"ENDOTHELIOMA" OF THE PLEURA

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INTRODUCTION

Perhaps as much because of the confusing character of the clinical phenomena, as of the rather striking appearances revealed after death, supposed primary malignant tumors of the pleurae have consistently appealed to medical writers as worthy of study and report. Further stimulus to investigation of this somewhat peculiar group has been furnished by the clearly apparent wide diversity of concepts as to derivation, or genetic significance, of these tumors. Rarely have the students of any other subject in medical science propounded such a bewildering array of contradictory theories, often without due allowance either for the limits of our knowledge or for the demands of good logic. Hence it must be granted that, while discussion of this subject may have certain practical applications, by far the more important considerations are wholly theoretical. So widely related, however, are these theoretical relationships, and so fundamentally important are the conclusions which may be reached, that any review which attempts to clarify or harmonize these conclusions has full justification for the effort.

It is quite true that such efforts usually result in the formation of a new group, or a new classification, and an already involved nomenclature is only further obscured. The less hesitation therefore accompanies this presentation of my study, because not only is no new name proposed, but, for reasons which seem sufficient, I am strongly suggesting dropping from the list of tumors a term which has never given any real service nor ever been satisfactorily employed. I hope, then, that the conceptions with regard to certain classifications of tumors may be simplified, not complicated, and that the necessary empiricism of earlier

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years may be more completely clarified by such generalizations as appear justifiable.

HISTORICAL NOTES

Among the physicians of ancient times, primary diseases, either of the pleurae, or of the lungs, were not recognized as separate entities. According to Wolff the first reference to tumors of the pleura was made by Joseph Lieutaud, who may be regarded as the founder of pathologic anatomy in France. In 1767 he published a work which contains accounts of about 3000 postmortem examinations. In this he mentions a boy who suffered from marked dyspnea following trauma, and who, at the postmortem, showed fleshy masses adherent to the pleurae and the ribs. In a second instance, a tumorous growth in the right chest had perforated the diaphragm. Broussais (1806) attributed thickening of the pleura and hemorrhagic exudate to tuberculosis, but Laennec (1819) ascribed some of these cases to cancer. He says: "Le plèvre comme toutes les membranes sèreuses et même les muqueuses, peut éprouver une alteration telle dans ses propriétés vitales, qu'elle vienne à secrèter une matière cancéreuse, au lieu de la sérosité qu'elle fournit naturellement." He thus affirms the primary character of certain tumors of the pleura, and even in this early period, although perhaps unwittingly, commits himself to the theory of the epithelial nature of the pleural cells.

Tumors of the pleura were also described by Hache (1834) and Charcelay (1837), but the possibilities of any accurate diagnosis or classification were necessarily limited. Their descriptions disregard the probable secondary character of the pleural growths, and also strongly suggest that they were really dealing with sarcomas, a group not then recognized. Nevertheless these reports show how strong an appeal for publication was made by the discovery of malignancy in the pleural cavity.

The majority of the writers of this period were content to designate all growths of the chest cavity as lung cancers, and little attempt was made to separate tumors of the pleura or mediastinum from those in the lung. This tendency is illustrated by the writings of Van Kleffens (1841), Watson (1841) and Canstatt (1843).
Menardière states that Andral (1837) described cancer of the pleura as occurring in small isolated nodules, or in large masses filling the entire cavity, and diagnosed a tumor of the latter type, which penetrated the chest wall and appeared beneath the skin, as an encephaloid cancer.

Herzog (1839), Gallardi (1839) and Gintrac (1841) all mention a disease of the pleura occurring as a primary cancerous tumor which spread out as deposits in the subserous connective tissue, showed a bloody exudate, and was designated by the term "Markschwamm." However, in each of these cases, another cancer, usually of the breast, was also present, and the pleural condition was manifestly secondary.

In one of his earlier treatises on pathologic anatomy, published in 1843, von Rokitansky actively opposes the idea of primary cancer of the pleura, and says in effect that pleural cancer always is secondary to a primary focus elsewhere. This conclusion was also reached by Wintrich (1854) and Wunderlich (1856).

Musset (1850) reported to the Anatomical Society of Paris a case in which the right pleura contained numerous cancer nodules, some pedunculated and some cauliflower-like. Both lungs had numerous small growths. In spite of the fact that there was a huge "encephaloid" cancer in the body of the uterus, Lebert, who examined these specimens, pronounced the case one of primary cancer of the pleura, stating that this was only the third case of its kind he had seen in over 500 postmortem studies. He frankly admitted that secondary tumors of the pleura were very common, but because of certain peculiar cells this growth contained, he regarded it as an exception to the general rule. He believed that the nodules in the lung were secondary to those in the pleura, although there was no metastasis to the mediastinal or bronchial lymph nodes. The following year (1851) Lebert mentioned two cases, in one of which the "multiple cancers of the pleura" had distended the lymph vessels as if they had been filled by artificial injection. The second resembled that of Musset's, and may have been the same case.

In 1852, Vidal exhibited, also before the Anatomical Society of Paris, the specimens from a case of cancer of the pleura. The
lung was not involved, but the growth was in two nodes at the mediastinum, and the liver contained one nodule. Broca had made a microscopic examination and pronounced it cancer. Urag (1857), under the title of "A case of pleural cancer," described nodules in the right pleura with a hemorrhagic exudate, and then finally mentioned that the scrotum contained a cystic cancer "the size of a child's head." This is an early instance of the practice of indicating by title or text that the pleural involvement is primary, and then describing in some other organ a malignant growth which much more reasonably represents the original tumor.

In the intervening years before 1870, I have been able to find only one more important case, that reported by Lepine in 1869. He diagnosed the condition as primary carcinoma of the pleura, but the patient was a child of ten years, and the microscopic studies were quite imperfect. However, judged only from the data submitted by the author, the diagnosis given rests on fully as secure ground, as the majority of all such diagnoses in all the literature up to the present time.

REVIEW OF MODERN LITERATURE

In the minds of most writers on this subject, the real clarification of our knowledge begins with a publication by Wagner in 1870 of the detailed description of a lesion which he designated as "Das tuberkelähnliche Lymphadenom." He described many examples of what he believed, and evidently with good reason, represented the miliary lesions of tuberculous pleuritis, which lesions he chose to call "Lymphadenoma." In one particular case, however, that of a woman aged sixty-nine years, there was thickening of the right pleura to two or three times the normal, and microscopic examination revealed spaces filled with epithelial-like cells of varying sizes and shapes. These spaces suggested to Wagner "veränderte Lymphgefäße," and the lesion an "epithelial cancer." No metastasis was noted, but in the apex of the right lung was a circumscribed mass "the size of an acorn." It was not until four years later that Wagner in the sixth edition of

1 Wagner's classic description likened the appearance of the surface of this thickening to the trabeculated hypertrophied bladder.
his "Handbuch der allgemeine Pathologie" discussed the subject of "der Endothelkrebs," and definitely assigned to this group the tumor just described.

The attention of others has not been attracted perhaps so much by the fact of Wagner's report of a single case, or by the name he gave to the condition, but by his description of the lymph-channels crowded with tumor-cells. Hence, in Eberth's report of a so-called epithelioma of the pia and lung, made the same year (1870), the reference to "anastomosing tubes in the pleura, lined with cylindrical epithelium," and his conclusion that the starting point of the process was "eine beschränkte Cancroidbildung in den Lymphgefässen oder vielleicht auch im Bindegewebe der Bronchien und der Pleura," was sufficient evidence to later writers that in reality this was another example of a so-called endotheliomatous new growth. For many years the confirmation of Wagner's observation in respect to lymph-channels alone was often wholly sufficient to justify this diagnosis. The fact that Eberth himself believed, and correctly, that he was dealing with a primary carcinoma of the lung seems to have received little consideration.

Two years later (1872), in a discussion of cancers of the lung, Perls described a case in which, in spite of softened cancer nodules in the lung with metastasis widely spread in the body, because the pleurae were thickened and showed irregular channels containing cells with epithelial appearances, he called the process "pleuritis carcinosa." In 1874 Schottelius following the same line of reasoning, named a quite similar tumor, "lymphangitis carcinomatodes." This same year, MenardiGre presented a thesis in which, disregarding his title, which indicated that his study was concerned with pleural cancers, his principle case was diagnosed as fibrosarcoma of the pleura. Two other cases without unusual features are called primary cancers of the pleura. He was evidently unfamiliar with the reports of the contemporary German writers on this subject. He cites both Niemeyer and Jaccoud as among those who assert that cancer is never primary in the pleura.
According to Darolles (1874) the cancer found in his case arose in the left pleura and was secondary in the left lung, both kidneys, the liver, the bodies of the vertebrae and the triceps muscle of the left arm. Although nodules were present in the bronchial walls, the pleural involvement was so prominent that Darolles was led into an error of deduction, which, crude as it may appear, is followed with almost unvarying regularity by succeeding writers, even to the present time.

Thierfelder (1875) was much impressed by Wagner's work and discusses at some length in his "Atlas" two cases which he designated as "primärer (endothel) Krebs der Pleura." He asserts his belief that "the growth of the cancer does not proceed by the gradual transformation of many endothelial cells, but by a huge proliferation of only a few." Thierfelder was one of the shrewdest observers and clearest thinkers of his time, and his general law of cancer growth has never been successfully assailed; but, in his second case, that of a man aged thirty-five years, he derived a tumor of the liver from a primary left-sided "Pleurakrebs" with metastasis to the lungs, as well as other organs, and assumed that it originated in the endothelium of the lymph vessels.

Eppinger (1875) mentions an endothelioma of the pia which metastasized to the pleura, lungs, epicardium and peritoneum. The larger size (up to 4 mm.) of the nodules in the pia, as well as their greater frequency on both brain and spinal cord, seem to have largely governed his conclusion as to their primary site. He believed they originated from the blood-vessel endothelium. In the following year (1876) he reported a case of tumor of the parietal and visceral layers of the left pleura, apparently arising from lymph vessel endothelium, and presenting growths in the liver, kidneys and spleen. On the visceral surface were small cysts which he concluded represented projecting lymph channels. He was the first to apply the diagnosis of endothelioma to tumors of the pleura.

In a general review of endothelial carcinomas, Schulz (1876) described a case from Wagner's clinic, giving a diagnosis of primary endothelial carcinoma of the pleura, but denominating
the cells as epithelioid, and expressing the opinion that the normal endothelial cells in the involved lymph-channels had been replaced by tumor cells. He further made the significant generalization that "die Endothelzelle ist ja überhaupt nur eine höher entwickelte Bindegewebszelle." Birch-Hirschfeld (1877) also regarded the endothelial new growths as belonging to connective tissue tumors, and he proposed the hypothesis that they represented a productive inflammation produced by infectious agents. At the other extreme is Demange (1879), who described a colloid carcinoma with nodules containing a gelatinous fluid, which he believed to be primary in both pleurae.

Somewhat unusual for this period (1878) is the frank admission by Boegehold that, although his patient exhibited all the signs, symptoms and pathologic appearances of endothelioma of the left pleura, still the primary growth was carcinoma of the stomach. This in contrast to Darrach (1878), who entitled his paper "Cancer of the pleura and uterus," and then described an amputation of the breast for carcinoma with recurrence in eight months and a second operation, and, at death, six months later, a growth in the scar as well as pleurae, lungs and most of the other organs of the body.

Böhme's (1880) primary tumor of the pleura, diagnosed by him a "sarcocarcinoma," seems closely to resemble those types usually called endothelioma, and is so accepted by Neelsen and others. The title only serves to illustrate the confusion incident to the presentation of this peculiar group. In a general study of diseases of the pleura, Kauders (1880) reports a case showing multiple soft nodules on the right pleural surfaces and bloody fluid in the sac. Although nodules were also present in the right lung, as well as in the opposite lung and pleura, he called the tumor a medullary carcinoma, primary in the pleura. He cites Rokitansky as authority for the occurrence of such tumors, although he admits that most authors believe that carcinoma of the pleura is never primary. He refers to two similar cases reported by Meissner in the previous year.

With the report of a typical case of "Endothelkrebs" of the pleura, Neelsen (1882) advanced the opinion, contrary to the
idea of Thierfelder, that the tumor represented a disease of the entire lymph vessel system, which condition he designated as "lymphangitis carcinomatodes." Nodules in the liver and muscle were for him independent growths. In the metastasis from the primary tumor, he found "the typical histological picture of cancer." He accounted for the glandular appearance of the lung nodules by "eine Umwandlung und Wucherung der Gewebselemente der Lunge selbst." He emphasized the presence in the tumor cells of a "colloid" degeneration which was not to be ascribed to fat droplets, but which he believed represented a phase of the cytoplasm of the endothelial cells. The tumor cells, according to his theory, spring not only from the endothelial cells of the lymph vessels, which cells he derives from the connective tissues, but also from the "flachen, sogenannten fixen Bindegewebskörperchen." He approaches the ideas of Birch-Hirschfeld in likening the tumor growth to an inflammatory process, "eine sogenannte Infectionsgeschwulst." His effort to explain what in all probability represented mucoid globules, as well as his endeavor to clarify the quite evident inconsistency of his conclusion, testify to the logical difficulties of his position. In his discussion of the literature, only seven cases, including one reported by Malassez (1876) of an encephaloid cancer of the lung, are recognized as authentic endothelial carcinomas of the lungs and pleura, thus hinting at the necessity for regarding such tumors of either tissue as closely related processes.

Without identifying the character of the growth, Schreiber (1882) describes a carcinoma of the right pleura which penetrated the seventh intercostal space and appeared beneath the skin. A similar happening from a sarcoma is also mentioned. Unverricht (1882) takes a very decided stand against the possibility of cancers developing primarily in the pleurae. His quotation from Fräntzel is particularly definite: "Sarcome und Krebse der Pleura kommen niemals primär, sondern nur secundär. . . ." He emphasizes a fact earlier mentioned by Trousseau, that neither in the character of the bloody fluid usually to be obtained from the chest in these cases, nor in the other signs or symptoms, can we absolutely determine the nature of the disease process.
After mentioning the cases of Vidal and Menardière, he then reports one of his own in which, following aspiration, tumor nodules developed under the skin at the site of the punctures, and at autopsy were found connected with the growth on the pleura. The further description closely resembles that of tumors usually designated as primary endotheliomas of the pleura, except for the presence of a pulmonary nodule "the size of a dove's egg," which he regards as the primary growth. He admits that clinically these processes are essentially "carcinomatous pleuritis, or better, a pleural carcinomatosis," although pathologically they are carcinomas of the lung. In a treatise on pathology published seven years later (1889) Lancereaux also expressed the opinion that carcinomas of the pleura are never primary.

A very large and useless burden to our medical literature is illustrated in a report made by Ayrolles (1884) to the Anatomical Society of Paris. His title is "Cancer of the pleura." The clinical diagnosis was carcinoma of the lung. The pathologic diagnosis, from examination of an excised lymph-node, was "sarcoma or carcinoma," and after death there was found, besides a growth in the left pleura and nodules in the right lung, an ovary "the size of an orange." No discussion or microscopic study is given to assist the bewildered reader.

Collier's (1885) case is diagnosed without further analysis as "primary malignant disease of the pleura," and, so far as I am aware, is the first study of such a condition reported in English. Collier mentions in his microscopic description "flattened epithelial cells concentrically arranged in alveolar spaces," and says that the metastasis in the abdominal lymph-nodes exhibited "colloid" degeneration. He does not describe the lungs, but found the mediastinal lymph-nodes involved. Hofmokl (1885) concluded that a single mass, "the size of a man's head," in the right chest of a boy of seven was an endothelial sarcoma, springing from the endothelium of the pleura or the lymphatics. The diagnosis in this case was further clouded by Bloch (1905), who suggested that it was a tumor intermediate between a true sarcoma and endothelioma.
Dutil's (1887) report concerned "un cas de cancer primitif de la plèvre et du pericarde" and was diagnosed a "cancer encéphaloïde." He made no reference to endothelial cells. In the following year (1888) Deruschinsky described a "primary sarcoma of the pleura." Nodules up to "the size of a hazelnut" were present in both lungs, and a tumorous process was present in several ribs. He asserts that his tumor resembled those seen by Schulz and Malassez, and intimates that the term "sarco-carcinoma" employed by Böhme might be used. He says that Klein and Schervinsky of the Golizyn Hospital in Moscow called this tumor a "sarcoma globocellulare." The confusion as to nomenclature, as well as conceptions of origin, could find no better single illustration than this case. In Pitt's (1888) case, microscopic nodules were present in the submucosa of the jejunum. He says that the apparent absence of any other primary growth forced him to conclude that it arose from the pleura. His diagnosis was not endothelioma, but cancer.

Leplat (1888) opens his thesis on pleuro-pulmonary cancer by grouping together all tumors of lungs, pleura and mediastinum, thus going back to what Wolff has designated as "the premicroscopic times." His only concession to more modern views is the opinion that primary carcinomas of the pleura "sont très peu nombreux."

The first two cases of "endothelioma of the pleura," diagnosed as such, to be published in American medical writings, were presented by Biggs (1890) to the New York Pathological Society. Both represented classical examples, with hemorrhagic fluids, thickened pleurae, nodules in lymph-nodes and other organs and nodules in lungs. There was no theoretic discussion of the difficulties mentioned by previous writers.

Up to this point, Wagner's conception of lymph channels filled with tumor cells governed the major number of theories as to the origin of these tumors. So far as can be learned, Engelbach (1891) was the first to raise the question as to whether in his case the tumor, which was diagnosed as an "endothelial carcinoma" of the pleura, arose from the endothelium of the lymph vessels, or from the cells lining the serous surfaces. As
we shall see later, this point, from certain theoretic considerations, is of supreme importance.

In reporting his case of primary cancer of the pleura, Rossier (1893) discusses the point which had attracted the attention of numerous earlier writers on this subject (Perls, Schottelius, and Schwenninger), namely, the differentiation of a true cancer metastasizing into lymph channels and one which supposedly arises from the lining cells of these channels. He believed with the others that the latter growth could be identified by the fact that the endothelial cells were involved, while the metastasis left them free and intact. With Neelsen, Rossier concludes that the tumors of the type reported by him start as a general growth and calls his tumor a "cancer diffus." However, the cells in this tumor are described as resembling those of certain gelatinous carcinomas, and he gives the impression that he is dealing with genuine cancer, which, only because of pleural involvement and lymphatic distribution, he is forced to call endothelioma.

Siegert (1893) again emphasizes the differentiation of endothelioma of the pleura and cancer by alleging that, in the latter, the endothelium does not take an active part, while in the former it does. Not one of the authors who take this view has established any trustworthy criteria for making the required distinction between the two types of lymphatic channels. The point is worthy of continued emphasis, as denoting on what a slender thread, in the minds of many students of this subject, depends their final conclusion as to the proper classification of these tumors.

In a clinical study of primary carcinoma of the lung with hemorrhagic pleurisy, De Renzi (1893) differentiates carcinoma of the lung and sarcoma of the pleura. He thus illustrates the tendency in Italian literature to treat all primary malignant tumors of the pleura as sarcomas. I have been unable to trace the development of this conception, and, indeed, it would appear to have arisen rather from a lack of close study of tumor genesis, than from any carefully considered and logically grounded opinion. Nevertheless, such a view may eventually prove to be the only possible one which can be successfully defended.
Petriaux (1893), in a rather superficial review of tumors of the pleura, quotes Marfan ¹ to the effect that true endotheliomas are really sarcomas or embryonic fibromas, and that the cases called primary carcinomas arise from the subpleural alveolar epithelium or terminal bronchial epithelium. In Fraenkel’s case, in which the lymphatics seemed to furnish a primary source, Marfan inquires whether “cet auteur n’a pas été trompé par l’envahissement secondaire des voies lymphatiques.” The importance of Marfan’s suggestion is emphasized in the description which Gebhardt (1894) gives of his tumor. He mentions spaces in the cell nests suggesting glandular formations, and also masses of mucus-like substance, such as is seen in the “colloid carcinomas” arising from bronchial mucus glands. This suspicion of glandular origin is further strengthened by statements that the bronchial wall at one point was thickened, as well as that many tumor nodules were present in the substance of the lung on the affected side. The author, in spite of these facts, concludes that it is clear that the origin of the tumor was from the lymph vessel endothelium. He asserts that two proofs of the origin of these tumors are necessary: first, that the cells arise from the lymph vessel endothelium, and second, that there shall be found no other epithelial-cell tumor process.

Teixeira de Mattos (1894), in agreement with Schulz, Neelsen and others, regarded the process in his case as a generalized one, the entire pleural tissue representing the primary source. However, here also there were nodules in the lung substance and, on microscopic search, tumor cells in the alveolar walls. Pirkner (1895) found involvement of the peritoneum and pericardium as well as of both pleurae. Although the cells resembled epithelium and formed gland-like spaces, there was no other primary cancer found. This fact, with an absence of metastasis to lymph-nodes, constituted for him the sole differentiation of his tumor from a true carcinoma. “Es gleicht . . . im anatomischen Bilde durchaus einem typischen Medulläarcinom.” His conclusion and admissions assume more importance because he

¹ “Les tumeurs primitives de la plèvre décrites par Wagner sous le nom de carcinome endothélial ou endotheliome doivent probablement être classées dans l’ordre des sarcomes,” p. 541.
believes that endothelial cells are essentially connective tissue elements, and that these growths represent a diffuse process arising from “die Bindegewebe der Pleura.”

Triviot (1895) makes the significant comment that some of the earlier authors disregarded primary lesions, as for example, Leplat, in his third case, passed over a small lesion of the intestine, and Pitt, a submucous nodule of the jejunum. Triviot then draws this very important generalization: “Il n’est pas rare, en effet, qu’une tumeur cancéreuse minuscule commande des metastases exubérantes.” Unfortunately he does not press this rule to its logical conclusion and, in spite of his quotation from Jaccoud to the effect “que le cancer de la plèvre n’est jamais primitif,” he says that primary malignant tumors of the pleura comprise three groups, sarcomas, endotheliomas and carcinomas. His ten illustrative cases are all copied from the literature and add nothing to the clarity of the subject.

The difficulties of diagnosis encountered by Brosch (1895) would have been justified only in the days before the microscope was available. He found tuberculous lesions of the right lung and tumors on the right pleura with caseous masses, as well as involvement of the right auricle. In spite of such clear signs, he made a diagnosis of endothelioma of the right pleura. His report was unaccompanied by microscopic studies or discussion.

A sensible and perhaps useful distinction is made by Cardarelli (1895) who, under the title “Primary sarcoma of the pleura,” discusses the clinical signs and frequency of primary malignant disease of the pleura. He states quite clearly that the disease is primary only in the clinical sense, while in anatomical terms it is almost always secondary and often with a comparatively obscure primary source.

Riva (1895), in a careful study of a tumor found in the right pleura of a negro, and diagnosed by him an endothelial carcinoma of the pleura, followed closely the ideas of Wagner and his adherents. He quoted Niemeyer and Jaccoud, however, as stating that all cancers of the pleura are secondary to those of the breast, lung or other organ, and he gives no particular support for his own conclusions.
In a general critical review of the whole group, Volkmann (1895) noted that in some endotheliomas the epithelial characters of their cells and their tubular and alveolar arrangement gave a very carcinomatous-like appearance. Hansemann (1896) admitted the difficulties embraced in the words "endothelium" and "endothelioma" and suggested dividing the tumors into classes, corresponding to their various modes of behavior. The result is an astonishingly unsuccessful effort at simplicity. When one staggers through the array of conceptions, marked by such titles as "Carcinoma endotheliale," "Sarcoma endotheliale," "Carcinoma sarcomatodes endotheliale," "Endotheliale Tumoren mit specifischen Entwickelung des Stromas" and "Adenoma endotheliale," it is not difficult to appreciate the force of Volkmann's (1896) reply when he says that no good purpose is served in attempting to evade the simple term "endothelioma" by qualifying it with "carcinoma" and "sarcoma," which distinctly these growths are not. Volkmann grants that the term includes many tumors of different nature, but in the present state of our knowledge this confusion cannot be avoided.

Italian writers on tumors of the pleura are accustomed to mention Zagari's (1896) elaborate treatise, but this work is rendered almost valueless for our purposes because the author combines malignant growths of the lungs and pleura in one group, professing his inability to separate them clinically, and recognizing no useful purpose in making pathologic distinctions. He barely mentions the endotheliomas, and of his seven reported cases only one is classified as a primary tumor of the pleura. He declines to identify this growth and quite evidently bases his diagnosis solely on the fact that the greatest amount of new tissue was in the left pleura, although the peritoneal cavity, the liver, and even the left lung, were also involved. There is no discussion of reasons for diagnosis and, although the histologic study disclosed epithelial-like cells, there is wholly lacking any attempt to indicate a group to which the growth should be assigned.

In the fifth edition of his pathologic anatomy, Birch-Hirschfeld (1896) again insists that these tumors are derived from the
lymph-vessel endothelium and the endothelial cells of the connective tissue, both of which, he asserts, are of equal importance. He expresses in different words an idea already familiar to us, when he says, “die Neubildung nicht von einem oder mehreren umschriebenen Herden des primär befallenen Organes ausgeht, sondern dass ein grosser Theil des Lymphgefass Systems in der ganzen Ausdehnung des Gewebes nahezu gleichzeitig erkrankt.” Naturally, having reached this point, he proceeds to the theory held by Neelsen, since a logical conclusion to the reasoning of both is the idea that such a process is probably not a tumor, but a productive inflammation caused by an infectious agent, which brings about a proliferation of endothelial cells of the lymph vessels and the connective tissue. This, or a similar theory, is really necessary to explain and harmonize the etiologic relationships generally assumed for these tumors, and their adoption by these earlier writers is not nearly so difficult to understand as is the ignoring of them by the later students of the subject. A primary diffuse tumorous process of a serous cavity is just as puzzling at this time as it was then.

It is a rather strange fact that neither up to this time (1896), nor since, have any studies comparable to those on carcinomas and endotheliomas been made on that other group of malignant tumors of the pleura, the sarcomas. It is true that the earlier literature contains a considerable number of isolated instances of large fleshy tumors in the pleural cavities, some, especially after Virchow’s teachings were accepted; having been definitely pronounced sarcomas. Notable among the more authentic reports are those of Gordon (1874), Glynn (1881), Hofmoki (1883), Weichselbaum (1888) and Saundby (1889). But in none of these are questions of histogenesis or differential diagnosis either raised or discussed. Occasionally doubt is expressed by the author as to the proper classification of a given tumor as, for example, the “Sarccarcinoma” of Böhme. More often doubt as to the justification for the diagnosis given is raised in the reader’s mind by the description. Thus Riedinger (1888), in Billroth’s work on Surgery, reports the case of a woman aged fifty-six years, who had a hemorrhagic exudate in the right
pleural cavity and at the postmortem examination "das Sarcom war herdweise über die ganze Pleura ausgesät."

The description first given by Blumenau in 1892, and repeated four years later, is more acceptable as an example of primary sarcoma of the pleura. Occurring in a man aged twenty-three years, who had hemorrhagic fluid in the left pleural cavity, the tumor consisted of a soft mass weighing 7 pounds, firmly attached to the posterior chest wall and the spinal column, and almost completely filling the left cavity. Nodules projected from the main tumor and were attached to the diaphragm and the left lower lobe. The visceral pleura showed numerous small nodules and the thoracic vertebrae were invaded. Microscopically, it was a round cell sarcoma. The youth of the patient, the single large mass, with or without extensions or metastasis, and the microscopic picture, constitute the chief distinguishing features of this type of growth.

It is not my purpose to discuss in detail the remaining cases of this important and interesting group of tumors. Their sole interest for the present discussion, aside from the problems of differential diagnosis which they present, lies in the strong probability that they represent the sole primary malignant growth which may be properly attributed to the tissues of the pleurae.

One further case, however, studied by Warthin (1897), deserves consideration. The tumor was found in the right pleural cavity of a man aged forty-five years, and was accompanied by a hemorrhagic fluid. A diagnosis of a spindle-cell sarcoma was made by Warthin from a study of the cells in the fluid withdrawn by puncture. At the postmortem a soft friable tumor, reaching "3 inches" in thickness, was found attached to the mediastinal and anterior portions of the parietal pleura. There were no extensions or metastasis. A microscopic study revealed "spindle-cells grouped around thin-walled blood vessels. . . . That the tumor cells arose from the endothelium there can be no doubt." Warthin further concluded that "from its histologic structure the tumor should be styled a spindle-celled hemangiosarcoma; from its origin, it should be classed
with the endotheliomas.” That blood-vessel endothelium
should give rise to sarcomas, and lymph vessel endothelium to
carcinomas, is no worse a dilemma than other problems which
the proponents of pleural “endotheliomas” are called on to face.

This fact is illustrated in a discussion by Benda (1897), whose
case differed somewhat from the usual type because of the
presence of polypoid masses on the pleural surfaces. Accord-
ingly, he adopts the suggestion submitted by Engelbach and derives
his tumor from the surface layer of cells. However, micro-
scopically the cells had such characters and were arranged in
such gland-like formation that “die Geschwulst hat somit
durchaus den Bau eines Carcinomes.” Benda therefore boldly
accepts the logic of the situation and, in agreement with the
celom theory of the Hertwig brothers, regards the serosa of the
body cavities as embryologically a true epithelium, and hence,
tumors derived from it quite naturally must be carcinomas. He
calls his tumor a primary carcinoma of the pleura. Manifestly,
it is a strict requirement of such an interpretation that all these
tumors come from the surface cells of the serosa, and not from
the lymph-vessel or blood-vessel endothelium,\textsuperscript{1} or any other
element of the subserosal tissues. Consequently he devotes
considerable attention to showing that his tumor first clearly
establishes the derivation of this group from the surface layer.
The peculiar formation of the tumor masses and their differences
from those reported by Bostroem, Neelsen and others, who
derive their tumors from the lymph-vessel endothelium, con-
vinced him of the correctness of his views. He remarks that, in
respect to the differentiation of carcinoma from endothelioma,
the criterion of the relation of the contained cells to those lining
the lymph channels, apparently so definite in the minds of others
(Rossier, Siegert), seems to him difficult of application, inasmuch
as such a differentiation does not always hold. The ideas
expressed by Benda serve further to obscure, rather than to
clarify, the ontogenetic relationships of the whole group of
pleural tumors. But, at least, he is consistent in his reasoning,

\textsuperscript{1}Although Kolossow (1893) stated that vascular endothelium had all “die
Merkmale” of epithelium, Benda does not think that it has the same derivation as the
serosal cells.
and is the first to introduce for purposes of pathologic interpretation the results of what were then the newer theories concerning the embryology of the body cavities.

Glockner's (1897) review of this subject is often mentioned, perhaps rather because of the quantity than the quality of his statistical material. He tabulates from the literature seventy-five cases of what he accepts as primary "sogenannte Endothelkrebs der serosen Häute." These include, therefore, tumors of the peritoneum as well as of the pleura. The comparative freedom of the pericardium was noted. To this long list he adds sixteen new cases, involving either peritoneum or pleura alone, or both together. In the reports of his own cases, he derives the tumor cells from the endothelium of the lymph vessels, distinctly excluding the serosal or blood-vessel endothelium. He apparently accepts von Recklinghausen's suggestion as to the connective tissue origin of these cells, as well as their adopted (or adaptive) epithelial characters. Colloid or mucoid droplets in the cytoplasm, a high cylindrical form, and even adenomatous arrangements, sometimes with papillary outgrowths suggesting cystadenomas, were described. Quite manifestly some of his peritoneal tumors strongly imply primary ovarian or gastric carcinomas, whereas in "Neoplasmen der Pleura war die zugehörige Lunge immer auch gleichzeitig betroffen." He closes by confessing his inability to place these growths in their proper group, although he believes they are nearer to the sarcomas than to the carcinomas.

Weismayr (1897) significantly, and with good reason, emphasizes the difficulty of deciding whether any given tumor of the pleura is really primary in that tissue. "It can often happen," he says, "that carcinoma, for example in the stomach, can run a wholly occult course, and it should not astonish anyone if they are overlooked." This difficulty in locating the original

1 "Eine einschlägige Erkrankung des Pericards stand mir nicht zur Verfügung."

2 "Das oberflächliche Endothel mit Sicherheit als Ausgangspunkt für die Wucherung auszuschliessen sei."

3 "Diese Ausbildung können wir geschehen lassen durch eine Erweiterung der Saftkanälchen, resp. eine Verminderung des Grundsubstanzt. Hierbei würden wahrscheinlich die Bindegewebszellen zu den Epithelzellen der Lymphgefäße umgewandelt werden."
growth, he thinks, may lead to wrong conceptions with respect to primary neoplasms of the pleura. However, he accepts the hypothesis that true carcinomas can originate in the pleural cavity, and cites the cases of Menardière, Kauders, Schreiber, Collier and Benda as authentic examples. He also concedes the occurrence of the other two types, sarcoma and endothelioma, and refers to some of the authors already mentioned in this review. He then reports five cases of his own, but with such imperfect details and such scanty justification for his diagnosis that nothing is added to our knowledge.

A very typical case, diagnosed as "endothelial cancer," is reported by Bongert (1897). Besides a hemorrhagic exudate in the pleural cavity of a man aged sixty-three years, the entire pleural lining was markedly thickened and the hilus of each lung, particularly the left, was invaded along the peribronchial connective tissues. Microscopic examination revealed, in this latter location, strands and islets of cells with epithelioid characters, and in places the growth "eine sehr grosse Ähnlichkeit mit einem Karzinom hat." Bongert concludes that the probable origin is the endothelium of the pleura. He excludes, "mit Sicherheit," the lung itself as a primary source. He then asserts with Volkmann that "the endotheliomata, without doubt, should be classed with tumors of the connective tissue group."

In the acceptance of wrong premises, like many other writers on this subject, Bongert finds himself in a tangle of inconsistencies.

The Russian medical literature, so far as it has been available to me, adds nothing original to the conception of tumors of the pleura. Thus Młodziyewski (1897) reported to a medical society in Moscow the details concerning a man aged thirty-two years, who had a dense tumorous growth in the left pleural cavity, invading the pericardium. This tumor he called an endothelioma of the pleura, basing his opinion on the extensive involvement, and lack of any other primary focus. In discussion, his colleagues disputed this view, one favoring the enlarged bronchial lymph-nodes, and another, the subpleural tissues, as primary sites.
Petersen's dissertation (1897) reviews seventeen cases of pleural endothelioma including one of his own, a man aged sixty-seven years, in whom the serous surfaces of the pleura, pericardium and peritoneum all contained nodules. The cells had an epithelial character and an alveolar arrangement, but as they were apparently in the lymph channels, he derived them from the lining endothelium. He felt compelled to admit that these growths more probably belonged to the sarcomas, and refers to the term "Desmoidcarcinom" used by Schottelius. Without discussion of the contradictory ideas involved, he prefers to adopt the simple term "endothelioma."

In Riedel's (1898) report of a case, he admits not only the presence of nodules in the lung, but further remarks with reference to the microscopic study: "Diese Bilder besitzen eine ausserordentliche Aenlichkeit mit den echten Carcinomen." This same resemblance furnishes the chief comment on the description of Podack's (1899) two cases—"Bilder, die ausserordentlich an Querschnitte von Drüsenschlächten erinnerten," "die durchaus den Bau tubulöser Drüsen vortäuschten," and so forth. He further adds that though the lungs were free, grossly, they were found on microscopic examination to be involved, a fact he believes true of a large number of published cases.

In reporting what he calls an endothelioma of the pleura, Butler (1898) describes a dense single mass in the left pleura weighing 11 pounds. He assigns this tumor quite properly, it would seem, to the connective tissue group, and briefly mentions the literature on primary sarcomas of the pleura. On the other hand, Lenhartz and Lochte (1898) emphasize the epithelial character of their tumor, and assert that in places it revealed itself as "a completely cancer-like structure." The arrangement of the cells suggested to them "a proliferating lymphangitis." They were able to collect only eighteen cases of this condition.

Pace (1899) returns to the days of Wagner and describes an example of generalized miliary tuberculosis of lungs and serous cavities, diagnosed at first an endothelioma, and only revealing
its true nature on microscopic examination. Pollman (1899) found difficulty in deciding whether the primary site, in a tumor occurring in a girl aged seventeen years, was in the spleen, lung or pleura, and also as to the nature of the growth. He finally concluded that even though it probably arose from the endothelium of the blood-vessels and spread along these channels, it was more like a connective tissue than an epithelial tumor. In spite of these questions he denominates the tumor “an endothelioma of the pleura and peritoneum.”

Closely corresponding to the more typical case is the one studied by Hessel (1900). Besides the thickening of the right pleura, nodules in the left pleura and metastasis to the neighboring lymph-nodes, there was a definite nodule in the left lung. Microscopically “schleimähnlicher Degeneration” was seen, and the picture presented bore a strong resemblance to that of an adenocarcinoma. He collected thirty-two cases, and analyzed them according to exudate, age, duration and so forth. He concludes that during life they cannot be distinguished from primary tumors of the lung. He is inclined to disregard the question of whether the lining cells of the pleura are epithelium or endothelium, inasmuch as the endothelium of the lymph spaces is manifestly a part of the process, and therefore, the designation “endotheliomata” becomes justified.

“Primary endothelioma of the pleura” is the title of a paper by Adler (1901). A gross tumor in the pleural cavity of a young man aged twenty-six years gave the impression of a sarcoma, and sections showed an alveolar arrangement. There was no evidence of origin from surface epithelium. He further reports a case of primary endothelioma of the lung, originating from the neoplastic proliferation of the connective tissue and the endothelium of the lymph spaces. He deplores the unfortunate compromising attitude of Hansemann, and suggests separation of endothelioma of the lung and pleura from carcinoma, and placing it in the group of connective tissue growths allied to sarcoma.

Many of the difficulties of interpretation of pleural tumors were encountered by Braun (1901). In his own case, a man of
thirty-eight years, with extensive involvement of the right pleura, there was also a carcinoma-like mass in both lungs and invasion of the bronchial lymph-nodes. However, the relatively greater extent of the growth in the right pleura led him to pronounce this as the primary growth, and the other nodules as metastases. But as the cells to him quite manifestly arose from the endothelium of the lymph channels, they could not be epithelial, in spite of the strong resemblance, and hence, also, could not represent carcinoma cells. The tumor must be a primary endothelioma. He says the seventy-five cases he found in the literature were like his, and closes by inferring that perhaps they really should be classified as sarcomas. Ferrio, who in 1901 discussed the diagnosis of tumors of the pleura by puncture of the chest, and with Bormans reported a case accepted as authentic by Bloch, made a more complete study of this and one other case in 1902 with Rovere. The usual picture was seen in the chest in each case, one a man of forty-nine years, and another of sixty-one years, and both on the right side. Although the cells were epithelial in appearance and in some places suggested gland formations, they were derived from the endothelium of the lymph vessels, and also in one case from the perithelial cells of the capillaries. The ideas of Benda were repudiated by these authors, who likened their cases to those described by Podack and Wagner.

Borrmann (1902), in his review, criticizes the basis on which numerous authors justified their diagnosis of endothelioma, namely, the relations of the tumor cells to the lining cells of the lymph channels. He agrees with Benda that no dependence can be placed on such criteria. True carcinomas growing in lymph channels may show every characteristic appearance of endothelial proliferation. He further adds that during the previous two years he had only described one blood-vessel endothelioma, and, except for psammomas, had seen no other tumor which he was willing to designate endothelioma.

Burkhardt's (1902) discussion of sarcoma and endothelioma, while not referring directly to tumors of the serosa, concludes that there is no clinical or pathologic distinction between true
sarcoma and endothelioma, and that the latter term should be dropped entirely. Rosenbach (1902) agrees with Neelsen that endotheliomas of the pleura are the ultimate consequences of an intense chronic inflammation. This opinion in his case is apparently based on the false notion that such tumors do not metastasize. The report of four cases by Delafield (1902) only serves to emphasize the fact, already frequently observed, that often the diagnosis rests on entirely insufficient, and very incompletely studied data. He concludes that these tumors arise from the endothelium of the lymphatics. The attempt of Sorgo (1902) to establish landmarks for the differentiation of primary and secondary tumors of the pleura is not particularly successful. His first case proved to be a primary adenocarcinoma of the esophagus, and the others are even less satisfactory as examples of primary pleural tumors. He quotes Birch-Hirschfeld as the first to affirm that carcinomas, even of larger bronchi, can run a latent course, and confirms this important fact by his own observation. In the writer's opinion, this is the most illuminating suggestion which the subject had received from any author, and it deserves and will be given further comment.

The thesis by Wichern (1902) contains an elaborate discussion of the origin and various applications of the term endothelium. He admits the difficulties in determining the limits or true significance of the endothelioma, and agrees with Ribbert that it is most difficult to define this tumor properly. However, he concludes that wherever endothelial cells show participation in the growth, it should be designated an endothelioma, leaving for future decision its relation to the carcinomas, or the sarcomas. His case happened to involve the peritoneum to a marked degree, but nodules were also present on the pleurae. His postmortem diagnosis was primary cancer of the peritoneum, but microscopic study revealed the usual lymph channel involvement, and hence his title was broadened to include primary endotheliomas of the pleuro-peritoneal cavities. He definitely excluded any tumor of the stomach or intestines, but failed to rule out malignancy in the ovaries or uterus. He was unwilling to derive his tumor from the serosal layer of cells.
On the contrary, Gutmann (1903) believes that in his own case, as well as in those of other writers, the primary tumors of the pleura originated from the surface layer of cells, which he thinks can be best designated as epithelium. He admits that the proof of this origin is often lacking, but Benda's case and his own, which resembled Benda's, seem to him to furnish abundant grounds for this conclusion. In his discussion, he quotes Ziegler who thought the masses of cells in the lymph channels came from the endothelium of the lymph channel, but admitted also the possibility of their development from the epithelium of the serosa. Gutmann notes also that Kaufmann is in full agreement with Ziegler when he says: "Die Endotheliome der Pleura gehen in den meisten Falle wohl auch von den Deckzellen (Endothelien) aus." However, in spite of his acceptance of the premises for the logical designation of such tumors as carcinoma, and the presence in his specimen of gland-like formations, he asserts that it is neither a sarcoma nor a carcinoma, and does not volunteer a substitute title. He says Hansemann told him in a personal communication that from April 1, 1895, to the present time (1903), with an average experience of 1300 to 1500 post-mortems each year, not a single case of primary tumor of the pleura had been observed.

The first of two cases described by Rondeau (1903) would readily be accepted by many as a very typical example of so-called primary endothelioma of the pleura, even when, microscopically, the bronchial walls were found to be involved and the structure of the tumor was that of an adenocarcinoma. Rondeau, however, concluded that it arose from the bronchial mucous glands. He quotes in his discussion, Meslay and Lorrain (1903), who evidently studied his second case, and delivered the following cryptic opinion: "Pour admettre le développement initial dans la plèvre d'un cancer epithelial, ce qui parait paradoxal, on est reduit aux hypothèses."

An interesting hypothesis is developed by Boinet and Olmer (1903) who described in detail "un cancer de la plèvre à distance," which was primary in the stomach in a man aged fifty-three years. The symptoms first appeared in the left chest,
and at postmortem the usual dense, white, connective tissue masses with a hemorrhagic exudate were found in the pleura. A very small, non-ulcerated induration at the pylorus was proved microscopically to be adenocarcinoma, and was regarded as the initial lesion with metastasis to almost every structure in the body. The authors advanced the theory that the extensive formation of fibrous tissue in the pleurae was the body's defensive action, and represented the relatively difficult conditions under which the cells proliferated at this site. Here also was presented the picture of a typical endothelioma giving the appearance "comme si vaisseau capillaire était le point de départ de la proliferation néoplastique." Nodules in the other organs, especially the brain, revealed an adenocarcinomatous arrangement, and pointed to the stomach as the original site. They conclude that primary tumors of the pleura are very rare, and that some of the published cases are doubtful, because of insufficient study. No better example of this conclusion could be furnished than the study of Lambrecht (1903), whose case, a man aged sixty-four years, had, as in the preceding case, a thickened pleura, but also a nodule in the brain and marked induration of the stomach. The microscopic study revealed in some places the appearance of "a scirrhous of the breast," and in others of "a medullary carcinoma" with cells of epithelial character. The author called this a primary cancer of the pleura, but was unable to decide whether it arose from the endothelium of the lymph channels, or of the pleural serosa.

A particularly careful histologic study has been made by Burtseva (1903) of a tumor in the left pleural cavity of a man aged forty-one years, in whom a diffusely thickened pleura with projecting polypoid masses and nodules in the lung were found at postmortem. The author says that the tumor cells looked like epithelial cells, and were occasionally arranged as in an adenoma, or even like a cyst, and describes colloid droplets in the cytoplasm, but because the main growth was in the pleural cavity, and all gradations could be recognized between the cells of the connective tissue spaces and those of the independent tumor nodules, she feels impelled to designate the tumor endothelioma.
The paradoxical character of this diagnosis is clearly recognized, and she even mentions groups of cells in spaces lined by flattened endothelium and resembling the "Injectionsbilder" described in carcinomas. She is unwilling to admit the participation of the surface cells in the process, but thinks the perithelial cells of the capillaries may be involved. Under various conditions hyperplastic endothelial cells may assume various forms, thus accounting for their resemblances to carcinomas in one case and to sarcomas in another. The nodules in the lungs are explained by having a supposed direct connection with the pleural growth. No writer on this subject in any language gives any clearer illustration of the effort necessary if one is to adopt the orthodox view of these tumors, and at the same time present a logical defense of this view.

Simons’ (1903) patient, a woman aged sixty years, shortly before the signs of tumor developed, had been struck on the affected side in a street car accident, and he concluded the growth was caused by trauma. His study of the tumor was too superficial to allow any estimate of its real character, although he admits the epithelial-like appearance of the tumor cells in the pleura.

In Basso’s case (1903), both peritoneum and pericardium were involved, and nodules were present in the lung, but the author believed the growth originated from the lymph channel endothelium of the pleura, and that the term "endothelioma" for such tumors should be retained. Bonheim (1904) reported three cases of endothelioma of the pleura, and emphasized his belief that they might come from either lymph channel or surface endothelium, producing nodules in the one instance, and uniform thickening in the other. His microscopic studies revealed "ganz carcinomartige Bilder." Scagliosi (1904) concluded that in his case the origin was from the lymph vessel endothelium, and hence, in spite of a "glandlike arrangement of the cells," should be called an endothelioma, whereas he admitted that those tumors arising from the surface cells should be designated carcinomas.
A thesis on primary malignant tumors of the pleura by Bloch (1905) attempts the most extensive and elaborate critical review of this subject which the literature affords. Including one of his own, he gives details of fifty-eight cases of primary endothelioma, and six cases of primary sarcoma, of the pleura. Many cases accepted by other writers,—for example, four of Glockner's five cases,—he rejects for various reasons. He distinguishes only two primary neoplasms of the pleura, endothelioma and sarcoma, regarding it impossible to ascribe to the pleura a primary carcinoma, although admitting that sometimes a glandular formation is present, and that the aspect of an alveolar carcinoma may be entirely reproduced. In his own case he derives the tumor from lymph-vessel endothelium. He disregards almost entirely the real controversial aspects of the subject, and actually does not make a single contribution toward unsnarling the intricate tangle of ideas, which, it is already quite manifest, surround the discussion of these tumors.

In Glockner's series only eight tumors were in children, according to von Hibler (1904), who described what he called an "Endothelkrebs" of the pleura in a boy, aged five and one-half years. The tumor was "the size of a man's fist," compressed the right lung and, penetrating the diaphragm, grew into the liver. Chiari, who made the microscopic examination, pronounced it an "endothelioma carcinomatodes," and also made the significant observation that the pleural cavity looked as if wax had been poured into it, thus presenting an appearance similar to that described by Schwalbe (1891) in sarcoma of the pleura. Even more puzzling is the conclusion of Otto (1904) who, according to Wolff, reports a sarcoma and an endothelioma, both primary in the pleura, the one represented by a fungous mass, and the other by a diffuse thickening.

As already noted, the Italian literature contains a fair proportion of contributions on this subject. Torri (1905) gives a somewhat elaborate discussion, and reports four new cases of primary malignant tumors of the pleura. One, he concluded, was a lymphangiosarcoma, the second, a hemolymphangiosarcoma, the third probably an endothelioma, and the fourth, a
spindle-cell sarcoma. He indicates that such tumors are relatively common, as these four occurred in 3840 postmortem examinations at the Pathological Institute of the University of Pisa, and that many of them are missed because they are diagnosed as inflammatory conditions of the pleura. He regards those tumors arising from the surface endothelium as carcinomas, and believes that Benda and Gutmann reported the only clear cut examples of this, to him, rare form. In the true endothelioma of the pleura, according to Torri, the process is generalized over the whole extent of the pleura, and does not originate from a circumscribed area. The various inconsistencies of these conclusions are not discussed by Torri.

Still less satisfactory is the study by Vaccari (1905), who bases his diagnosis of primary endothelioma of the pleura solely on the fact that in that location was the largest amount of tumor tissue and also the most connective tissue, and hence the oldest growth from a genetic standpoint. This conclusion was reached even with a large nodule, 5 cm. in diameter, in the left upper lobe of the lung. The report of Siragusa (1905) of a single case, is quite characteristically extensive when compared with the net results of his study. He regards Zagari’s contribution as the most important one yet made, and then proceeds to agree with almost everyone who has written on the subject. The tumor in Siragusa’s case was in a woman aged fifty years, and is finally pronounced an endothelioma arising from the lymphatic endothelium of the pleura and particularly marked by collections of lymphocytes. As in Vaccari’s case, the nodules in the lung are considered secondary. In reporting two cases of what he calls primary endothelioma of the pleura, Dal Lago (1908) is inclined to agree with Torri. One of his cases is quite evidently a sarcoma. In both, the lungs were involved. He concludes that the term “pleuro-pulmonary cancer” as proposed by Zagari would be more rational.

Many papers have been published dealing with the cytodiagnosis of the hemorrhagic fluid so often accompanying these tumors. One by Bordot (1905) concludes that, while malignancy in the pleura can often be ascertained by this method, there is
nothing which will indicate whether it is primary or secondary. A similar conclusion is reached by Erben (1906) who further adds that even when some other primary focus is not found, still its presence in another organ is not ruled out, "da er vollständig latent bleiben kann." Such an occurrence is cited by Dahmen (1905) who discusses this feature with reference to huge metastatic nodules in the liver from barely visible gastric cancers.

Mönckeberg (1906), in a general review of the subject of endotheliomas up to 1905, deprecates what has seemed to him in large part an unfruitful discussion over the relation of endothelium of serous cavities to that of blood and lymph vessels. As they all serve to bound streams of plasma, they are morphologically and functionally a unit. He does not attempt to settle any other aspects of the problem.

Claret (1907) in his case report, complacently agrees with the conclusions of Bloch. Insufficient data proved no bar to Delatour (1908) in making a diagnosis of endothelioma of the pleura in five cases, none of which were examined after death. One case showed at operation a carcinoma of the uterus, but the bloodstained pleural fluid evidently represented to the author a pathognomonic sign of endothelioma. Guichard (1911) did not even find fluid in his case, but only a soft mass on resecting a rib. Nevertheless, he called the case primary cancer of the pleura.

Glass (1908) enters into an extended discussion of the derivation and naming of various types of endothelium. He apparently agrees with Ribbert that many endotheliomas of serous cavities are undoubtedly carcinoma. However, he believes that few tumors arise from the surface endothelium of the pleura. His own case, a woman aged sixty-six years, had the usual tumor of the pleura with a marked carcinomatous appearance on microscopic examination, even to the presence of mucoid tissue. He derived the tumor from lymph-channel endothelium and called it an "Endothelkrebs." He was able to collect and analyze thirty-three similar cases.

After a somewhat comprehensive review of the various theories regarding the origin of endothelium, Dreesen (1909) describes a case in a man aged twenty-six years, in which the
surface layer of the right pleura apparently was alone involved and showed papillary masses, which, microscopically, completely simulated carcinoma in both the arrangement of the stroma and the parenchyma. He agrees with Benda that the surface serosa is a true epithelium, and that tumors derived from it are true carcinomas. Hence his title, "Ueber den sogenannten 'Endothelkrebs' der Pleura."

Patterson (1909) has published the most thorough study of this subject which appears in the English language. His own case, besides the usual features, showed "the lower lobe (right lung) infiltrated by a tumor mass about the size of a small orange." He accepted from the literature ninety-six cases of pleural endothelioma, and analyzed these in various clinical and pathologic aspects. Unfortunately, his own case, possibly primary in the lung, furnishes a doubtful example, and his excellent summaries of the ninety-six cases do not include attempts to harmonize the conflicting views.

Ribbert's (1909) contribution is wholly on the theoretical side. He notes the two opposing groups of authors, one deriving the pleural endothelioma from the serosal surface cells, the other, from the endothelial cells of the lymph channels. The latter view appears to him absolutely wrong. The supposed transition stages from tumor cells to normal endothelial cells, lining lymph vessels, are improperly interpreted, and other tumors may reproduce all these appearances by the changing influences exerted on the tumor cells. He then endeavors to strengthen his argument by a typical bit of sophism, which many Anglo-Saxon readers will find difficult to appreciate. His major premise asserts that "in general the elements of an organ by proliferation will originate only homologous tumors." If, then, tumors arise from lymph vessel endothelium they should reproduce lymph vessels; but these tumors do not possess lymph channels at all, and even if they did, these channels would be part of a primary inflammatory overgrowth of connective tissue, and could not at the same time be regarded as tumor tissue. "Eine Endothelwucherung ist demnach unmöglich." Ribbert accepts fully the theory which derives serosal cells from the entoblast, and he
regards them as true epithelial cells. The work of von Brunn (1900), who demonstrated that these cells are ciliated, and of Borst (1900), who apparently conclusively proved that the serosal cells, particularly of the pleura, often contain and secrete mucus, confirmed for Ribbert their epithelial character. However, he thinks that the proof, offered by Benda, for example, that tumors arise from these cells, is incomplete, and that the possibility must be admitted that they can take origin from "misplaced lung epithelium." In either case they must be considered as, and named, carcinomas. Consequently Ribbert completely removes every basis governing the fundamental conception of endotheliomas, and the logical inference of his conclusions would result in removing the term endothelioma, at least of the pleura, from our classification. It is quite manifest that, with such premises, no other conclusion would be possible.

The ideas expressed by Ribbert evidently did not receive general endorsement, for Fraenkel (1911), who in 1892 had reported a case of primary endothelial cancer as an example of Neilsen's "Lymphangitis prolifera," nineteen years later, and two years after Ribbert's publication, gave a lecture on endothelioma of the pleura, and described three additional cases. While inclined to follow Borst by classifying one of the tumors as an intermediate type of sarcoma, the others were too much like carcinomas and the question of their true significance is left open. On the other hand, Sprunt (1911) in his report accepts Ribbert's views, concludes that his tumor arose from the surface endothelium, and frankly calls it an "adenocarcinoma." Thus for the first time is expressed the end result of Ribbert's reasoning, namely, the derivation of a glandular carcinoma from the lining cells of a body cavity.

Herxheimer (1911) differentiates those primary pleural tumors coming from the endothelial cells of the lymph channels, and those from the surface cells. The latter he calls "Deckzellen-Carcinome." However, he warns us that many so-called primary tumors are really secondary, and as an example cites a case with enormous tumor in the pleura, but in which the primary site was a very small, richly cellular bronchial carcinoma. The
results of Ribbert’s teaching are quite manifest in the thesis of Braude (1911), who worked with Orth. This author sharply differentiates the serosal cells, which he accepts as a true epithelium, and the endothelium of the lymph channels, which he regards as essentially connective-tissue cells, and therefore, incapable of giving origin to any sort of a tumor other than sarcoma. Hence he denies absolutely the existence of endothelioma of the pleura. His three cases are interesting. One was in an elderly woman whose right pleura was studded with wart-like nodules. The right lung also contained numerous nodules up to a “cherry-pit” in size. Microscopic examination revealed a typical adenocarcinoma with, in places, papillary formations in cysts. He concluded that this tumor arose from the “Deckzellen.” The second case was also in a woman who had carcinoma of the right lung originating in the alveolar epithelium and extensively invading the right pleura as well as the abdominal viscera. He remarks how easy it would be in such a case, to overlook the primary site and to pronounce the secondary growth in the serosa an independent process, and adds: “The changes in the lymph vessels and tissue spaces of the pleura show a picture that more or less resembles the endothelioma, or so-called endothelial cancer of Neelsen, Glockner and others.” Hence, he concludes, most of the cases described in the literature as endotheliomas must have another origin. His third case was also in the right pleura of an elderly woman, and here he located the primary site deep in the costal pleura with metastasis to the left lung and left kidney. This was also a carcinoma, and was supposed by the author to arise from misplaced embryonal epithelium. The striking feature of this report is the boldness of his denial of the existence of pleural endothelioma, and his warning about the danger of missing a primary pulmonary growth, and on the other hand, his labored efforts, in the presence of admitted lung involvement, to derive the tumor from such unlikely sources as serosal cells and misplaced epithelial remnants.

Somewhat similar conclusions are reached by Witzel (1912), who follows Ribbert’s and Braude’s teachings. His case was a man aged fifty-two years, whose left pleura was covered by a
dense whitish layer of tumor tissue. Nodules up to “the size of a walnut” were present in the left lung and there was also involvement of the right pleura, the mediastinal lymph-nodes, spleen, liver, brain and axillary nodes. The cells were not differentiated in adenomatous formation, but appeared to the author as definitely epithelial in character. He calls it a scirrhus type of pleural carcinoma arising from the serosal layer. He also denies the possibility of an endothelioma, but further emphasizes that the lung could not be a primary site, inasmuch as all the clinical symptoms arose in the pleura.

The tumor described by Candela (1912) is somewhat different from any so far reported. It occurred in the left chest of a man aged thirty-eight years. A lymph-node removed from the left axilla before death in part resembled sarcoma and in part endothelioma. At the postmortem a typical sarcomatous mass was found filling the left pleura and invading the left lung, diaphragm, muscles of the thorax and the liver. Histologic study revealed a very vascular growth, and led the author to derive the tumor from the endothelium of the blood vessels. He classifies it with the other endotheliomas supposed to arise from lymph vessel endothelium, but admits extreme difficulty in differentiating it from sarcoma.

More like earlier reports is the description and discussion of a case by Bernstein (1913) of a woman, aged sixty-nine years, whose left pleura was markedly thickened, and the left lung invaded. The epithelial character of the cells and their tendency to glandular arrangement caused him some doubt as to whether the tumor was not primary in the lung, but its size and lymph channel involvement forced him to favor the pleura, and hence the designation “lymph-endothelioma.” Lichatzewoi (1913) grants that primary carcinomas of the pleura are very rare, and that certain authors even deny their existence. In his case, a woman of twenty-nine years, masses were present in the left lung, around the left clavicle, in the bronchial nodes and also in the right lung, but the extensive involvement of the left pleura led him to call the growth primary carcinoma of that part. As there was no differentiation in the cells, he suggested the term “carcinoma simplex.”
Although the gross and microscopic descriptions of the growth in Bernard's (1913) case strongly suggest carcinoma, quite comparable to the one reported by Benda, the author diagnoses it as sarcoma, basing his opinion on the discovery of intercellular fibrillae in the cell nests contained in the lymph channels. He admits the possibility that these cells may have arisen from the endothelium of the serosa, and also grants the resemblance of the cells to endothelium. This case is mentioned because it possibly illustrates how difficult it often becomes for authors properly to interpret extensive pleural involvement by any kind of a malignant growth.

Lesieur, Savy, and Mazel (1913) endeavor to differentiate sarcoma of the pleura from an endothelioma. The former, they assert, is usually larger and softer than the latter, and usually occurs as a single mass, while the latter is multiple, or presents an irregularly thickened pleura. They diagnosed the tumor in their case as sarcoma, but Collet (1913), whose thesis is largely a rehash of Bloch's work, includes this among the carcinomas. A still more paradoxical diagnosis is offered by Latreille (1913), who called his growth “primary sarco-endothelioma of the pleura” originating from the endothelial cells, in spite of the fact that in some places the cells “donnent l’illusion de véritables formations glandulaires.” Nodules were present in the lung, but the growth in the pleura was more massive and hence regarded as primary. Roger and Lapeyre (1913) made a diagnosis of primary cancer of the pleura, solely on the results of the examination of 1400 c.c. of blood-tinged fluid. The difficulties of this procedure have been reviewed by Sorgo (1902).

Clarkson (1914) is authority for the statement that out of 10,829 postmortem examinations at Munich, there were only two cases of primary endothelioma of the pleura. Altogether he could find records of only forty-one cases. His own case disclosed the usual features, and there was no discussion of the diagnosis. About sixty cases are admitted by Rosenbaum (1914), and he adds two of his own. In discussion, he accepts the evidence of the epithelial character of the serosal layer of cells, but finds that his own cases show many signs of primary
lymph vessel involvement. Consequently, until a more certain origin for these tumors is generally accepted, he prefers to withhold positive assertions with respect to their classification or source. This admission is one more advance, inasmuch as the nature and significance of the dilemma, as well as the absence of any satisfactory solution, is clearly recognized. Keilty (1917) found, in the records of the pathologic department of the University Hospital, Philadelphia, nine cases of primary endothelioma of the pleura in 5000 postmortem examinations. His own case showed cell groups "much like glandular epithelium," and there was definite involvement of the lung, but the diagnosis of a primary endothelioma of the pleura evidently presented no difficulties to the mind of the author. Similarly, without any critical analysis, a tumor in a man aged fifty-one years, involving right pleurae, diaphragm and right lung, was called a primary carcinoma of the pleura by Miari (1919). The only unusual circumstance in Kornitzer's (1919) case was the presence of a leiomyoma in the left pleural cavity and of what he called an endothelioma in the right side. He exhibited more interest over the double tumor occurrence than over the correct diagnosis of the right pleural growth.

Demole (1918) has given a very thorough review of these questions in a thesis in which he reports the occurrence of a tumor presumed by him to be primary in the right pleura, and presenting metastatic involvement of the lungs, left pleura, pericardium, liver and brain. The adenomatous arrangement of the cells and, in places, the papillary or dendritic tendencies of their growth, led the author to designate the tumor as a papillary carcinoma. He accepts fully the theory which designates the lining cells of the coelomic cavities as true epithelium. In fact it is necessary to adopt this hypothesis in order to defend his conclusion. The author then proceeds to a careful analysis of the reported cases of endothelioma of the pleura and concludes that most of them represent carcinoma, either primary or secondary. He grants the difficulties involved in making this decision and admits that any given tumor of serous cavities, which, at first might be considered as primary, on the discovery
of even a minute carcinoma in some epithelial structure, would then be adjudged to be a metastatic growth. He does not wholly deny the possibility of endothelioma arising from pleural lymphatic endothelium, but believes such tumors are extremely rare.

The tumor reported by Bayne-Jones (1919) was in a boy aged sixteen years, and is described as carcinoma originating from the lining cells of the pleura. He says "At present most histologists regard the lining cells of the pleura as epithelial-like cells derived from the mesoderm. It is certain that these cells do not arise from endoderm, but from the cells of the mesoderm when this layer splits to form the pleural cavity. These cells have many of the characteristics of epithelium, and are commonly designated 'mesothelial epithelium.' It is appropriate, therefore, to regard this primary neoplasm of the lining cells of the pleura as an epithelial tumor . . . a carcinoma of the pleura." He found two cases in 5000 postmortem examinations at the Johns Hopkins University Hospital. Du Bray and Rosson (1920), following Adami, propose the term "primary mesothelioma of the pleura" for their tumor. The submucosa of the bronchi was involved as well as the alveolar spaces of the lung parenchyma, and the growth was of an epithelial nature. They concluded it arose on the surface of the parietal pleura. They "do not see the justification of calling these tumors carcinomas" and "the term 'endothelioma' is not appropriate."

The controversial features of these tumors, however, have not made any profound impression on recent American writers, and some entirely disregard them. This is true of McDonnell and Maxwell (1920), who called their tumor an endothelioma and noted, besides metastasis to other organs, peribronchial involvement and nodules in the right lung. Likewise, Eastwood and Martin (1921) in England are content with the term "mesothelioma" as a compromise, and references to Bloch and Patterson suffice for purposes of discussion. One of the more recent papers by Wood and Walter (1921) is concerned with a tumor of the left chest which microscopically had "the general appearance

1 Described by Sprunt.
of adenocarcinoma, probably of mesothelial origin." The term "mesothelioma" is therefore employed, and the necessity for explanation of past differences in opinion and classification thereby apparently entirely avoided.

The latest reference to work on this group of tumors that I have been able to find is that of Remond and Colombies (1922). These authors discuss chiefly the points of view adopted by various French writers, and then give details of the case of a tumor in the left side of the chest of a woman aged sixty-one years. This tumor had invaded the pericardium and there were also nodules in both lungs and the liver. The cells had the appearance of epithelium, but no adenomatous characters were mentioned. The authors are inclined to accept Bloch's interpretation of the histologic significance of these cells, although they admit Bloch said that often a latent carcinoma in some organ represented the primary growth. They indicate the difficulties of deciding as to whether these tumors are really endotheliomas, sarcomas, or carcinomas, and leave the question open without hazarding any decisive opinion.

Finally it would be fitting to review the conclusions of some of those who have earned a right, by reason of years of study and experience, to be regarded as authorities on questions of tumor nomenclature and classification. Under such circumstances, one naturally turns first to Virchow. I have been unable to find a single direct reference to this noted pathologist's opinions on this type of tumors. At a meeting of the Berlin Medical Association in 1893, in discussing a demonstration by Pick, who had exhibited a supposed primary carcinoma of the peritoneum, Virchow remarked that while it was undoubtedly a carcinoma and there was clearly no carcinoma in the uterus, still it was doubtful as to its primary site in the peritoneum. "Wahrscheinlich steckt noch irgend wo im Körper ein noch nicht aufgefundener Tumor, aus dem sie hervorgegangen sind." This would perhaps indicate his unwillingness to follow unquestioningly in the paths laid down so easily by other writers.

From the older authors we cannot expect any particularly critical views. Klebs (1889) accepts fully the occurrence of
endotheliomas of the pleura and their close relation to the connective-tissue group, although in certain widely metastasizing forms he admits the propriety of the term "Endothelkrebs." A similar view is expressed by Thoma (1896). Ziegler (1895) in the eighth edition of his work on General Pathology groups the endotheliomas with sarcomas. This view is retained by Warthin in the eleventh edition, although in a note he indicates the tendency, doubtfully justified in his opinion, to classify these tumors as endothelial cancers. McFarland (1901) also classifies these growths with the malignant connective-tissue tumors, but notes their close histologic resemblance to carcinomas. Adami and Nicholls (1909) classify the endotheliomas as "the most important malignant growth" affecting the pleura where it is found "more frequently than elsewhere." They say "the growth originates in an overgrowth of the lining cells of the pleura." In the first volume of this work Adami calls these tumors "mesotheliomata...originating from the endothelium (or epithelium, whichever term is preferred) covering the serous surfaces. ... Histologically they often present a strikingly cancerous appearance." He quite evidently was of the opinion that the new designation would make further controversy as to their origin unnecessary.

Mallory (1914) dismisses the subject very briefly by saying that theoretically the most interesting of the primary tumors of the pleural cavity is "the carcinoma which arises from the lining mesothelial cells." Stengel and Fox (1915) place endotheliomas with the sarcomas, and derive them from the endothelium of the lymphatic, or rarely, the blood-channels. They say that sometimes the tumor is designated endothelial cancer and "resembles cancer very closely in histologic appearances in some cases." McCallum (1920) recognizes some of the controversial features of these tumors. He says "they are apparently primary in the lining cells of the pleura...and can be distinguished from those which occur as metastases from primary tumors situated elsewhere." However, the method by which this distinction can be made is not clearly set forth, and he admits that the "nature" of the cells "cannot be positively
stated from a study of their morphology.” He notes that “some investigators insist that they (the cells) are derived from the endothelium of the underlying lymphatic channels, but the majority, including Ribbert, refer them to the serosa cells and consider them epithelial tumors.”

Borst, who is widely quoted on all matters pertaining to tumors, largely because of his excellent book on this subject, has epitomized his views in the chapter on tumors written for the first volume of Aschoff’s Pathology (1920). He groups the endothelioma and perithelioma under the sarcomas, and considers the growths of the serous cavities as special forms, noting also that some call these mesothelioma. He thinks that perhaps the controversy concerning their origin may be settled by granting the occurrence of two types, one from the lymph-vessel endothelium, and the other from the serosal cells. In this case, he remarks, one must attempt to separate the malignant “Deckzellengeschwulst” of Marchand from the lymphangiendothelioma of the serous membranes. Beitzke, who treated specifically the subject of pleural tumors in the second volume, takes a similar view. However, he indicates that those tumors from the “Pleuradeckzellen” must be denominated carcinoma, and he also grants how almost impossible it is to determine the true source of any particular pleural tumor, so that the classification of this group must often be regarded as undecided.

Of all the writers on pathologic anatomy, Kaufmann is probably the most favorably and widely recognized. Consequently his views concerning this tumor group carry considerable authority. As early as 1906 he reported the case of a woman aged seventy years whose right pleura was involved in the usual manner. There was also metastasis to the lungs. He identified this growth as an endothelioma, admitting that others designated it a carcinoma. Its differentiation from an ordinary cancer was proved for him by a progressive transformation to tumor cells of the cells lining the lymph spaces, in which process they adhered closely to the walls, whereas, in carcinomas, they tended to draw away. In the seventh and eighth edition of his book on special pathologic anatomy (1922) he emphasizes that the endotheliomas
belong histogenetically to the connective-tissue tumors. He admits the possibility that some may arise from the "Deckzel- len," but insists that these also should be called endotheliomas, and that the term "Endothelkrebs" should be avoided, as true carcinomas can only come from epithelium. In his chapter on pleural tumors he further discusses this point, stating that while earlier the "coelom theory" of the Hertwig brothers had caused certain observers to regard the serosal cells as epithelium, and hence tumors springing from them as carcinomas, later investigators showed that these cells were the result of a splitting of the mesenchyme, and hence modified mesenchyme or connective-tissue cells. He admits that they may form fibrillae like true connective-tissue cells, but also epithelial-like structures such as are found in the pleural endothelioma, which have been designated as mesothelioma or malignant "Deckzellen" tumors. However, he feels certain that, especially grossly, such tumors bear little or no resemblance to carcinomas in other locations.

He reports two further cases of tumors, one in the left pleura of a man aged thirty-six years, and the other in the right side of a man aged sixty-three years. He also refers to a widely distributed growth in a man aged fifty-four years, whose left lung was extensively invaded, and describes the common occurrence of secondary carcinoma of the pleura, but fails to show in what special manner these differ from the supposed primary tumors.

This review of authors' opinions may be fittingly closed by a brief consideration of those of Ewing (1922), the dean of American oncologists. He regards the endothelial cells as occupying an intermediate position between epithelium and connective-tissue. However, he does not think that embryological data "warrant fundamental distinctions between the various cells now commonly grouped as endothelium, since all are of mesodermal origin." Neither does the "lining character" of the coelomic cells "warrant their identification with any form of epithelium, such as is derived from ectoderm or endoderm." The dual tendencies of these cells cause them, under pathologic conditions, to assume on the one hand "epithelial qualities," and on the other "certain potencies of connective-tissue."
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However, he urges, in view of the uncertain position of the endotheliomas as tumors, that "the diagnosis should be accepted only when the evidence is clear and conclusive." After a brief review of the literature of this type of tumors of the pleura, he concludes by asserting that the proper classification of endothelioma of pleura and peritoneum still remains a somewhat fruitless matter of discussion, and indicates that while he approves of the title "endothelioma," he is inclined to agree with Birch-Hirschfeld and others "that all these tumors have sarcomatous qualities."

My own experience until recently has been quite in line with that of other workers. Having already observed a fairly typical example of this tumor, there was little hesitation in July, 1913, in making a diagnosis of "probable pleural endothelioma" in the case (A-13-108, University of Minnesota, Department of Pathology) of a man aged sixty-two years, who had been suspected clinically of having a carcinoma of the lung. At the postmortem examination the right pleural cavity contained, besides fibrous adhesions, masses covering the inferior portions of the parietal pleural surfaces, including the diaphragm. At these points there was fusion with the visceral pleura, and there were similar masses in the lower lobe of the lung. All of these masses were soft, greyish-white and, in the lung especially, revealed yellowish-white areas of necrosis. The peribronchial lymph-nodes were enlarged by tumor invasion, and the liver contained several nodules. The periportal lymph-nodes were involved, and nodules were present in the omentum along the greater curvature of the stomach and in the left adrenal. A note made at the time of the examination states that "the distribution of the tumor gives a general impression that its starting point was on the pleural surfaces." Microscopically, a typical medullary type of carcinoma was found, but as it filled the lymph-channels with undifferentiated masses of large cells, "endothelioma" was suggested to the mind of the examiner, and the primary growth was located in the pleura, with metastasis to the right lung and the other organs mentioned. The absurdity of such a conclusion is quite apparent, although comparable
errors are by no means rare in published reports, and furthermore this case has never been, and never will be, reported as an example of endothelioma. Rather it furnishes a quite typical instance of a certain fairly common form of carcinoma of the lung.

More than two years later (December, 1915), an examination was made of a woman aged fifty-seven years (A-15-382) from whose right chest, during life, hemorrhagic fluid had been aspirated on several occasions. The clinical diagnosis was a tumor of the right pleura. "This cavity was found lined by a whitish, felted layer of soft tumor substance, ranging from 1 to 1.5 cm. in thickness. The right lung was collapsed, and not markedly invaded by tumor, except in the peripheral portions." Metastatic growths were present in the spleen, kidney, liver, left adrenal and lymph-nodes of the mediastinum, as well as along the aorta. Microscopic study revealed a typical adenocarcinoma (Fig. 1) with a tendency to branching papillary outgrowths. The diagnosis at the time of the examination was "malignant tumor of the right pleura, probably lymph-endothelioma." Except for the rather soft consistency of the pleural portion of the tumor (tumors of this class usually having a dense fibrous character) the case as a primary malignant tumor of the pleura is fully as acceptable as the majority of those which have been published. Whether it would be called a carcinoma, or an endothelioma, or some other related term, would depend wholly on the personal predilection of the author. Further study, however, not only emphasizes the adenomatous and, therefore, the carcinomatous appearance of the tumor, but also the fact that the invasion of the lung consists of definite pulmonary nodules, any one of which would be quite sufficient in extent and structure to serve as a primary source of the entire tumor process. This very important point will be discussed in more detail later.

A third instance occurred in May, 1919 (A-19-102), in a man aged sixty-two years, whose left chest, when aspirated, had revealed bloody fluid. At the postmortem examination the left pleural cavity was almost completely obliterated by a dense, greyish-white, fibrous mass which quite evidently lined the
visceral and parietal surfaces, and left only two small spaces between the two layers. No masses were found in the lung parenchyma. The hilus was surrounded by tumor tissue. Metastatic growths were present in the liver, spleen, pancreas, kidneys, prostate, peritoneal surfaces and various lymph-nodes. The microscopic picture is quite similar to the second of these three cases, except that there was less tendency toward glandlike formations, in short, less differentiation. The diagnosis at that time was "endothelioma of the pleura." This tumor was still more free from any clear inferences of error in diagnosis or classification. It would readily pass muster, after the most critical analysis, if the standards set for such growths should remain as in the past. The fact that the report of the case does not involve a discussion of origin from pleural surface versus
pleural lymph-channels, and that it proved to be a frank adenocarcinoma (Fig. 2) does not in any way affect the main issue.

These three cases were found during a service of twelve years at the University of Minnesota in which were made a total of slightly more than 3000 examinations. In the Mayo Clinic there can be found record of only one case (A331788). This was a man aged seventy-five years, whose left chest had been aspirated elsewhere several times, giving at first abundant blood-tinged fluid and later, smaller amounts of blood-streaked purulent exudate. During the four days he was here, two unsuccessful attempts were made to find fluid in the chest. A clinical diagnosis of probable pulmonary malignancy with infection was suggested. The examination after death showed acute pericarditis and pneumonia, besides the tumor. This
involved the left chest in the usual manner, the masses being very
dense. The lung apex was markedly infiltrated, and there was
metastasis to the liver, adrenals and kidneys. Microscopically
the connective-tissue was very abundant, and the epithelial-like
cells arranged in single columns or narrow cords. A few cells
showed mucoid droplets, and in occasional areas an adenomatous
arrangement could be seen. The original clinical diagnosis is
quite evidently the more logical one, although "pleural endo-
thelioma of the scirrhous type" is the one recorded in the post-
mortem records.

DISCUSSION

Even the most superficial survey of the literature on this
subject would strongly suggest the existence of a clinical entity
which deserves special consideration. The almost uniform
agreement among authors in their description of the principal
signs and symptoms in cases of so-called primary endothelioma
(or carcinoma) of the pleura, indicates that, in general, the same
region of the body has been attacked, and in each instance, by a
somewhat similar process. A brief review of this clinical picture
will serve to demonstrate the nature of the disease. The onset is
insidious and quite extensive involvement of the pleurae as well
as other organs may occur before any complaint becomes note-
worthy. In the earlier stages, the subjective symptoms of
neuralgic pains, and a sense of fullness in the chest are often
present. Physical examination will reveal dyspnea, dullness and
diminished conduction on the affected side of the chest, and
often appreciable deformity of that side. This deformity may
consist of a bulging of the whole side, with or without edema, or
simply an obliteration of the intercostal grooves. Later, in the
more prolonged cases, this increase in size may be replaced by a
definite retraction between the ribs, and even of the whole side.
The respiratory excursion is limited, and the diaphragm may be
absolutely stationary. Quite uniformly the Roentgen-ray reveals
thickening of the pleura and the presence of fluid. On paracen-
tesis, in which operation the needle may encounter a definitely
resistant tissue layer, the fluid which is obtained is usually
hemorrhagic, varying from a slightly tinged serum to an exudate
which resembles venous blood. The amount ranges from a few cubic centimeters to several liters. Careful search at this stage may discover firm enlargements of lymph-nodes, either of the clavicular or axillary chains. If one of these is removed and examined, a carcinoma-like tumor is usually found. There is rarely any fever, cough is often absent, and the pulse is accelerated. Cytologic study of the fluid sediment shows the usual elements of the blood, and in addition, varying numbers of large swollen cells singly, or in clumps or small plaques. The cytoplasm will contain fat droplets and glycogen granules, and occasionally mucoid globules, while the nuclei are vesicular, or will show a few mitotic figures.

The removal of the fluid often gives marked relief. The general course of the disease, however, is steadily and, usually, rapidly worse. The fluid re-collects in progressively shorter periods of time, and often shows an increase in its hemorrhagic character. The dyspnea and other pressure signs are accentuated and encroachment on the normal pleural, pulmonary and cardiac areas, with varying degrees of displacements, becomes increasingly evident. Occasionally the peritoneal cavity shows ascites and enlargements of its viscera. Loss of weight and strength are prominent signs throughout, and death is produced either by a terminal pneumonia, or by direct embarrassment of the cardiac or respiratory mechanism. The duration of the disease from the onset of symptoms may extend from only a few weeks to a year or more. The differential diagnosis lies between tuberculous pleuritis, carcinoma of the lung, secondary carcinoma of the pleura with a latent primary growth in some other organ, and primary malignancy of the pleura itself. This primary malignancy may be denominated as probable sarcoma, mesothelioma, carcinoma, or endothelioma, but the latter, for obvious reasons, is the more popular term. The important fact in respect to differential diagnosis is that a positive decision is often absolutely impossible with regard to primary carcinoma of the pleura and carcinoma of the lung, as well as latent carcinomas in other organs, such as the esophagus and stomach, with secondary marked distribution to the pleura. In short, the
clinical syndrome just given only indicates that the pleural surfaces are involved by a malignant process, and tells little or nothing of the site of the primary growth.

From the pathologic standpoint and that of the postmortem examination, it would at first appear that we should find ourselves on much more stable ground. With the actual appearance and location of the various lesions and, finally, their microscopic study freely available, certainly there can be little room for dispute as to the real source of the tumor, even if questions of ontogenesis and classification remain undecided. In other words, with freedom of investigation once granted, it would be an extreme case in which the pathologist would admit the slightest hesitation in locating definitely the primary and secondary sites of any given tumor. His ability and authority, in this particular respect, are accepted with less reservation than almost any other pronouncement he may make, and when the particular group of tumors under consideration are encountered, the literature certainly affords the pathologist, as well as the clinician, abundant support for these views. The picture usually presented at the postmortem examination is clear cut and apparently decisive. The pleural surfaces on the affected side in whole, or in part, are either studded with discrete nodules, or diffusely thickened by a greyish-white growth which is often very dense and tough. The cavity separating the visceral and parietal layers practically always persists and contains hemorrhagic fluid. Occasionally bands pass across this, and the roughened surfaces show tags and projecting papillary formations. The lung is pushed out of position and atelectatic, but often no gross involvement is described. The various lymph-nodes of the region, the opposite pleural surfaces and opposite lung, as well as the peritoneum and abdominal organs, are often the sites of metastatic nodules, although some cases are described without metastasis. Microscopic study as a rule shows the tumor to be composed of a dense connective-tissue stroma with columns, islands or strands of epithelial-like cells, filling spaces which in every respect correspond to lymph-channels. These cells contain fat, glycogen, and often mucoid globules. Quite
usually an adenomatous arrangement of the cells is observed, and this is sometimes so striking that, without knowledge of the gross appearances, no hesitation would be offered in pronouncing the tumor carcinoma. Indeed, as the theory of the entodermal origin of cavity endothelium became more widely accepted, this diagnosis was more frequently made, thereby further obscuring the fundamental concepts which for years had dominated the group of tumors called endothelioma.

My attention was first attracted to the extended consideration of this whole group of tumors by experience with a case which seemed at first sight to afford a typical example of endothelioma of the pericardium. In the second of these series of studies this case will be reported in more detail. It will suffice here to mention that the tumor occurred in a woman (Case A357673) aged forty-two years, who suffered from repeated collections of markedly hemorrhagic fluid in the pericardial sac. At the postmortem examination the cavity was enormously dilated and contained over one liter of bloody fluid. Both visceral and parietal surfaces were thickened by a dense growth, presenting a roughened surface (Fig. 3), and in every way resembling those pleural growths previously described. There were extensions to the left pleura, and marked involvement of the mediastinal, peribronchial, cervical and abdominal lymph-nodes. No other primary source could be found, even after extended search, and I believed that I was undoubtedly dealing with an exquisite and typical specimen of a very rare instance of a primary endothelioma of the pericardium. The microscopic study, to my astonishment, revealed, instead of masses of undifferentiated epithelial-like cells in lymph-channel spaces, a perfect example of an adenocarcinoma (Fig. 4) quite evidently arising from some mucous glandular epithelium. A further review of the case, with careful dissection of the left lung, revealed numerous yellowish-white nodules in the walls of the bronchi near the hilus, and sections demonstrated these as nodules situated in the midst of the mucous glands of the bronchial submucosa. My dilemma was similar to that faced by many other observers who studied these same tumors apparently arising from the pleural
surfaces. The site of the primary growth had been unhesitatingly pronounced to be the pericardium, and on fully as justifiable grounds as those governing the localization of the majority of so-called primary pleural neoplasms. Analysis of the reasons for this selection shows that they are, in large part,
assignable to the principal lesion, which has produced not only the most important of the clinical phenomena, but also the most extensive pathologic alteration. In other words, the diagnosis is based almost wholly on quantitative changes, and so strong an appeal is presented on this ground alone, that the temptation is present to disregard all other considerations and to adhere to the standards of judgment approved in general throughout the medical world.

Fig. 4. Section of Epicardium. (× 60.)

However, the paradox presented of an apparent endothelioma with all the microscopic characters of an adenocarcinoma seemed to demand more extensive study, and accordingly the experiences, opinions and arguments of other students on this subject have been extensively reviewed and the results summarized in the foregoing pages.
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It has been made apparent that several other problems have arisen and these present further complications to the orderly arrangement of ideas. The earlier writers were almost unanimous in considering the tumor as arising from lymphatic endothelium, and this conception is to some extent present in the minds of many of the later writers. The logical necessity of selecting some one point of origin was evaded by many of them by assuming a simultaneous malignant proliferation of an entire system of subpleural lymphatic endothelial cells, and hence arose the comparison of the process to an infectious inflammatory disease. Then appeared those who derived these tumors from the serosal layer of cells, and they boldly explained the carcinomatous appearances of the tumor by seizing on the "coelom theory" which derives the pleural, pericardial and peritoneal endothelium from the entoderm, and pronounces these cells to be true epithelium. The diffuse nature of the process was disregarded, and the question seemed to be settled by calling the tumors carcinoma. Even adenocarcinoma might arise from these cells, for their ability to secrete mucus had apparently been shown by several workers. But this solution only placed in greater prominence the other horn of the dilemma. Many endotheliomas had been ascribed, and their origin traced, to the pleural lymphatics. Very few of these tumors could, with any certainty, as Ribbert pointed out, be assigned to the serosal layer of cells, and even here misplaced lung epithelium might as reasonably explain the tumor process. Very few would be rash enough to assert that the lymph endothelium was also an epithelial tissue, and consequently carcinoma could not possibly arise from it. We would have, then, carcinoma, and never endothelioma, arising from serosal cells, and endothelioma, never carcinoma, from lymph-channel cells, both tumors primary in the pleura and presenting quite similar clinical and pathologic appearances. This argument purposely presents a reductio ad absurdum, but it seems fully justified by the views expressed in the literature.

The additional conception of mesothelium and mesothelioma furnishes little relief to those who feel compelled to derive
carcinoma from pleural tissues. The usefulness, or propriety, of the designation of serosal cells as mesothelium is certainly subject to grave doubt, and the establishment of the tumor class, mesothelioma, fails to solve the problems which the study of these growths presents.

The more logical solution would seem to lie in an entirely different direction, and before formulating this, several further points, continually touched on in this review, deserve more extended comment. First and most important is the fact that primary carcinomas of various organs, such as uterus, stomach, breast and esophagus, may and do metastasize to the pleural cavities. When this occurs, appearances ranging from tiny isolated nodules to extensive diffuse involvement may be presented. In the latter cases it may not be possible to distinguish clinically or pathologically the condition in the pleura from a so-called primary pleural tumor. Indeed, if it were not for the fact that some other primary growth had been discovered, many such cases would pass muster, and probably be reported as primary endotheliomas or carcinomas of the pleura. The logical conclusion concerning such conditions is that many tumors are assigned to the pleura as their primary site solely because no other primary growth is, or can be, found. Even more commonly do primary cancers of the lung show advanced pleural invasion, and it happened in several cases that this invasion was so great, and the tumor of the lung so comparatively insignificant, that the secondary invasion was adjudged to be present in the lung, a position which can rarely receive support from conservative pathologists. It would seem to be a well supported generalization that whenever primary carcinoma of any organ can be definitely identified, the pleural growth represents metastatic involvement and may never be considered primary. Such reasoning is based on readily demonstrable facts. It is well known and widely accepted that, when malignant tumor cells once gain access to a serous cavity by implantation, or by lymphatic extension, they may rapidly and diffusely involve most, or all, of the exposed surfaces and give rise to relatively abundant tumor growth.

1 The discussion of this point will be developed in a further contribution.
This leads us to the consideration of a further important fact, namely, that primary cancerous growths may remain throughout their entire course comparatively small and insignificant. Death in such cases is often brought about as a result of metastatic involvement of other tissues. A small non-obstructive cancer of the stomach with huge metastatic growths in the liver, a tiny pigmented mole with involvement of almost the entire body, and chorioepithelioma of the uterus with extensive tumor formation in both lungs, are examples of a condition which is quite common in practice, as well as in medical literature. A further corollary is contained in the suggestion advanced by several of the previous writers on this subject (Sorgo, Erben, Dahmen). They speak of a latent primary growth, thus inferring the possibility, which would seem perfectly rational, that certain malignant tumors may be subject to partial, or perhaps even total, inhibition at the site of their original growth. If, however, such tumors have already given rise to metastatic extensions, these cells in turn may find themselves in a much more favorable environment, and their growth under these conditions may bring about most bulky and destructive tumors, completely outshadowsing the primary source. The principle of the inhibition of the growth of tumors in certain locations would seem to be well established. Only thus, for example, can be explained the latent character of metastasis from certain tumors of the testicle, or of sarcomas of the long bones, after complete removal of the primary growth. Years may elapse before the secondaries reach demonstrable proportions. A further proof of this conception is furnished by those tumors which exhibit a slow growth for a considerable period of time, and then when, perhaps, inhibitory influences are overcome, break their bounds and rapidly produce death.

My thesis appears to be firmly established. If we once grant that no endothelioma or carcinoma of the pleura can be justifiably diagnosed as primary, in the presence of a known primary growth of another organ, and if we further grant the strong possibility that even if the primary growth in another organ is not known, it may be so small and insignificant as to have
escaped observation, then, *ipso facto*, the diagnosis of primary endothelioma, or carcinoma, or mesothelioma, of the pleura falls to the ground, and cannot be justifiably made under any circumstances. The case of supposed endothelioma of the pericardial cavity furnishes an excellent example of this latter possibility. The final evidence pointed without question to the bronchial mucous glands as the primary source, and yet so obscure or latent was this original tumor that it could not be positively identified after the most careful search.

It would be impossible for any unprejudiced, competent critic to review the published accounts of tumors of this type without suspecting that either the true primary growth was found and described and wrongly interpreted, or else that it was not found because of insufficient investigation or its insignificant character. In a large majority of the cases, beyond hardly any doubt, the so-called primary malignant tumors of the pleura represent metastasis or extensions from a primary carcinoma of the lung. It is not my intention here to argue the question of the justifiability of completely eliminating from medical nomenclature the endothelioma as a tumor type in the other tissues of the body. I am, however, firmly convinced that at least so far as the pleura is concerned, no diagnosis of primary carcinoma, mesothelioma, or endothelioma, either from lymphatic endothelium or serosal surface cells, can ever be justified on any logical ground.

**CONCLUSIONS**

1. Since the beginning of medical scientific literature reports and studies of primary malignant tumors of the pleura have appeared with comparative frequency.

2. These tumors have largely been diagnosed as endothelioma arising from the endothelium of the pleural lymph-channels, although many other terms, such as endothelial cancer and lymphangitis proliferans, have been applied.

3. In later years, following a theory which derived the serosal cells of the pleura, pericardium and peritoneum from the entoderm, several authors have derived tumors from these cells and frankly denominated them carcinomas.
4. My experience with four tumors of the pleura have been similar to that of other writers on the subject, but on encountering a typical appearing "endothelioma" of the pericardium, which was revealed by microscopic study to be an adenocarcinoma, a review of the entire question appeared necessary.

5. This review apparently proves that only the sarcomas can be classified as primary malignant tumors of the pleural tissues, and that all other growths are secondary, representing extensions, implantations or metastasis from an unrecognized or latent primary source, usually the lungs.

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