of Muscular Pulmonary Arteries

In 63 of the 77 cases of atrial septal defect the intima was normal, in 12 there was slight, and in two moderate, intimal fibrosis. Severe intimal fibrosis was not observed in these cases. Since intimal fibrosis, in contrast to medial hypertrophy, increases with age, comparison with controls of similar age groups is necessary. Although these groups are relatively small, our data do not suggest a significant difference in intimal thickness in cases of uncomplicated atrial septal defect and normal cases (fig. 3).

When the cases of atrial septal defect were divided according to low or moderate pressure, there were no significant differences in the pulmonary arteries; when divided according to low flow-ratio and high flow-ratio, it appears that in low flow there is slightly more intimal fibrosis than in high flow (fig. 4). When, however, we take into account that the average age is somewhat higher in the group with low flow-ratio (28.1 years) than in the group with high flow-ratio (17.5 years), then there is obviously no significant difference in intimal thickness between the two groups.

Other Changes

As to the pulmonary veins, no significant changes, either in the media or in the intima, were found as compared with normal lungs. Other vascular changes such as thrombi, plexiform lesions, and others were not observed. Hemosiderosis of the lung tissue was seen in some cases but hardly more than in the normal control group.

The morphological findings observed in the seven cases in which the atrial septal defect was complicated by minor malformations of a different nature and in the two cases of a
primum defect did not differ markedly from those in the cases of isolated atrial septal defect, but the numbers are too small for further evaluation.

**Ventricular Septal Defect**

Of the 99 cases of ventricular septal defect only 44 could be considered uncomplicated, since the defect in the ventricular septum appeared to be the only lesion. Of these 44 patients 27 were male and 17 female. Their ages varied from 4 months to 30 years with an average of 9.1 years.

Cardiac catheterization was performed prior to the operation in all cases. The right ventricular pressure was known in all, but data about the pulmonary arterial flow were available in only 34 cases. In 15 out of these 34 patients the pulmonary arterial flow was calculated to be twice that in the systemic circulation or less. In 19 cases the ratio between pulmonary and systemic flow was more than 2.

The 44 cases in which the pulmonary arterial pressure was known were divided into a low pressure group with a systolic pressure of 60 mm Hg or less and a high pressure group with a systolic pressure over 60 mm Hg. Each group comprised 22 patients. There were only three patients in whom a high pressure was combined with a low flow.

**Media of Muscular Pulmonary Arteries**

This was normal in 16 patients. Medial hypertrophy was slight in 14 and moderate in 13 patients (fig. 1). Severe hypertrophy was not observed in the uncomplicated cases. In one case the media was moderately atrophic.

The incidence and degree of medial thickness of the pulmonary arteries are plotted.
Incidence of degrees of intimal fibrosis of pulmonary arteries in normal controls and cases of atrial septal defect, divided according to three age groups. Incidence increases with age, but there is no significant difference between cases of atrial septal defect and controls.

according to flow-ratio and pressure in the pulmonary artery in figure 2.

Intima of the Muscular Pulmonary Arteries

The intima was normal in 32 cases. In eight there was slight intimal fibrosis, in two it was moderate, and in another 12, severe. The intimal changes also were plotted against the flow-ratio and pressure (fig. 4).

Other changes in pulmonary arteries were rare. In one case rupture of the internal elastic membrane and in another recent thrombi in arteries were observed. Plexiform lesions occurred in two cases, those of children 3 and 7 years of age. In both, there were also marked medial and intimal lesions.

Other Changes

Only occasional alterations occurred in the pulmonary veins, no more than were observed in the control group. Hemosiderosis, on the other hand, was more pronounced in cases of ventricular septal defect than in the control group. It was clearly more marked in cases with a high pressure than in those with low pressure and in cases with a high flow than in those with low flow.

Ventricular Septal Defect with Complications

The group consisted of 55 individuals, 29 males and 26 females, ranging in age from 4 weeks to 34 years, with an average age of 7.0 years. In four of the eight cases with slight pulmonic stenosis the media was atrophic, in two normal, and in two others moderately hypertrophied. In the group with other complications medial hypertrophy of the pulmonary arteries was more pronounced than in the isolated defects. It was slight in 10, moderate in 21, and severe in five patients.
In contrast, the incidence of intimal fibrosis was approximately the same as that in the uncomplicated group. The pulmonary veins again, were unremarkable. Hemosiderosis, however, was even more severe than in uncomplicated cases. In one case, that of a girl of 11 years with a patent ductus arteriosus in addition to a large ventricular septal defect, who died 10 days after barding of the left pulmonary artery, multiple plexiform lesions were found at autopsy in the intrapulmonary arteries. In the lung biopsy, taken at operation, no plexiform lesions were observed, although severe medial hypertrophy and intimal fibrosis were noted.

**Patent Ductus Arteriosus**

Of the 82 cases of patent ductus arteriosus, 74 were isolated, that is, the patent ductus was the only malformation. In the eight remaining cases there were four instances of coarctation in addition to the patent ductus, three of a small ventricular septal defect, and one of slight aortic stenosis. Of the patients without complications, 23 were male and 51 female, with ages varying from 5 months to 43 years. The average age was 8.6 years.

Cardiac catheterization was performed in only 19 cases. The right ventricular pressure was 60 mm Hg systolic or less in nine cases, and over 60 mm Hg in 10. Data about flow in the pulmonary circulation were available in only seven cases. In two of these the ratio between pulmonary and systemic circulation was 2 or less, and in five it was more than 2.

**The Media of the Muscular Pulmonary Arteries**

The media was within normal range in 41 of the 74 uncomplicated cases. In 11 medial hypertrophy was slight and in six moderate. Thinning of the media did occur in a number of cases. In nine medial atrophy was slight, in five moderate, and in two severe. Apart from the few cases of pronounced medial atrophy, the results for the medial thickness did not differ greatly from those obtained in our control cases and in the cases of atrial septal defect (fig. 1). In view of the limited number of cases in which data about flow and pressure were known, it was not possible to make an adequate division into low and high flow-ratio and pressure groups as we did in ventricular septal defect.

The intima of the muscular pulmonary arteries was normal in 60 cases of uncomplicated patent ductus arteriosus, slightly thickened in 11, and moderately thickened in three.

**Other Lesions**

Other lesions of the pulmonary arteries, such as intimal elastosis and rupture of the internal elastic membrane, were rare; thrombi or emboli and plexiform lesions were not observed. Alterations of the pulmonary veins were no more frequent than in the normal control group and the same applied to hemosiderosis.

Of the eight patients with a patent ductus arteriosus that was complicated by other, though minor, malformations, three had normal media in the pulmonary arteries, while the other five had medial hypertrophy varying from slight to severe. In five, the intima was normal and in three others there was intimal fibrosis varying from slight to moderate. The other features of the pulmonary vessels in these cases were not remarkable.

**Discussion and Conclusions**

The alterations of the lung vessels in cases of atrial septal defect, ventricular septal defect, and patent ductus arteriosus, particularly in the presence of pulmonary hypertension, have been extensively studied. Medial hypertrophy, intimal fibrosis, and occasionally plexiform lesions are the most prominent among these vascular changes. Since lungs from autopsies have generally been studied, the material thus obtained may give a one-sided picture. Although material from lung biopsies may not be completely representative as well, since obviously only operable cases are included, the results will better reflect the early lesions and the development of the pulmonary vascular changes in these congenital cardiac malformations.

In cases of atrial septal defect a pronounced pulmonary arterial hypertension is not commonly observed. The moderate increase in pressure, which occurs frequently, is generally
attributed to the increased flow through the pulmonary vascular bed, usually in the absence of an elevated vascular resistance. It is often accepted that an increased flow is liable to produce patchy intimal fibrosis and even that a significant fibrosis of the intima with partial obliteration of the arterial lumina may be held responsible for the occasional occurrence of marked pulmonary hypertension in cases of atrial septal defect. This concept is based in part on the classical treatise of the pulmonary vascular pathology in cases of congenital heart disease by Edwards. Edwards stated that the small muscular pulmonary arteries in atrial septal defect are commonly the site of focal intimal fibrosis and suggested that turbulence and abnormal vibration in the vessels, due to the large flow, were responsible for the lesions rather than the elevation of the pressure.

There can be little doubt that, in many patients with atrial septal defect who come to autopsy, alterations of the pulmonary arterial media and intima may be found especially in the presence of pulmonary hypertension. Although uncommon, these cases will constitute a relatively high percentage of the total mortality in atrial septal defect and certainly of the cases reported in the literature. It turned out that in our lung biopsies the medial thickness of the muscular pulmonary arteries did not differ significantly from that in normal controls. As we have shown earlier in cases of atrial septal defect, it is possible that a slight or moderate medial hypertrophy may be masked by dilatation of vessels, resulting in a normal medial thickness in spite of an increased mass of the media. We have no way of establishing such an effect in the limited number of arteries in our biopsy sections, but in any event there was no difference in medial thickness in cases with low and high flow (fig. 2).

Even more striking, in view of previous reports, was that the intimal thickness generally was the same as that in normal individuals. Slight, and occasionally moderate, intimal fibrosis did occur but certainly no more than in the control series. While this throws some doubt upon the concept that flow plays an important role in the formation of intimal lesions, our observation that there is no more intimal fibrosis in the group with atrial septal defect with a high flow-ratio than in the group with a low flow-ratio (fig. 4) does not support the hypothesis that a large flow, even if it should produce turbulences in these small vessels, gives rise to intimal thickening. Also Heath and Whitaker could not find vascular changes in two cases of atrial septal defect with a large flow.

A gradual vascular obliteration as an excessive form of this intimal fibrosis has been supposed to be the basis for the occasional occurrence of pulmonary hypertension in atrial septal defect. Although severe intimal fibrosis may occur in these uncommon cases, it is unlikely in view of our results, that intimal thickening of the pulmonary arteries is the initiating factor for the development of pulmonary hypertension.

In ventricular septal defect the average medial thickness was distinctly increased as compared to the normal. Although in the 44 cases of isolated ventricular septal defect no severe medial hypertrophy was observed, the incidence of moderate and slight changes in medial thickness was at least twice as high as in the control group and as in the group of atrial septal defect. The relation between pressure and medial thickness in these cases is striking. In the low pressure group the medial thickness shows approximately the same incidence as that in the normal controls, although the number with moderate hypertrophy is higher. In the high pressure group a normal media is found in less than 20% of the cases.

When, on the other hand, the low flow-ratio group is compared with the high flow-ratio group, there is hardly any difference in incidence of medial hypertrophy. Although, in principle, the low flow group could be assumed to be heterogeneous, consisting partly of patients with a flow-ratio that was not markedly elevated from the beginning and partly of patients with a flow-ratio that was diminished secondary to severe pulmonary
vascular alterations, it is unlikely that this played a significant role, since only three patients fell into the latter group. Our findings, therefore, suggest that medial hypertrophy in ventricular septal defect is particularly associated with pulmonary hypertension and not with increased flow. This is consistent with what we found with regard to atrial septal defect.

The intimal thickening in ventricular septal defect was in approximately the same range as in our controls, but the average age of our patients was 9.1 years. At this age no age changes could be expected. It must be concluded, therefore, that in ventricular septal defect intimal fibrosis is more pronounced than in normal controls of a comparable age.

When our cases of isolated ventricular septal defect were divided according to pressure and flow-ratio, the results were far more striking, since the intima was normal in all cases of the low pressure group but in less than 50% of those in the high pressure group. Here again, the difference between the high flow-ratio and low flow-ratio groups was much smaller, so that also with regard to intimal fibrosis pulmonary hypertension is apparently more important than increased flow.

The thickness of the media of muscular pulmonary arteries in the group of 74 cases of isolated patent ductus arteriosus, on the whole, was in the same range as that in our groups of normal controls and of atrial septal defect (fig. 1). In view of the limited hemodynamic data collected in the cases of patent ductus, a reliable evaluation of the pressure-medial thickness relationship was not possible.

The incidence of intimal fibrosis in this group appeared to be virtually identical with that in cases of atrial septal defect, but the average age in our cases of patent ductus was 8.6 years, and as a consequence there should have been very little intimal thickening in this group. On comparison with a normal control group of approximately the same age, it appears that the incidence of intimal fibrosis is increased. A correlation with pulmonary arterial pressure and flow in this group was not possible because of insufficient hemodynamic data.

Plexiform lesions were observed in our biopsies in only two instances, both in cases of isolated ventricular septal defect with severe pulmonary hypertension. Incidentally these two cases were the only ones in the whole material of over 1,000 biopsies, representing various forms of acquired or congenital heart disease, in which plexiform lesions occurred. It is likely that the incidence in our patients may have been greater since, as we have seen, there was one patient in the group of complicated ventricular septal defect in whom such lesions were demonstrated at autopsy, while the biopsy was negative in this respect. The risk of a lung biopsy not being representative is of course greater for those alterations that occur more or less scattered in the lung than for those with a more uniform distribution. Although plexiform lesions, which are generally regarded as a sign of long-standing or severe pulmonary hypertension carry on the whole a poor prognosis, both patients with such changes in their biopsies are still alive and relatively well 3 and 2⅓ years, respectively, after a banding operation of the pulmonary artery.

In general, pulmonary venous alterations were inconspicuous in all our groups. Thrombi in arteries or in veins, either recent or organized, were rare. Hemosiderosis, on the other hand, although hardly more marked in atrial septal defect and patent ductus arteriosus than in normal controls, was pronounced in cases of ventricular septal defect. The influence of either flow or pressure on this lesion was undecided within this group. Its failure to show a definite increase in cases of atrial septal defect, even in the presence of a very high flow, suggests that pulmonary hypertension is the main factor.

The effect of complicating heart lesions varies. In the complicated atrial septal defect group, consisting of seven cases of minor additional malformations and two of a ventrally situated defect, the impression was that the picture of the lung vessels was similar to that of the uncomplicated cases and the same

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applied to the eight complicated cases of patent ductus arteriosus.

When a ventricular septal defect, however, was complicated by slight pulmonic stenosis, the stenosis apparently still provided some protection to the lung vessels since the media was moderately hypertrophied in only two of the eight cases. Other complications, however, tended to increase the incidence of medial hypertrophy and intimal fibrosis of the pulmonary arteries and that of hemosiderosis.

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References


On the Double Duty of a Critic

My ancient friend Francis Grierson remarked in one of his essays, "Many writers are slow to praise, fearing that frank enthusiasm will be taken as a mark of critical incapacity." Yet few demur at wholesale condemnation. For most readers destructive critics are naturally impressive and they somehow feel it is more perspicacious to detect imperfections and weaknesses than it has to point out merits. Actually, "star-finding," as Frank Harris called it, requires a far greater acumen and skill. This is a point to remember at a time when appreciation is virtually a forgotten word in critical circles.—Van Wyck Brooks: From a Writer's Notebook. New York, E. P. Dutton & Co., Inc., 1958, p. 113.
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