It is difficult to say whether it was by fate, accident, or purpose that I became involved in studying the pulmonary circulation. It was probably by all three. I always wanted to be a biologist—well, not always. At the age of 3 years I decided to be a tulip vendor, at 6 nurseryman, at 10 a farmer, but from 12 on I wanted to be a biologist. However, when I was preparing to enter the university, it was pointed out to me, not without reason, that my employment prospects as a biologist would range from being unemployed to working as a school teacher. The latter possibility particularly filled me with horror, so I decided to embrace the medical study as a second choice.

That study was interrupted during the war and the German occupation of Holland. I had to hide from the Germans to avoid forced labor in our neighbor's country. For two years I was a farm laborer in the countryside; two of us had 18 cows to milk twice a day (Fig. 1). Only after the liberation could I pursue my studies.

In 1946 I became a student assistant at the histologic laboratory of Utrecht University. My research assignment involved counting ova in the ovaries of mice under various circumstances. But I also had to assist in the practical microscopic course. While screening a cross section of a lamprey (Petromyzon fluviatilis) for good examples of cartilage and chondroid tissue, I stumbled upon some very strange structures in the aorta of this fish (Fig. 2).

That afternoon had remarkable consequences. I received permission to drop the
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Figure 1. During World War II, I worked as a farm laborer milking cows.

Figure 2. Cross section of lamprey aorta.

Figure 3. Model of structures found in lamprey aorta.

eggs and to take up the arteries. I studied serial sections, made models (Fig. 3), and used them in the rheologic laboratory of the Technical Academy in Delft. In the meantime I graduated and got a job in the histology department.

The early fifties were exciting years for me, if only because three things happened within a short period: I married, finished my thesis, and decided to switch from histology to pathology.

A marriage may not seem essential to one's scientific career, but in my case it was. Noek, my wife, gave up her nursing job and, from the first day, became completely involved in my research, helping me in a thousand ways. When I say "from the first day," this may be taken literally. On the evening of the day we married, we left for Naples where I was going to work at the Zoological Station with a government grant.

My thesis, which I defended 10 days before my marriage, included a study of
the structures found in the aorta of the lamprey. It appeared that these structures were also very numerous at branching points in other systemic arteries, although smaller and less spectacular (Fig. 4). Here they consisted of circularly arranged smooth muscle fibers around the orifice of a branch that protruded into the lumen of the parent artery. Except for the branchial arteries, we found them throughout the arterial tree, not only in the lamprey but also in other fishes and even in frogs. To a lesser extent they occur in mammals but only in systemic (Fig. 5) and not in pulmonary arteries.

Later it became clear that these ringlike structures can be found in pulmonary arteries of newborn infants and, in the presence of pulmonary hypertension, also in older children (Fig. 6) and adults. In other words they appeared whenever there was an increased pulmonary arterial muscularity. But that was later, after I switched to pathology.

The reason I made the move to pathology was that I thought that in histology the emphasis was turning more and more to biochemistry and biophysics and that I was losing contact with medicine. I never regretted that decision. I received my training at the pathology department in Utrecht, and in 1956 we went to London with a grant for a year to study at the Postgraduate Medical School.

Any corpuscle entering the systemic circulation risks getting stuck in the pulmonary vasculature. This is what happened to me. In Professor Henry Dible’s Department of Pathology I worked in particular with Vic Harrison (Fig. 7). In view of my interest in vessels, Harrison suggested that I have a close look at certain arterial alterations occurring in congenital heart disease with pulmonary hypertension. There were at that time contrasting opinions about these glomuslike, glomeruluslike, or plexiform lesions. Some believed that they were congenital malformations, others that they were acquired and the result of the high pressure in the pulmonary circulation, still others that they represented pulmonary arteriovenous anastomoses.

Vessels containing these peculiar alterations were traced over hundreds of serial sections, and reconstruction drawings were made (Fig. 8). I have always been fascinated by the plexiform lesions.

Figure 4. The structures were numerous at branching points in other septemis arteries.
and still believe that observations from that study give a clue to their pathogenesis. Their location immediately after an arterial ramification, the same spot where fibrinoid necrosis is found in these cases, and the destruction of the media in the area occupied by the plexus suggest a causal relationship between arterial necrosis and the resulting fibrin clot and the plexiform lesion.\(^5\)

On my return to Holland in 1957, I moved from Utrecht to Leiden University, where there was a very active department of pathology. What did not change was my interest in pulmonary vascular pathology. I started to do morphometry of pulmonary arteries and developed a method for distinguishing medial hypertrophy from vasoconstriction.\(^6\)

Professor Gerard Brom, the thoracic surgeon in Leiden, was very interested in hypertensive pulmonary vascular disease, and over the years I received more and more lung biopsies, taken routinely during cardiac surgery for congenital heart disease, later also for acquired heart disease. This material formed the basis for a great deal of research in close cooperation with Jan Nauta and Hans Weeda and led to several publications.\(^11\)–\(^13\)

Then the faculty invited Jesse Edwards (Fig. 9) to Leiden. I was familiar with his work, in particular with his Lewis O’Connor Memorial Lecture,\(^4\) and I very much wanted to talk to him. I devised a strategy, but it was not as easy to implement as I had thought. During the reception following his lecture, a solid mass of faculty members surrounded him, impenetrable for a beginning pathologist. Fortunately, the inevitable moment came at which he absented himself, and I managed to meet up with him in the corridor and guide him to my room, where I had laid out a small exposition of my work on the pulmonary vasculature. His reaction was positive, and I asked him if I could come to Rochester to work with him.

One year later, in 1959, Noek and I went to the Mayo Clinic. It was the beginning of a marvelous year. Although we both worked very hard, it felt to us like one long holiday. Noek started to work as a nurse in St. Mary’s Hospital and in the evenings and weekends helped me with my work. As a research assistant I was employed in the morbid anatomy department and spent every moment I could
Figure 6. These ringlike structures can be found in the pulmonary arteries of children with pulmonary hypertension.

Figure 7. Vic Harrison.

spare from the routine work on the morphology of the lung vessels.

Our experience with morphometry was very useful. However, it was such time-consuming work that I could not do what I hoped and thus I asked Noek to help me. It soon was evident that she enjoyed this work and did it very meticulously. She always refused to learn anything about the condition of the patient until she had produced the final data, so as to avoid bias. Because all records have always been kept, the number of vessels morphometrically assessed over the whole period can be estimated as over 500,000. Some of my friends used to say “She is doing the work; he is just talking about it.” I do not think this is a fair assessment, but it certainly illustrates the magnitude of the work.

In our first publications from the Mayo Clinic, her work was acknowledged as “with the technical assistance of . . . .” Her input in subsequent studies certainly was not limited to technical assistance, so from then on she became a full coauthor. I
insisted on this point; Noek herself had no ambitions in this direction but enjoyed sharing the adventure.

To have Jesse Edwards as a teacher was a privilege and to work with him a pleasure. He was always relaxed and helpful, whatever the pressure of his own work. My study of the pulmonary circulation brought me in contact with many others engaged in the same field, including Howard Burchell, Jim DuShane, Henry Neufeld, and John Shepherd, all of whom contributed to my education.

In 1960 I returned to Leiden, but with an assignment: write a book with Edwards and Heath on the pathology of the lung vessels. This project took up much of my time and was almost finished when, in 1962, I was appointed professor of pathology at the University of Amsterdam. So that I could finish the book I requested and was given a delay in my appointment until January 1, 1963.

The Department of Pathology of the University Hospital in Amsterdam was built in 1930. Although not practical in all respects, with its large rooms and wide corridors, it was a beautiful building (Fig. 10). The department was understaffed and underequipped. There were, however, compensations. Several cupboards were full of microscopes, all dated from before 1930 and many were early nineteenth-century specimens, some outfitted
with candlelight illumination. I really got excited with I found an eighteenth-century sun microscope (Fig. 11) in prime condition. It was to be used in a dark room and had a mirror projecting through a hole in the shutter, catching the sunlight and projecting an image of whatever is put on the object holder on the opposite wall. There were also some nineteenth-century microtomes, in which the object was moved by means of a screw (Fig. 12).

The department also had an enormous library but one almost devoid of books less than 20 years old. I did have a treasure of antique medical books and atlases from Van Leeuwenhoek and Bonet to Cruveilhier and Virchow. While taking good care of the antiquities, I was handicapped by the lack of people and modern equipment and books. Nonetheless this meant that I had a free hand to shape the department according to my own views, particularly because in the early sixties money was not a major problem.

Over the years some diversity developed in our department with regard to scientific topics, but cardiovascular pathology took priority and pulmonary vascular pathology remained my personal interest. At this time we paid much attention to the normal lung vessels, arteries, veins, and anastomoses, in all age groups.

Noek had experience tracing vessels in serial sections and applied this to the study of anastomoses. Always working at home, she worked her way through 44 series with over 20,000 histologic sections. Venovenous anastomoses appeared to be numerous, but anastomoses between

![Figure 10. Department of Pathology of the University Hospital in Amsterdam.](image1)

![Figure 11. An 18th-century sun microscope.](image2)
pulmonary arteries were not found in normal lungs, and those between bronchial and pulmonary arteries were very scarce.

One day Noek told me that she regularly found branches of pulmonary arteries supplying the interstitium of the lung and the bronchial walls (Fig. 13) and branches of bronchial arteries ending up in alveolar capillaries. I found this difficult to believe, so I checked the vessels she had marked. I had to admit that she was right; we published the findings of these pulmobronchial and bronchopulmonary arteries together.\(^{14}\)

Another subject that fascinated us was primary pulmonary hypertension. The reports on its morphology dealt with a few cases at best and were often confusing or contradictory. In some cases, the lung vessels were described as being completely normal. It was evident that more material was needed for an adequate evaluation.

We started collecting all publications on primary pulmonary hypertension that we could find. This was a lot of work because in the sixties the literature was not as computerized as it is now. We found approximately 600 cases in over 200 papers. Between 1967 and 1969 we sent hundreds of circular letters to colleagues all over the world requesting slides or paraffin blocks from their cases, particularly from the ones that had been published. The response was very satisfactory. We received material from 162 cases out of 51 departments in 14 countries. In 156 cases the material was adequate and subjected to morphometry.

In 110 out of these 156 patients, the morphology of the lung vessels was identical to that observed in congenital heart disease with a shunt. In 31 patients there were only thrombotic lesions, while in the remaining 15 cases there was a variety of patterns of vascular changes, including veno-occlusive disease and lesions of pulmonary venous hypertension (Table 1). Thus, in our material there were more than three times as many cases of what was later called plexogenic arteriopathy than cases with exclusively thrombotic changes. Although in our publication on this topic\(^{15}\) we warned against the inevitable selection in the material, this ratio has sometimes been cited as a realistic proportion. However, in the 1960s the term "primary pulmonary hypertension" referred to the primary form of plexogenic arteriopathy. Those were the cases we requested, and so was it generally understood.

Later the term "primary pulmonary hypertension" received a completely different meaning. In October 1973, at a meeting in Geneva of a World Health Organization committee on primary pulmo-
Table 1
Cases Submitted Under Diagnosis Primary Pulmonary Hypertensiona

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic thromboembolism</td>
<td>31</td>
</tr>
<tr>
<td>Chronic pulmonary venous hypertension</td>
<td>5</td>
</tr>
<tr>
<td>Pulmonary venoocclusive disease</td>
<td>5</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>1</td>
</tr>
<tr>
<td>Chronic bronchitis and emphysema</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary schistosomiasis</td>
<td>1</td>
</tr>
<tr>
<td>Vasoconstrictive primary pulmonary hypertensiona</td>
<td>110</td>
</tr>
<tr>
<td>Total</td>
<td>156</td>
</tr>
</tbody>
</table>

aLater called “plexogenic arteriopathy.”

Note. (Reprinted with permission from reference 15.)

Pulmonary Hypertension, two recommendations were made with regard to terminology. First, it was decided that the morphologic entity characterized by concentric-laminar intimal fibrosis, fibrinoid necrosis, and plexiform lesions should have its own name. For that reason, the two pathologists on the committee, Donald Heath and I, were asked to come up with a suggestion. While having lunch together, we invented the term “plexogenic arteriopathy”—plexogenic to indicate that this condition potentially would lead to one of its final and certainly most characteristic alterations: the plexiform lesion. Our proposal was accepted that afternoon. The other recommendation was to no longer use the term “primary pulmonary hypertension” for the morphologic entity of plexogenic arteriopathy but for all cases in which there were no clinical indications for the cause of the elevation of pressure.

In retrospect I think that this was an unfortunate decision. If the clinicians are unable to explain the elevated pressure, it should be called “unexplained pulmonary hypertension.”2 By using the term “primary pulmonary hypertension,” clinicians suggest that they have made a diagnosis rather than having failed to do so. Maybe that is the reason the term used in this sense has become so popular.

The report of the committee meeting3 pointed out that clinically unexplained pulmonary hypertension usually appears to be based on one of three morphologic conditions: plexogenic arteriopathy, thromboembolic arteriopathy, and pulmonary veno-occlusive disease. Although this may be so usually, whatever the form or whatever the underlying morphology, the cause of an elevated pulmonary arterial pressure may sometimes elude the clinician’s diagnostic possibilities. This can happen not only with very rare diseases, such as capillary hemangiomatosis or pulmonary arterial medial defects, but also occasionally with more common conditions that present in an unusual fashion, such as tumor embolism. Occasionally unexplained pulmonary hypertension appears at autopsy to be caused by tumor embolism, usually from a gastric or mammary carcinoma that had remained asymptomatic. In a case like that the term “primary,” as used in the World Health Organization’s definition, seems out of place.

A direct consequence of our involvement in primary pulmonary hypertension was the analysis of various histologic patterns and thereby a classification of morphologic entities in pulmonary vascular disease.7 For a thorough and systematic study of a case with abnormal lung vessels, with or without pulmonary hypertension, classification is of great help. It certainly helped us get an overview of what to expect in the way of vascular lesions in the lungs and under what circumstances these might occur. Noek joined me in publishing a book on pulmonary vascular pathology. This book, which appeared in 1977,8 has always been particularly dear to me.

With increasing frequency we re-
ceived open lung biopsy specimens, taken not during correction of cardiac disease but as a separate procedure. In part, this was done in patients with unexplained pulmonary hypertension to establish a diagnosis. However, we also received many biopsy specimens from patients with known congenital cardiac defects to decide whether pulmonary vascular disease was reversible and correction of the defect permissible. Our experience with hundreds of peroperative biopsies in such cases and comparing there specimens in the same patient with those taken during a banding procedure of the pulmonary artery, and subsequently during corrective surgery, appeared very important in this respect.9,16

Other activities included the production of experimental pulmonary hypertension by hypoxia or by application of fulvine, and in particular the morphology of vasoconstriction. These electron-microscopic studies were done in cooperation with Kurt Dingemans.1

Since my retirement in 1985 from the University of Amsterdam, I have been fortunate to have the opportunity to work in the Department of Pathology of the Erasmus University in Rotterdam. Although this is a part-time job and I do only pulmonary and pulmonary vascular pathology, it keeps me busy in a pleasant way with diagnostic and experimental work.

Traveling is often a consequence of involvement in scientific work. Some like it and others do not. I liked it, but I had a great advantage: I never went alone. Noek and I traveled to all continents. Together we have had many adventures, both unpleasant and delightful. We shared a great hobby—birdwatching—and, wherever we were, we used any opportunity after the congress or symposium for that purpose. Another important dividend of traveling was that we made good friends all over the world. We were always grateful for that.

Noek died very suddenly a couple of months ago. A joint venture has come to an end. I am grateful for the opportunity to pay a tribute to her and to the work she did over almost 40 years (Fig. 14).

Figure 14. Noek Wagenvoort.

References

5. Wagenvoort, C. A. The morphology of cer-


