CHRONIC PULMONARY EMPHYSEMA (AN EXPERIMENTAL STUDY)

I. Historical Review

H.T.G. Strawbridge, M.D., M.R.C.P.E., F.R.C.P.(C).*

From the Departments of Pathology, The University of Liverpool, England, and the Winnipeg General Hospital, Winnipeg, Manitoba, Canada

It appears that certain aspects of the anatomy and pathogenesis of human chronic vesicular pulmonary emphysema have received relatively little attention in recent years, and the review which follows is intended solely to emphasize these aspects of the subject.

The traditional subdivisions of chronic vesicular emphysema will be used, viz.: compensatory (complementary or vicarious); senile; hypertrophic (obstructive, essential substantive or idiopathic).

Morbid Anatomy

Kountz and Alexander [1] in 1934, gave references to the earliest usage of the term emphysema, but no systematic account of pulmonary emphysema was available until 1819 when Laennec [2] published his treatise. Laennec distinguished between vesicular emphysema, where the distending air was contained within the air spaces of the lungs, and interstitial emphysema.

The first microscopic description of vesicular emphysema was that of Rainey [3] in 1848. The earliest emphysematous change was dilatation of the alveoli and widening of the meshes of the capillary net; subsequently, gaps or pores appeared in the alveolar walls. Progressive enlargement of these fenestrations led to destruction of the alveolar walls. Extension of the process caused fusion of the neighboring air sacs and the formation of larger bullae. Rokitansky [4] in 1861, confirmed this description and considered the process an atrophy of lung tissue. Rokitansky recognized senile emphysema and described vicarious or complementary emphysema developing about areas of consolidation. He next separated off substantive emphysema, his description corresponding to that of hypertrophic or obstructive emphysema today.

A year later, Waters [5] gave an excellent histologic account of the lesions. The earliest stage was dilatation of the alveolar ducts and alveo-

This series of articles is based upon part of a thesis submitted to The University of Edinburgh for the degree of Doctor of Medicine.

Received for publication, November 6, 1959.

* Present address: Department of Pathology, The Winnipeg General Hospital, Winnipeg, Manitoba, Canada.

lar sacs. The elastic fibers became more widely separated but showed no other change. At this stage there appeared "perforation of the walls themselves." "This is at first but slight. Here and there a circular or oval opening may be seen in the membrane: as the disease progresses, these openings become more numerous, and larger: in some instances the whole of the walls of the air sacs and the septa of the alveoli being perfectly riddled with small openings, so that a horizontal section of the lung substance has a cribriform appearance. These openings are for the most part either circular or slightly oval. They exist in all parts of the walls, and are often seen in the septa between the alveoli, before the air sacs are sufficiently distended to obliterate the septa." Waters went on to describe the formation of the larger lesions by an extension of this process. His work has been quoted verbatim as it is the last detailed account of this type to appear in the English literature.

In 1864, Niemeyer[6] confirmed the work of the previous authors. He distinguished between acute and chronic emphysema and emphasized that the histologic changes in chronic vicarious or complementary emphysema were identical to those in the generalized substantive (hypertrophic) variety. Later, Rindfleish[7] insisted that dilatation preceded the appearance of fenestration. Hertz[8] considered that no anatomic change preceded dilatation and fenestration and that, even in established lesions, the elastica appeared normal.

Eppinger[9] in his classical work of 1876, emphasized the distinction between acute and chronic emphysema and maintained that the former was attended by no permanent anatomic changes in the alveolar septums. Eppinger's histologic description of fenestration agrees with that of previous writers. In addition, he gave the first account of changes in the elastic fibers and fiber bundles in emphysema. In the latter lesions the fine fibers were lost, and all that remained were the coarser fibers which ran around the edges of the fenestrations but did not usually show any morphologic changes. However, he thought he could detect more recently formed fenestrations, the edges of which were irregular. In these cases, elastic fibers ran right up to the irregular edge and ended in an apparently frayed manner. He inferred from this that the fraying was the earliest lesion in chronic emphysema. It is important to note that Eppinger never observed any fraying of the elastica which preceded fenestration, and stated that the two changes were always seen together. He considered that the fraying preceded fenestration, but did not demonstrate this.

Kläsi[10] considered that the fenestration arose out of a desquamation of alveolar epithelium. He insisted that the elastica was one of the last structures to be destroyed. Orth[11] and Virchow[12] agreed on the atrophic

nature of the process. Orth insisted that the term emphysema should not be used in senile cases unless actual distention were present.

In 1893, Kohn[13] drew attention to the existence of pores in the alveolar walls. According to Henle,[14] these pores had first been described by Adriani in 1847, but, following the suggestion of Hauser,[15] they became known as the pores of Kohn. Subsequent discussion as to the nature and significance of the pores is irrelevant; but fairly recent work by Macklin[16,17] and Loosli[18] convincingly demonstrates these structures in the lungs of man, rabbits and other mammals.

Hansemann[19] in 1895, accepted the pores as normal structures. Sudsuki[20] in 1899, was unable to confirm Eppinger's findings. He saw no evidence of fraying of the elastic fibers. Sudsuki[20] and Hansemann[21] considered that a mechanical widening of the pores of Kohn constituted the initial lesion in emphysema. Eppinger[22] restated his original views in 1902, without adding any further evidence. Ribbert,[23] Tendeloo,[24] and Spalteholz[25] agreed with Sudsuki.

Orsós[26,27] made a detailed study of the elastic and collagenous fibers of normal and emphysematous lungs in 1907 and 1936. In acute emphysema he considered there was simple dilatation of the air spaces but no other changes. He divided chronic emphysema into senile and hypertrophic emphysema and stated that these were attended by permanent tissue changes as described by previous authors. He considered that tearing of elastic fibers and their subsequent degeneration were the essential lesions. No visible changes preceded rupture. They retracted in a serpiginous manner and appeared as scattered heaps of elastic tissue which degenerated into indifferently staining masses. The changes first appeared in the finest (intercapillary) fibers. Orsós insisted that these "degenerative" changes were seen principally in senile emphysema. In hypertrophic emphysema, the above changes were also present but a much more prominent feature was a reparative increase in the numbers of all types of elastic and collagen fibers. He stated that all the changes, in elastica, alveolar membranes and capillaries, were seen in progress at the same time, and he could detect no definite sequence of loss of the various elements. Like Eppinger, he argued that extension of fenestration could result only from a loss of elastic and collagen fibers. In short, he did not show that the lesions in the elastica were primary but inferred that this was so.

Loeschcke,[28–31] in a series of articles between 1921 and 1928, agreed with the older writers with regard to the destruction of lung tissue by fenestration, but could see no antecedent alteration in the elastic tissue. Even in advanced lesions, the elastica was remarkably resistant and any changes seen were those of a strengthening and thickening of the

individual fibers. Far from considering that the primary lesion resided in the elastica, he considered that, of all tissues, this best survived the atrophic process of emphysema. In contrast, Laguesse[32] in 1927, without presenting any evidence, maintained that loss of the finer elastic fibers caused the fenestration. Letulle[33] considered that there was some condensation of elastic fibers in the walls of bullae and emphasized that sclerosis was a frequent occurrence in all types of chronic emphysema. Antoniazzi[34,35] and Luisada,[36] in 1934, were similarly impressed by the occurrence of sclerosis.

Hartroft,[37] in 1945, was concerned with the microscopic features of emphysema as seen in thin sections and pointed out the falsity of the then popular idea that the free ends of alveolar septums projecting into alveolar ducts were evidence of rupture of the alveolar tissues. But, in contrast to the 19th century workers, he considered that serial section and measurement were the only ways to detect early emphysematous alterations. Bezançon and Delarue,[38] in 1947, considered emphysema as essentially an atrophic process. But at the same time they pointed out that interstitial fibrosis also occurred in the lesions. Heppleston,[39] in 1953, stated that dilatation and destruction of lung tissue occurred in hypertrophic emphysema but did not give details of the process.

Pathogenesis

It is generally accepted that emphysema results from an abnormal total or partial distention of the lungs by air. Theories of pathogenesis may be divided into those concerned with remote pathogenesis, i.e., mechanisms which cause abnormal air tension in the lungs; and intimate pathogenesis, i.e., the exact mechanism whereby abnormal air tension or other factors damage the lung tissue. Much more attention has been given to remote than to intimate pathogenesis. It is proposed, therefore, to place emphasis on the intimate factors.

Laennec,[2] in 1819, postulated that strong inspiratory effort was able to overcome the resistance of bronchial catarrh but that weaker, passive expiration was unable to expel the air, so that overdistention resulted. He, thus, founded the inspiratory theory but did not attempt to explain precisely how overdistention damaged the lungs.

In 1845, Mendelssohn[40] propounded the expiratory theory. He argued that when expiration was obstructed, the accessory respiratory muscles tended to drive the air into the upper and anterior parts of the lungs, producing overdistention and emphysema. He considered that the strain of coughing was the main factor concerned. This original statement of the theory differs in no essential from the various modifications which subsequently have been advanced.

Rainey[8] accepted the operation of mechanical factors but believed that in the presence of fatty changes in the alveoli, even normal respiratory effort could damage the lungs. Gairdner,[41] in 1851, considered that bronchial obstruction produced collapse of the segment of the lung supplied. This necessitated compensatory expansion of the remaining portions of the lungs. If this exceeded functional limits, emphysema resulted. He thus regarded all forms of emphysema as being compensatory or complementary in nature. The same theory was again propounded by Gordon[42] in 1944. Freund,[43,44] in 1858 and 1859, considered that degenerative elongation of certain costal cartilages led to the fixation of the chest in the classical barrel-shaped position and that this caused overdistention and hence emphysema.

In 1862, Waters[5] believed that, in addition to mechanical factors, unspecified "constitutional factors" were responsible for an inherent weakness in the lung tissue. With regard to intimate pathogenesis, Waters believed that mechanical distention caused loss of elasticity and then loss of capillaries which in turn led to impairment of nutrition and the atrophic changes of emphysema. He appeared to regard capillary loss as an ancillary mechanism.

In 1864, Niemeyer[6] clearly stated that in local or complementary emphysema, the overdistention of expansile lung around a consolidated, collapsed or scarred focus led to the development of acute or chronic emphysema, depending on whether the primary lesion was temporary or permanent. This view has been accepted without comment by nearly every subsequent writer on the topic. In hypertrophic emphysema, he considered that both expiratory and inspiratory forces could be operative. Villemin,[45] two years later, was not satisfied that mechanical factors could be operative in every case, but favored the expiratory theory. He considered the primary lesion was a hypertrophy of the alveolar epithelium followed by degeneration and desquamation.

Isaakssohn,[46] in 1871, believed that thrombosis of alveolar capillaries was primary and that atrophic changes followed this. Rindfleisch[7] accepted both inspiratory and expiratory forces as being operative. Almost in passing, he stated that the disappearance of vessels was an essential factor in the genesis of the lesions. Thierfelder[47] considered the obliteration of vessels by pressure as contributory.

Eppinger,[9,22] in 1876 and 1902, accepted mechanical factors as the remote mechanism of genesis. The intimate pathogenesis depended on damage of the finest elastic fibers, leading to permanent dilatation and to fenestration. He regarded chronic emphysema as a pressure atrophy, based upon primary damage to the elastica by distention. Orth,[11] in 1887, regarded the senile lung as simple senile atrophy if there was

no distention, but as senile emphysema if distention was present. Senile atrophy resulted entirely from involutionary changes, but senile emphysema required the additional operation of external mechanical factors. He considered that raised intra-alveolar pressure operated by "direct mechanical action." He also argued that compression and obliteration of capillaries led to local impairment of nutrition due to ischemia.

Grawitz,[48] considered that the peripheral localization of the larger lesions could be explained on the basis of poorer blood supply and fewer anastomoses. Hansemann [19,21] and Sudsuki,[20] in 1899, accepted the mechanical theories and considered that fenestration was the result of a mere mechanical widening of pre-existing alveolar pores with the addition of "pressure necrosis" of their margins. Orsós,[26] in 1907, considered that inflammation played an important part in the hypertrophy of elastica and reticulin, which he described in all forms of chronic emphysema other than pure senile emphysema. Wiesel [49] stated that vascular sclerosis was, in fact, the cause and not the result of emphysema. In 1902 and 1910, Tendeloo [24,50] considered that emphysema was a pressure atrophy resulting from abnormal distention. He saw no changes in the elastic fibers and postulated that loss of elasticity was due to stretching of these fibers beyond their elastic limits in the manner of an overstretched rubber band. Although this had been implied by previous authors, Tendeloo appears to be the first to state the thesis precisely.

In 1911, Loeschcke [51] propounded his modification of the thoracogenic theory of emphysema. He related the development of emphysema to primary changes in the spine, which caused thoracic deformity and overdistention of some parts of the lungs. Loeschcke did not claim that all types of emphysema resulted from this mechanism. His views on intimate pathogenesis are most succinctly expressed in his article of 1922.[29] He maintained that distention, however caused, was the essential factor in all forms of chronic emphysema. The distention caused obstruction to the flow of blood through the capillaries, either by mechanical deformity or by direct occlusion due to raised intra-alveolar pressure. The diminished blood supply was responsible for the tissue atrophy seen in chronic emphysema. The larger peripheral lesions were, in part, the result of poorer peripheral blood supply.

From about 1910 onwards, the general trend of work on emphysema was directed more towards functional investigation rather than pathogenesis. Views on pathogenesis were concerned with mechanisms of remote rather than intimate relationships. It is proposed, therefore, to cite only those authors who refer specifically to problems of intimate pathogenesis.

In 1913 and 1923, Münzer [52,53] and Engelen,[54] without supporting

evidence, postulated that emphysema was the result of pulmonary arteriosclerosis. On the other hand, H. R. Miller,[55] in 1925, found no direct connection between such sclerosis and emphysema. Winter[56] maintained that oft-repeated distention acted not by damaging the elastica but by tearing and obliterating capillaries. Bard,[57,58] in 1925 and 1928, adhered to the view that in the absence of mechanical factors, emphysema could develop out of constitutional weakness of the lungs. Letulle[33] considered that inflammatory weakening of the lung was as important as the mechanical factors. Antoniazzi,[34,35] in 1934, also emphasized the importance of local inflammatory factors.

Kountz and Alexander,[59] in 1933, concluded that senile emphysema was really a condition involving primary changes in the thoracic cage and that the lungs were normal or slightly overexpanded. Christie,[60,61] in 1934 and 1944, considered that the primary functional defect in hypertrophic emphysema was a loss of pulmonary elasticity. He rejected all distensive and vascular theories, maintaining that compressive expiratory stresses and strains in coughing and spasms of asthma produced violent pressure changes which damaged the alveolar walls and resulted in loss of elasticity. Distention followed as a consequence of this. Christie appeared to regard the damage to the alveolar walls as a direct mechanical effect.

In 1938, Korol[62] considered that ischemia due to thrombosis and endarteritis was a major factor in the production of emphysema in tuberculosis. Later he asserted[63] that vascular sclerosis was in fact the primary lesion in all forms of emphysema and that emphysema should be regarded as an ischemic atrophy of lung tissue. Fleischner,[64] in 1950, remarked that capillary collapse or occlusion might lead to an atrophy of alveolar walls. In 1953, Cudkowicz and Armstrong[65] described occlusive changes in bronchial arteries and considered that ischemia, thus produced, might be responsible for the fibrosis noted in emphysematous lesions. Abbott, Hopkins, van Fleit and Robinson[66] argued that a variety of irritants could produce bronchial spasm and distention of the lung, leading to occlusion of capillaries. At the same time, bronchial obstruction produced a reflex vasoconstriction in the related portion of the lung. They considered that emphysema should be regarded as an ischemic atrophy functionally produced.

Discussion

Since the original microscopic description of chronic emphysema by Rainey in 1848, there has been virtually complete agreement that the basic lesion is destruction of the alveolar walls by the process of fenestration. From the earliest times the changes have been considered as evi-

dence of atrophy of lung tissue. This view persisted in the 19th century, but in the first half of the present century emphysema was generally regarded as the result of tearing and rupture of lung tissues. Recently, passing references to the anatomy of emphysema again mention that it is an atrophic process, but the descriptions remain two-dimensional, perhaps due to the abandonment of the thick sections used by the older writers.

In many respects, views of pathogenesis appear to have conditioned, rather than been conditioned by, the outlook on the anatomic nature of the process. It has long been evident that mechanical factors are of prime importance in the genesis of compensatory and hypertrophic emphysema. The early anatomists saw evidence of tissue atrophy but not of mechanical rupture. This led to theories intended to supplement or replace the purely mechanical views. Thus Rainey[3] and Villemin,[45] respectively, considered that fatty change and desquamation of alveolar epithelium were responsible. Waters[5] considered that "constitutional" weakness of the lung might account for the lesions if mechanical factors were absent. This unsubstantiated statement has been repeated frequently, but there is no record of any anatomically proved case in which complete absence of any causative factor could be demonstrated.

Eppinger's inference[9] that distention caused fraying of the elastica, leading to fenestration, although supported only by Orsós,[26,27] led to uneasy acceptance that overdistention damaged the lung mechanically as the initial step in pathogenesis. However, Tendeloo's statement[50] that the changes in elastica were functional and not anatomic provided a convenient explanation for the general failure of anatomists to see changes in these fibers. The only other attempt to provide a purely mechanical basis for the lesions was the work of Hansemann[21] and Sudsuki.[20] Their theory of a mere mechanical widening of pre-existing alveolar pores failed to account for the appearance of abnormally large numbers of pores.

Thus, in spite of the anatomic discussions of Loeschcke[30] and the work of respiratory physiologists, who have shown that many factors other than the elastica are involved in resultant lung "elasticity," it is largely on the above evidence that distention, produced by the remote mechanical factors, is considered to produce loss of elasticity and the lesions of emphysema.

The possibility that emphysema might result from primary vascular changes was first considered by Isaakssohn[46] in 1871, who believed capillary thrombosis was responsible. Since then Wiesel,[49] Münzer,[52,53] and Korol[62,63] have postulated that pulmonary vascular sclerosis is the primary lesion. In general, however, vascular lesions have been

regarded as being secondary either to the emphysema or to its remote cause. Apart from this "primary" vascular approach, several 19th century authors of the "mechanical school" of thought, including Waters,[5] Thierfelder,[47] Eppinger[9] and Orth,[11] have commented that in the course of mechanical distention, capillaries are apparently stretched and occluded. But they considered that this was merely an ancillary mechanism, albeit an important one, as did Fleischner.[64]

Only Loeschcke[29] stated emphatically that the atrophy characteristic of all forms of chronic emphysema resulted from capillary occlusion in the distended areas. More recently, on more theoretical evidence, Abbott and co-workers[66] arrived at a similar conclusion.

This modification of the vascular theory has received but little attention, but as first suggested by Rindfleisch[7] in 1871, it could well provide the link between the mechanical and nutritional theories. It would explain why the distensive forces produce the histologic appearance of a tissue atrophy.

Another aspect of the problem merits further consideration. In his original description in 1848, Rainey[3] described condensations of fibrous tissue around the larger lesions. More recently, Orsós,[26,27] Letulle,[33] Antoniazzi,[34,35] Luisada,[36] and Bezançon and Delarue[38] considered that emphysema was as much a sclerotic as an atrophic process. In general, scarring has been regarded as a remote causative mechanism rather than an integral part of the emphysematous process itself. It could, however be argued that both scarring and the emphysema result from the inflammatory endarteritis as was suggested by Korol.[62] Alternatively, inflammation could lead to direct vascular destruction and the production of emphysema.

Only brief mention has been made of so-called senile emphysema, and this reflects the amount of attention which this subject has received in the literature. It was originally regarded as simple senile atrophy of the lungs. The older writers dismissed it briefly before considering hypertrophic emphysema but emphasized that the histologic appearances were identical to those in other forms of emphysema. At the present time there is no systematic account of the anatomic changes in senile emphysema or of the "normal" senile lung. Orsós[26,27] alone considered that pure atrophy was the hallmark of senile emphysema in contrast to the regenerative changes in other types. This view has not been confirmed or even seriously considered and might be of importance. Other writers have usually contented themselves with the statement that large bullae are absent and that the lungs collapse normally. The fact that the elderly are not exempt from known cases of emphysema does not simplify the problem. Indeed, Loeschcke[30] did not accept

senile emphysema as an entity but considered that thoracogenic factors were more important in the genesis of emphysema in this age group. Kountz and Alexander[59] suggested a similar thoracogenic theory but insisted that the lungs were usually normal. Rappaport and Mayer,[67] in 1954, accepted that senile lungs may show atrophy in the absence of distensive forces. They thought this resulted as much from disuse, due to improper expansion, as from "senile" atrophy. Such lungs they regarded as showing senile atrophy and were not considered pathologic. If distensive forces, usually thoracogenic, were present, the condition should be called senile emphysema. They thus adopted a compromise between the views of Loeschcke[30] and of Orth.[11]

It seems to the writer that if the term senile emphysema is to be used, it should be restricted to cases where the lungs show emphysematous changes which cannot be ascribed to etiologic factors other than senility itself. If the lungs are normal, the condition is, by definition, not emphysema. If etiologic factors other than senility are present, the emphysema should be included in the appropriate group, regardless of the age of the subject. The remaining cases of emphysema in the elderly, without demonstrable cause, would constitute true senile emphysema. Until a more detailed knowledge of the "normal" senile lung is available, there is little evidence for considering that emphysema in the elderly differs either anatomically or etiologically from emphysema in other age groups, and the relationship between emphysematous alterations in the senile lung and changes in the senile thoracic cage, in the absence of bronchopulmonary disease, must await clarification.

Summary

The literature provides ample evidence for regarding all forms of chronic emphysema as an atrophy of lung tissue. The atrophy manifests itself by the development of progressive fenestration in the alveolar walls which leads to the ultimate destruction of the lung tissue in the affected area. The changes can only be appreciated in thick sections. There is no acceptable evidence that changes in the elastic tissue precede the appearance of fenestration. A few writers have suggested that inflammatory sclerosis is an essential part of the emphysematous process.

There is less agreement on certain aspects of the pathogenesis of chronic emphysema. Hypertrophic and compensatory emphysema are generally regarded as being the direct result of mechanical stresses and strains on the alveolar tissues. There is little to suggest precisely how the stresses produce the emphysematous lesions. Attempts to explain the atrophic lesions of emphysema on the basis of primary vascular changes

have met with little support. The view that abnormal distention of the lung leads to vascular occlusion and consequent tissue atrophy has been advanced from time to time. This mechanism has received little attention and, generally, has been regarded as merely ancillary to direct "mechanical" damage.

Senile emphysema is regarded by many as being a simple senile atrophy of lung tissue, but there are no systematically documented accounts which establish the condition as an anatomic entity, distinct from chronic emphysema in the elderly, due to causes which may be operative in any age group.

References

1. Kountz, W. B., and Alexander, H. L. Emphysema. *Medicine,* 1934, **13,** 251–316.
2. Laennec, R. T. H. Treatise on Diseases of the Chest and on Mediate Auscultation. Forbes, J. (transl.). Longmans, Rees & Co., London, 1834, ed. 4, pp. 141–162.
3. Rainey, G. On the minute anatomy of the emphysematous lung. *Med.-Chir. Tr., London,* 1848, **31,** 297–304.
4. Rokitansky, C. Lehrbuch der pathologische Anatomie. W. Braumüller, Wien, 1861, 3rd Aufl. Band 3, pp. 45–57.
5. Waters, A. T. H. Researches on the Nature, Pathology and Treatment of Emphysema of the Lungs, and Its Relations with Other Diseases of the Chest. J. Churchill, London, 1862, 114 pp.
6. Niemeyer. Ueber Emphysem der Lunge. *Berl. klin. Wchnschr.,* 1864, **1,** 425–427; 433–435; 444–448.
7. Rindfleisch, E. Lehrbuch der pathologischen Gewebelehr, mit Einschluss der pathologischen Anatomie. Engelmann, Leipzig, 1886, 2nd Aufl., pp. 343–349.
8. Hertz, H. In: Ziemssen's Handbuch der speciellen Pathologie und Therapie. Vogel, Leipzig, 1874, Band 5, pp. 334–388.
9. Eppinger, H. Das Emphysem der Lungen. *Vrtljschr. prakt. Heilk.,* 1876, **4,** 1–80.
10. Kläsi, C. Anatomische Untersuchungen über das Entstehen des vesiculären Lungenemphysems. *Virchows Arch. path. Anat.,* 1886, **104,** 353–381.
11. Orth, J. Lehrbuch der speciellen pathologischen Anatomie. A. Hirschwald, Berlin, 1887, Band 1, pp. 493–499; 538–546.
12. Virchow, R. Emphysema pulmonum. *Berl. klin. Wchnschr.,* 1888, **25,** 1–6.
13. Kohn, H. N. Zur Histologie der indurirenden fibrösen Pneumonie. *München med. Wchnschr.,* 1893, **40,** 42–45.
14. Henle, J. Handbuch der systematischen Anatomie des Menschen. F. Vieweg u. Sohn, Braunschweig, 1873, Band 2, pp. 278–298.
15. Hauser, G. Ueber die Entstehung des fibrinösen Infiltrates bei der croupösen Pneumonie. *Beitr. path. Anat.,* 1894, **15,** 527–542.
16. Macklin, C. C. Pulmonic alveolar vents. *J. Anat.,* 1934–1935, **69,** 188–192.
17. Macklin, C. C. Alveolar pores and their significance in the human lung. *Arch. Path.,* 1936, **21,** 202–216.
18. Loosli, C. G. Interalveolar communications in normal and in pathologic mammalian lungs. *Arch. Path.,* 1937, **24,** 743–776.

19. HANSEMANN, D. Ueber die Poren der normalen Lungenalveolen. *Sitzungsb. d.b. preuss. Akad. d. Wissensch. zu Berl.*, 1895, **44**, 999–1001.

20. SUDSUKI, K. Ueber Lungen-Emphysem. *Virchows Arch. path. Anat.*, 1899, **157**, 438–457.

21. HANSEMANN, D. Untersuchungen über Entstehung des Lungenemphysems nach Präparaten des Herrn Sudsuki aus Tokio. *Berl. klin Wchnschr.*, 1899, **36**, 437–439.

22. EPPINGER, H., and SCHAUENSTEIN, W. Krankheiten der Lungen. *Ergebn. allg. Path. u. path. Anat.*, 1902, **8**, 267–365.

23. RIBBERT, H. Lehrbuch der speciellen Pathologie und der speciellen pathologischen Anatomie. F.C.W. Vogel, Leipzig, 1902, Aufl. 1, pp. 406–411.

24. TENDELOO, N. P. Studien über die Ursachen der Lungenkrankheiten. J. F. Bergman, Wiesbaden, 1901–1902, 480 pp.

25. SPALTEHOLZ. Diseases of Bronchi, Lungs and Pleura. In: Nothnagel's Encyclopaedia of Practical Medicine. W. B. Saunders & Co., Philadelphia and London, 1903, p. 263.

26. ORSÓS, F. Über das elastische Gerüst der normalen und der emphysematösen Lunge. *Beitr. path. Anat.*, 1907, **41**, 95–121.

27. ORSÓS, F. Die Gerüstsysteme der Lunge und deren physiologische und pathologische Bedeutung. *Beitr. Klin. Tuberk.*, 1936, **87**, 568–609.

28. LOESCHCKE, H. Die Morphologie des normalen und emphysematösen Acinus der Lunge. *Beitr. path. Anat.*, 1921, **68**, 213–223.

29. LOESCHCKE, H. Ueber das Lungenemphysem in Tagang der südwestdeutschen Pathologen in Mannheim, 21 u. 22 mai, 1922. *Centralbl. allg. Path.*, 1922, **33**, 1–2.

30. LOESCHCKE, H. Atmungswege und Lungen. 2. Storüngen des Luftgehalts. B. Das Lungenemphysem. In: Handbuch der speziellen pathologischen Anatomie und Histologie. Henke, F., and Lubarsch, O. (eds.) J. Springer, Berlin, 1928, Band 3, Teil 1, pp. 612–700.

31. LOESCHCKE, H. Pathologie des Emphysems. *Ztschr. wissensch. Bäderk.*, 1928, **3**, 116–136.

32. LAGUESSE, G. E. Sur les pores interalveolaires du poumon humain. *Arch. sc. méd.*, 1927, **51**, 45–57.

33. LETULLE, M. L'emphysème pulmonaire. Ses lésions; leur histopathogénie. *Arch. méd.-chir. de l'app. respir.*, 1928, **3**, 89–107.

34. ANTONIAZZI, E. Observationi sulla morfologia e la patogenesi dell'enfisema polmonare degli apici. *Lotta contra la tuberc.*, 1934, **5**, 257–262.

35. ANTONIAZZI, E. Modificazione dello stroma connettivo-elastico del polmone nell'enfisema polmonare cronico. Loro rapporti con la patogenesi e le forme cliniche della malattia. *Riv. pat. e clin. tuberc.*, 1934, **8**, 101–109.

36. LUISADA, A. Über Lungendynamik. *Ergebn. inn. Med. u. Kinderh.*, 1934, **47**, 92–184.

37. HARTROFT, W. S. The microscopic diagnosis of pulmonary emphysema. *Am. J. Path.*, 1945, **21**, 889–903.

38. BEZANÇON, F., and DELARUE, J. Structure, remaniements et mode de formation des "bulles" d'emphysème pulmonaire. *J. franç. méd. et chir. thorac.*, 1947, **1**, 209–235.

39. HEPPLESTON, A. G. The pathological anatomy of simple pneumokoniosis in coal workers. *J. Path. & Bact.*, 1953, **66**, 235–246.

40. MENDELSSOHN, A. Der Mechanismus der Respiration und Cirkulation oder das explicirte Wesen der Lungenhyperämien. B. Behrs, Berlin, 1845, 384 pp.

41. GAIRDNER, W. T. On the pathologic states of the lungs connected with bronchitis and bronchial obstruction. *Monthly J. M. Sc.*, 1851, **13**, 2–19; 238–254 (also 1850, **11**, 122–138; 230–246; and 1851, **12**, 440–453).

42. GORDON, I. The mechanism of hypertrophic pulmonary emphysema. *Dis. Chest*, 1944, **10**, 180–189.

43. FREUND, W. A. Zur Histologie der Rippenknorpel im normalem und pathologischen Zustande. A. Gosohorsky, Breslau, 1858, 65 pp.

44. FREUND, W. A. Der Zusammenhang gewisser Lungenkrankheiten mit primären Rippenknorpelanomalieen. F. Enke, Erlangen, 1859, 127 pp.

45. VILLEMIN, J. A. Recherches sur le vésicule pulmonaire et l'emphysème. *Arch. gén. méd.*, 1866, **6**, 385–405.

46. ISAAKSOHN. Pathologisch-anatomische Veränderungen der Lungengefässe beim Emphysem. *Virchows Arch. path. Anat.*, 1871, **53**, 466–469.

47. THIERFELDER, F. A. Atlas der pathologische Histologie mit erklärendem Text. Fues, Leipzig, 1872, Lief. 1, Tafel VI.

48. GRAWITZ, P. Ueber Lungenemphysem. *Deutsche med. Wchnschr.*, 1892, **18**, 201–202.

49. WIESEL, J. Der heutige Stand der Lehre von der Arteriosklerose (Atherosklerose) und ihre medikamentöse Behandlung. *Wien klin. Wchnschr.*, 1909, **22**, 401–408; 455–461.

50. TENDELOO, N. P. Lungendehnung und Lungenemphysem. *Erbegn. inn. Med. u. Kinderh.*, 1910, **6**, 1–28.

51. LOESCHCKE, H. Ueber Wechselbeziehungen zwischen Lunge und Thorax bei Emphysem. *Deutsche med. Wchnschr.*, 1911, **37**, 916–921.

52. MÜNZER, E. Die Erkrankungen der Herzgefässystems im Lichte moderner Untersuchungsmethoden. *Zentralbl. Herzkrankh. u. Gefässkr.*, 1913, **5**, 484–502.

53. MÜNZER, E. Gefässklerosen. Sklerosen der Arterien und Arteriolocapillaren im Gebiete der Aorta and Arteria pulmonalis. *Ergebn. ges. Med.*, 1923, **4**, 162–207.

54. ENGELEN, P. Sklerosen im Gebiet der Arteria pulmonalis. *Deutsche med. Wchnschr.*, 1923, **49** (ii), 1015–1016.

55. MILLER, H. R. Sclerosis of the pulmonary artery and its branches. *M. Clin. North America*, 1925–1926, **9**, 673–716.

56. WINTER, D. Ueber die Entstehung, Bedeutung and Verhütung des chronischen Lungenemphysems. *Monatschr. Ohrenh.*, 1913, **47**, 370–384.

57. BARD, L. De la pathogénie de l'emphysème pulmonaire diathésique. *Ann. méd.*, 1925, **17**, 201–208.

58. BARD, L. La pathogénie et les formes cliniques de l'emphysème pulmonaire chronique. *Arch. méd.-chir. de l'app. respir.*, 1928, **3**, 108–124.

59. KOUNTZ, W. B., and ALEXANDER, H. L. Nonobstructive emphysema. *J.A.M.A.*, 1933, **100**, 551–555.

60. CHRISTIE, R. V. The elastic properties of the emphysematous lung and their clinical significance. *J. Clin. Invest.*, 1934, **13**, 295–321.

61. CHRISTIE, R. V. Emphysema of the lungs. *Brit. M. J.*, 1944, **1**, 105–108; 143–146.

62. KOROL, E. Pulmonary emphysema in tuberculosis. *Am. Rev. Tuberc.*, 1938, **38**, 594–605.

63. KOROL, E. Observations on cystic and bullous emphysema of the lungs: a study of 100 cases. *Dis. Chest*, 1947, **13**, 669–672.

64. FLEISCHNER, F. G. The pathogenesis of chronic substantial (hypertrophic) emphysema. *Am. Rev. Tuberc.*, 1950, **62**, 45–57.

65. CUDKOWICZ, L., and ARMSTRONG, J. B. The bronchial arteries in pulmonary emphysema. *Thorax*, 1953, **8**, 46–58.

66. ABBOTT, O. A.; HOPKINS, W. A.; VAN FLEIT, W. E., and ROBINSON, J. S. A new approach to pulmonary emphysema. *Thorax*, 1953, **8**, 116–132.

67. RAPPAPORT, I., and MAYER, E. Emphysema and the senile lung. *J. Am. Geriatrics Soc.*, 1954, **2**, 581–591.