HODGKIN’S DISEASE OF THE LUNG

SYLVAN E. MOOLTEN, M.D.

(From the Laboratories of the Mount Sinai Hospital, New York)

The frequency of pulmonary involvement in Hodgkin’s disease is best appreciated in statistical comparisons drawn from large series of cases. According to Versé (1), lesions within the lungs are present in about 40 per cent of all cases. Of the 18 most recently autopsied cases in the Mount Sinai Hospital pulmonary lesions were present in 9, and in 2 others lesions existed within the mucosa of the trachea and bronchi. According to F. Kraus and others, this is merely part of a generalization of a disease primarily of the lymphatic tissue (2). However, in perhaps 10 per cent or even more of the cases with pulmonary involvement the clinical and morphological evidence would seem to indicate that the disease actually began within the lung substance (1). Cases of isolated Hodgkin’s disease of the gastro-intestinal tract, though infrequent, are well known (3, 4). Such observations, as well as those of isolated Hodgkin’s disease of the lung, deserve special attention because of the fact that many students of the disease have come to look upon it as the manifestation of an infection whose portal of entry into the body, like that of tuberculosis, may be either the gastro-intestinal or the respiratory tract.

This and other similarities between Hodgkin’s disease and tuberculosis in no way compel one to accept an etiological relationship between the two; in fact, there are many broad similarities between Hodgkin’s disease and the granulomatous manifestations of syphilis as well, or of actinomycosis. These considerations are of importance, rather, in relation to the possible inflammatory nature of Hodgkin’s disease, a theory which within recent years has gained many adherents both abroad and in America (5–13).

There are certain peculiarities in the pulmonary lesions of Hodgkin’s disease which, both from the standpoint of the nature of the disease and of the intimate structure of the lung, give exceptional interest to the study of this subject.
CASE REPORTS

CASE 1: C. B. S., a salesman of forty-seven, was admitted to the Medical Service of the Mount Sinai Hospital (service of Dr. B. S. Oppenheimer) Jan. 15, 1930. Seven months before this, mild feverishness and chilliness were noted by the patient, and he lost appetite and weight. Two and one half months later he complained of sharp pain in the chest, behind both shoulders, during inspiration. His physician made a diagnosis of Hodgkin's disease on the basis of the roentgenological finding of enlarged paratracheal and tracheobronchial lymph nodes. Immediate relief followed institution of radiotherapy. Subsequently pains appeared in the sacral region, radiating to both groins. Enlargement of the cervical lymph nodes was now observed for the first time. There was also some recurrence of pain in the chest, but no cough. Upon admission to the hospital, generalized enlargement of lymph nodes was observed, the abdominal nodes seeming to be particularly enlarged and hard. The spleen was not palpable. A small area of dullness, râles, and bronchovesicular breath sounds was discovered at the base of the right lung. Roentgen films showed dense, enlarged lymph nodes in both hilar regions and diffuse consolidation within the right lung at the hilum. There was no clubbing of the digits. The temperature curve was of febrile type, mounting occasionally to 103° F. The blood showed hemoglobin 80 per cent (Sahli), red blood cells 5,000,000, white cells 8,000, polynuclears 83 per cent, lymphocytes 13 per cent, basophiles 1 per cent, mononuclears 3 per cent. The systolic blood pressure was 100 mm. Hg, diastolic 74. The basal metabolic rate was +12 per cent. Biopsy of a lymph node was reported "Hodgkin's disease"; inoculation of a chicken gave a negative result.

Following resumption of radiotherapy the patient's fever increased and he grew weaker. Roentgen films showed advance of the infiltration at the right hilum (Fig. 1a) and a similar process in the left. There was further loss of weight and the patient became somewhat anemic. Pleural effusion developed, then edema over the sacrum. The liver became swollen, and urobilinuria was observed, but no jaundice. There were frequent attacks of diarrhea. After two months in the hospital death ensued.

Comment: The clinical history in this case is marked by the predominance of pulmonary symptoms and signs, anticipating by several months the discovery of enlarged superficial lymph nodes. These facts suggest the possibility that the disease may have been primary in the lung, though definite proof is lacking. In this case, as in many described in the literature of Hodgkin's disease of the lung (14, 15, 16, 17), the response to radiotherapy was favorable while the disease was confined chiefly to the mediastinum; as the spread within the lung itself became more manifest, there appeared to be virtually a complete loss of effectiveness of radiotherapy.


Description of Lungs (Gross): Both lungs are adherent on either side of a large mediastinal mass, against which they are compressed by an effusion of thin, turbid, greasy fluid. The mass occupies chiefly the anterior mediastinum and is firmly fused with the external surface of the parietal pericardium; it is impossible to separate the lungs from this mass because of its extensive growth into each lung across the obliterated mediastinal pleura. On cut section it is revealed as a solid tissue composed of yellowish rounded areas of homogeneous character separated by pearly white, finely fibrillar connective tissue. Individual lymph nodes are recognizable only in the periphery of the mass and are enlarged and infiltrated. Within the main mass the outlines of individual lymph nodes are obliterated beyond recognition. A discontinuous line of anthracotic pigment marks the obliterated pleura across which the infiltration invades the lung; except for this line no landmarks remain to indicate where the infiltration from the mediastinum becomes intrapulmonic (Fig. 1n). The periphery of the mass within the lung substance, however, exhibits a somewhat different character from the rest; the continuity of the infiltration is increasingly broken up into separate nodular areas separated by grayish white tissue.
in which minute pin-point openings representing partly obliterated alveoli can be distinguished. The latter type of infiltration merges insensibly with the surrounding collapsed but otherwise normal appearing parenchyma of the lung. While most of the mediastinal portion of each lung is solidly involved, the most massive lesion occurs about the hilum. The larger lymph nodes are effaced here; the smaller ones are infiltrated but still discrete. In addition there are numerous prolongations of firm yellowish white infiltration in the form of coarse tapering streaks extending toward the periphery of the lung, conforming to the shape and distribution of the bronchi and arteries which they surround. Transverse section of such infiltrated bronchi and vessels reveals this infiltration as a complete massive encasement greatly increasing the cross-section area of these structures and presenting as nodules. In some areas the smallest bronchi are involved, appearing on cut section as mililiary nodules the size of a pinhead, within the centers of which a tiny lumen is at times detected.

In several areas the infiltration of the parenchyma reaches the periphery and yellowish firm nodules project upon the pleura. A large part of the right lung and upper lobe of the left lung are thus involved; the left lower lobe is affected only in its hilar region, the remainder being atelectatic. The infiltration within the involved parenchyma has a lobular distribution in many places, often confluent, particularly in the right middle lobe.

The mucosal surface of the larger bronchi exhibits several rounded plaques and flat nodules, many of which are confluent. Neither these nor the surrounding dense mass of infiltration cause appreciable narrowing of the bronchial lumen. Within the smaller bronchi there is found a gelatinous greenish exudate which becomes rapidly inspissated on exposure to air.

**Description of Lungs (Microscopic):** The cell mixture comprising the granuloma includes fibroblasts, leukocytes, and numerous examples of a cell possessing some of the features of the undifferentiated reticulum cell as observed in lymph nodes (18). The last is distinguished by its nucleus, which is large, elliptical or bilobed, vesicular, with distinct nuclear membrane and sharply defined, large, round eosinophilic nucleolus; its cytoplasm is pale, variable in amount, frequently in syncytial union with its neighbor cells of similar type. Many cells of this type are seen in mitosis, often of anomalous configuration. Their nuclei are at times somewhat hyperchromatic and monstrous, or
may be round and multiple; the latter type, in particular, corresponds to the typical Sternberg-Reed giant cell. In numerous areas, some of considerable size, the predominant cells are fibroblasts compactly arranged within a mesh of delicate collagen fibrils; at times cells are seen possessing some of the characteristics of both reticulum cell and fibroblast. Elsewhere thick interweaving collagen fibers displace the cellular constituents, forming a dense avascular scar tissue, usually devoid of specific cellular elements. In general the histologic structure of the infiltrating tissue is one of great polymorphism, containing areas of active reticulum cell proliferation side by side with areas of fibroblastic organization, varying degrees of vascularization by large, thin-walled capillaries, and large numbers of small round cells; among the latter plasma cells and lymphocytes predominate and in places are densely massed together. Occasional polynuclear leukocytes occur, chiefly eosinophiles.

In its manner of invasion and replacement of the lung tissue the granuloma exhibits certain well defined characteristics. Where a large bronchus is affected the most extensive infiltration is seen in the outer layers of its wall and in the adventitia of its accompanying artery, yet permeating to some extent the inner layers of its wall even to the mucosa. In a bronchus of smaller size the entire wall may be transformed into a tube of granuloma, with obliteration of all layers. Intermediate stages occur in which part of the muscularis can still be recognized, the cartilages remaining intact or showing early circumferential atrophy, and the submucosal glands still present but separated and distorted by dense cellular infiltration of the stroma. The mucosa is often demuded of epithelium or lined by a single layer of flat cells. Rare multinucleated giant cells are seen lying upon the mucosa. The normal folds of the mucosa are lost, accentuating the tendency to dilatation of the bronchi, which in places is considerable. Masses of closely packed necrotic leukocytes occupy the lumen.

Typically the infiltration extends without interruption from the wall of the bronchus into the surrounding alveoli; these are invaded simultaneously through their lumina (intracanaliculare spread) and within their walls (interstitial spread) in a striking manner, which will be described more fully below. In general, however, the peribronchial infiltration remains more or less circumscribed and, regardless of its extent, maintains the shape of the bronchus.

The branches of the pulmonary artery associated with these bronchi share in this process; the changes, however, are distinctly less developed and for the most part confined to the adventitia. In some of the smaller arteries or arterioles the media is also affected; the muscle fibers are separated and distorted and often atrophic; in many such vessels an intimal change is observed, consisting of a pronounced cellular proliferation of fibroblastic character leading to extreme narrowing of the lumen (Fig. 2A) and even its complete obliteration. Sternberg-Reed giant cells are observed here occasionally. Thromboses are not seen. Despite these marked vascular changes, infarcts are not seen.

Veins are less frequently affected than arteries, possibly because of their separate course within the lung, independent of the bronchi. Nevertheless, in areas where they lie in the path of widespread parenchymal advance of the granuloma the veins are rapidly infiltrated and obliterated, appearing to offer almost no resistance to the granuloma; this is in striking contrast to the arteries (Fig. 2A). Within such large infiltrations the veins are represented only by a ring of single or concentric layers of elastic fibrils, which persist apparently unchanged, and are revealed by special staining.

The lymphatic vessels are involved, as a rule, only in association with major structures within which they lie. Bronchi showing massive involvement no longer exhibit recognizable lymph vessels; bronchi with slight involvement show distinct lymphatic channels, often dilated and containing many free cells, including cells specific to the granuloma.

Occasional bronchi and blood vessels show no departure from the normal. Rarely a minimal lesion is discovered in the outer wall of a bronchus, consisting of scattered plasma cells and a number of proliferating reticulum cells similar to those found in characteristic portions of the granuloma. The latter cells are often situated next to blood or lymph vessels which, however, show no participation by their endothelium.

The evolutionary stages of the granuloma are revealed in their purest form where the specific cell growth takes place within the alveoli. The elementary lesion consists
**Fig. 2. Case 1**

A. Artery of medium size showing granulomatous infiltration of adventitia and media with extension into intima, causing marked fibroblastic proliferation and narrowing of lumen (elastica stain).

B. Granulomatous involvement of small vein within area of massive infiltration (pneumonia granulomatosa). Note preservation of elastica despite extensive specific lesion (including Sternberg-Reed giant cells) within intima causing obliteration of lumen (elastica stain).

C. Pneumonia granulomatosa: granulomatous organization of fibrinous exudate filling alveoli and communicating through Cohn's pores; predominance of fibroblasts.

D. Area of healed granuloma composed of scar tissue with compactly arranged collagen fibers and scattered alveolar remnants showing proliferation and desquamation of epithelium.
apparently of the growth of the specific cell mixture into the alveolar septum, i.e. between the basement membranes (alveolar membrane of Seemann) (19) of contiguous alveolar sacs, with marked widening of the septum. At the same time the alveolar lining cells are apparently stimulated to proliferate upon these basement membranes with the result that both surfaces of the thickened septum become lined by a continuous layer of cuboidal epithelium. Many of these cells are shed into the lumen as large round "foam cells" or pigment-containing phagocytes. Somewhat later there occurs an invasion of the alveolar air spaces by buds of granuloma passing from alveolus to alveolus through their natural ducts and through the "pores of Cohn," without destruction of the alveolar walls. Infiltrations of both types quickly coalesce into a uniform consolidation, and all alveolar outlines are obliterated beyond recognition; nevertheless, by means of elastic stains their natural framework can be demonstrated and often appear entirely preserved. Alveolar epithelial cells are few in such areas and are usually regrouped into small, gland-like formations containing in their lumina masses of degenerating foam cells and free cholesterol crystals.

The alveoli adjacent to infiltrated territories are not without change. In many instances the principal finding is a "catarrh"; the alveolar septa are congested, and their lining cells proliferated, swollen, and in process of desquamation, filling the lumen with their rounded, vacuolated, degenerated forms ("foam cells"). Amorphous, finely granular material is also found in such alveoli, in part suggestive of cellular detritus, in part of coagulated albuminous exudate. Rarely polynuclear leukocytes are found.

A more intense exudative reaction occurs in many alveoli in the form of an outpouring of fibrin; this is accompanied by a greater desquamative and leukocytic reaction. It reaches its maximal intensity within the alveoli immediately adjacent to areas of granulomatous consolidation. In this zone the alveoli are distended with masses of fibrin undergoing organization by cells of the granuloma type which have apparently emigrated from the contiguous granulomatous nodule. Elsewhere the organization of the fibrinous exudate is accomplished by fibroblasts, and the appearance is that of organizing pneumonia (Fig. 2c). In many places the simple fibroblastic type of organization is seen to pass gradually into the granulomatous organization, the loose granulation tissue showing more and more frequently the specific cell types of the disease lying among the fibroblasts, and the alveolar walls showing beginning interstitial infiltration. Finally the organization becomes completely reformed into lymphogranuloma and all trace of pre-existing alveolar outlines is obliterated, except as revealed by elastic stain.

The ultimate fate of the granuloma, whatever its situation or mode of development within the lung, is fibrosis. In its most typical form (Fig. 2b) this is represented by tightly bound wavy fibers of collagen, occasionally hyalinized, as seen in dense scar tissue. Blood vessels are scanty, leukocytes and cells of specific granuloma type are rare or absent. A few arteries of medium or large caliber are buried within the scar tissue. Relics of former alveoli appear as scattered clefts, elongated and irregularly created, at times rounded, at times branched, and lined by low cuboidal epithelium; foam cells fill their lumina. At the periphery of such areas transitions into cellular granuloma may be seen, often showing active growth along their edges. Occasional bronchi or arteries exhibit fibrous thickening of their outer walls in place of former cellular infiltration; in some this forms a dense outer mantle of scar tissue.

Case 2: S. N., a housewife aged fifty-two, was admitted June 6, 1926, to the Medical Service of the Mount Sinai Hospital (service of Dr. B. S. Oppenheimer). Enlarged lymph nodes had been present for three years, associated with generalized pruritus and loss of weight. At the time of admission there were noted some cyanosis and slight clubbing of the fingers. Roentgen examination of the chest revealed widening of the superior mediastinum, and radiotherapy was given to this region. During the succeeding seven months, however, the patient slowly grew worse, and on Jan. 18, 1927, she was readmitted, in a markedly weakened state; she was extremely pale, dyspneic, and somewhat icteric. Examination showed hemoglobin 25 per cent (Sahli), red blood cells 2,400,000, white blood cells 10,400, polyneutrophils 78 per cent, lymphocytes 16 per cent, mononuclears 6 per cent. The urine contained bile. The liver and spleen were now con-
HODGKIN'S DISEASE OF THE LUNG

considerably enlarged and hard. A roentgenogram of the chest showed some increase in the extent of the mediastinal mass; moreover, in place of the former sharp line of demarcation from the adjacent lung, it now exhibited on the left side an "infiltrating border" (type 2 of the classification of Wessler and Greene) (20) (Fig. 3a). Despite transfusions and other supportive treatment, the patient's condition rapidly grew worse, icterus became intense, and she died Feb. 3, 1927.

Fig. 3

A. Case 2: Roentgenogram taken two weeks before death, showing mediastinal infiltration with extensive spread into left lung.

B. Case 2: Lesions of smallest bronchi and bronchioles of pseudo-miliary character.

C. Case 3: Nodule of granuloma showing interstitial infiltration of alveolar septa. Note Sternberg-Reed giant cells within septa and cuboidal-cell lining produced by proliferation of alveolar epithelium.


Description of Lungs (Gross): A dense tumor mass occupies the upper mediastinum, covering the upper half of the pericardium; it is adherent to the overlying ribs and sternum. On section the mass is composed of yellowish tissue, mainly fibrous, without finer structure. The upper lobe of the left lung is fused with the mediastinal mass and widely infiltrated across its pleural boundary; the latter is largely indistinguishable except for an irregular narrow line of anthracosis. The depth of penetration of the lung varies; there is uniform infiltration for 3 to 4 cm. and further prolongations along the septa and blood vessels. The right upper and middle lobes are similarly fused with the mediastinal mass but much less invaded across the line of fusion. Both lower lobes are free; posteriorly they are poorly aerated and compressed. The bronchi show infiltration. At the apex of the right lower lobe is a small wedge-shaped grayish area with central softening.

Description of Lungs (Microscopic): The histologic constitution of the granuloma in this case is typical, practically the same type and proportions of specific cell elements being found as in the preceding case; the exudative features, however, are less prominent, and polymuclear leukocytes are very few. The catarrhal changes in the alveoli are well marked; large masses of foam cells occupy the lumen and degenerate into amorphous granular débris. Fibrin, however, is very scanty, and the characteristics of the pneumonia granulomatoso are lacking. Spread of the granuloma within the parenchyma occurs chiefly through the air-spaces of the alveoli and by interstitial invasion of their walls. Often filling of the lumen occurs before significant thickening of the wall, and its last recognizable remnant is a narrow cleft; this is lined with epithelium and filled with degenerating foam cells and cholesterol crystals. In many nodules, however, interstitial infiltration is more conspicuous, giving an appearance of interlacing bulky trabeculae of cellular infiltration enclosing rounded spaces lined by epithelium. Fibrosis occurs frequently. The spread along the bronchi and bronchioles is massive, and the entire thickness of their walls is permeated with granuloma; in the case of the arteries the adventitial coat only is significantly infiltrated. In a few areas the finest bronchial ramifications are affected, and the microscopic field is studded with smaller and larger nodules which, at first glance, suggest hematogenous miliary dissemination (Fig. 3a). Careful examination, however, reveals in most of these nodules the centrally or eccentrically situated bronchiole or arteriole. Similar nodules are found occasionally composed largely or entirely of dense scar tissues; similarly certain small bronchi and arteries present irregular fibrous expansions of their outer walls in which little or no trace of cellular infiltration can be detected.

Case 3: A. S., a man of twenty-nine, ship's purser, was admitted to the medical service of the Mount Sinai Hospital (service of Dr. B. S. Oppenheimer) Oct. 18, 1932. The patient had visited the tropics on several occasions in the course of various sea voyages. Two years prior to admission he became unduly fatigable and listless; about a year later he began to have night sweats and lost some weight. Following a trip at sea he regained his weight and felt well. Seven months before admission his symptoms recurred, and enlargement of the superficial lymph nodes was discovered. Three months later enlargement of the spleen was noticed. Biopsy of a lymph node confirmed the clinical diagnosis of Hodgkin's disease and radiotherapy was administered with considerable benefit. At this time the patient complained of pain in the left side of his chest, made worse on deep breathing. Frequent unproductive cough accompanied this new symptom. At the time of admission he had been having daily fever for some time, and edema of the ankles; he was somewhat jaundiced and appeared anemic. His blood showed hemoglobin 50 per cent, red blood cells 2,790,000, white blood cells, 1,300, polymonuclears 95 per cent, lymphocytes 2 per cent, basophiles 1 per cent, mononuclears 2 per cent; the icterus index was 35, direct van den Bergh reaction was positive, indirect 1: 33,000 (bilirubin 3.0 mg. per cent). The blood Wassermann reaction was negative. The superficial lymph nodes, the liver, and the spleen were considerably enlarged. A friction rub was heard at the base of the left lung with occasional râles. Roentgen examination of the chest revealed enlargement of the paratracheal and left tracheobronchial groups of lymph nodes.
The course in the hospital was marked by progressive jaundice and anemia. The total leukocyte count never rose above 2400, with a persistently low proportion of lymphocytes. The systolic blood pressure ranged about 80 mm. Hg, the diastolic about 60. For three weeks the temperature varied between 100° and 105° F.; for the next few days there was pronounced hypothermia, the temperature at times dropping below 94° F., then rising to normal on the day of death.


Description of Lungs (Gross): Both lungs are voluminous and heavy, hypercrepitant anteriorly and poorly aerated posteriorly. Their surface is mottled with dark purplish areas of congestion. The pleura is hemorrhagic and covered with a thin deposit of fibrin over a considerable part of the left lung, and both lungs on section exhibit hemorrhagic firm areas of pneumonic consolidation, also areas of grayish red granular appearance. A number of nodules of firm, yellowish white tissue are found in both lungs and in the visceral pleura. In the latter situation they are few in number and exist as tiny rounded granules in the course of surface lymphatics; in addition, a few larger nodules deeper in the lung project slightly above the pleura. Near the hilum of each lung they occur in considerable numbers, lying along the bronchi and blood vessels and surrounding them; the regional lymph nodes are infiltrated and fused with them. In the left lung the nodules are massive and confluent with one another and with the bronchi, vessels, and lymph nodes, by means of a diffuse infiltration containing much coarse, fibrillar, whitish tissue of resistant character. This infiltration can be traced directly into the substance of the wall of the left main bronchus and adventitia of the accompanying blood vessels. When this bronchus is opened, an ulceration is observed in its mucosa, extending from near its orifice into the beginning of the upper lobe bronchus. The edges of the ulceration are irregular and its base is covered with grayish brown exudate.

Description of Lungs (Microscopic): The areas of hemorrhagic pneumonic infiltration observed grossly show the corresponding microscopic picture, viz. alveolar exudate of fibrin, red blood cells, and variable numbers of polymuclear leukocytes; bacterial masses are frequent, also blood-pigment within phagocytes. There is considerable alveolar epithelial desquamation. The intervening lung tissue between these areas shows mild diffuse catarrh.

The yellowish white nodules seen grossly are revealed as lymphogranuloma tissue, conforming closely to type. Sternberg-Reed giant cells are abundant, often showing monstrous nuclei. The peribronchial and perivascular infiltration is most extensive nearest the hilar regions, where sections show widespread solid growth of the granuloma from these points into the surrounding alveoli. The border alveoli are filled with bulky fibrin plugs undergoing granulomatous organization. The alveolar septa are thickened by interstitial infiltration.

Within an area of non-specific catarrhal inflammation a small area of granuloma is discovered secondarily involved in a mild way by the acute non-specific process (Fig. 3c). The proliferating cells of the alveolar lining which have covered the infiltrated septa have become secondarily detached singly or in strips. Within the same lumen as these cells lie granuloma cells, including Sternberg-Reed giant cells, also free, or engaged in a delicate fibrin mesh. It is possible to make very direct comparison of the two types of cell. The freshly desquamated ("irritated") alveolar epithelial cells still possess a polygonal or cuboidal shape, are of uniform size, and contain round, regular nuclei within homogeneous acidophilic finely granular cytoplasm. The granuloma cells have been already described, and show much variation. It is impossible to define cell types of intermediate form between these two, nor do the desquamated alveolar cells depart from their customary morphology, as in non-specific pulmonary lesions of many sorts.

The bronchi contain mucus, also masses of fibrin and blood with many bacterial colonies. The ulceration in the mucosa of the left upper lobe bronchus is superficial; the submucous glands are destroyed in part but the loss of substance does not extend to the cartilage; the bed of the ulcer is typical granuloma tissue with superficial necrosis.
Case 4: P. R., a woman of forty, was observed for swelling beneath the lower jaw, which on biopsy showed "progressive reticulum cell proliferation, probably Hodgkin's disease" (18). She had a slight cough; roentgen examination of the chest was negative. During the ensuing nine months radiotherapy was given to the region first affected. Toward the end of this time enlarged nodes appeared in the right axilla and in the left side of the neck, and the right breast enlarged. Cough grew worse and bubbling sounds were heard by the patient in her chest during breathing. She was admitted to the Bayonne Hospital, Sept. 14, 1932, where roentgenograms of the chest showed marked widening of the superior mediastinum and a convex mass continuous with it within the upper part of the left lung. Examination of the blood showed hemoglobin 64 per cent, red blood cells 3,900,000, white blood cells 7,850, polynuclears 78 per cent, lymphocytes 12 per cent, mononuclears 10 per cent. Breath sounds were poorly transmitted throughout the left chest. The right breast was enlarged and its skin reddened and irregularly thickened ("peau d'orange"). The liver and spleen were not palpated. The condition grew slowly worse, the mediastino-pulmonary mass seen in the roentgen film grew larger, and an effusion developed in the left pleural cavity. The patient died Oct. 9, 1932. Autopsy was performed by Dr. Antopol.


Description of Lungs (Gross): A large mass of enormously swollen lymph nodes, infiltrated and bound together by yellowish white tissue, occupies the superior mediastinum about the trachea and bronchi; the lower portion of the mass bulges downward from beneath the bifurcation of the trachea, compressing the structures at the base of the heart and invading the contiguous area of the pericardium. Anteriorly it invades the thymic region and fills the anterior mediastinum.

At both hilar regions the infiltration extends in a massive manner into each lung, surrounding and infiltrating the bronchi and prolonging itself along their arborizations. The edge of the infiltration, particularly at the hilum where it is most massive, exhibits an indefinite fuzziness, and fades gradually into the surrounding lung tissue. The left lung is adherent in its upper mesial portion to the adjacent region of the infiltrated mediastinum and is occupied near its apex by a mass measuring 4.5 cm. in diameter, continuous with the hilar mediastinal infiltration; on section it appears granular and very cellular, with necrotic portions; it is poorly delimited from the surrounding lung tissue.

When the trachea and bronchi are opened, their submucosa is seen to be infiltrated; there is a superficial ulceration in the region of the carina, and marked narrowing of the orifices of both main bronchi, the right being partly obstructed, the left almost completely occluded.

Description of Lungs (Microscopic): Histologically the infiltration is revealed as granuloma of usual type with an abundance of exudative elements, both leukocytes and fibrin. The extent of alveolar involvement in proportion to the degree of bronchial infiltration is considerable. Masses of compact fibrin fill the alveoli bordering upon the areas of granuloma (Fig. 4a, b) and appear to provide the principal avenue of its advance within the parenchyma. In some areas simple fibroblastic organization of the fibrin has occurred in one part of the field, granulomatous organization in another. Interstitial infiltration of alveolar septa is moderate, rarely producing the extreme thickening seen in other cases (Fig. 4c). Occasional respiratory bronchioles are seen whose lumen is almost entirely obliterated by dense plugs of fibrin undergoing granulomatous organization (granulomatous bronchiolitis obliterans) (Fig. 4d).

Comment

Peribronchial Spread of the Disease: The common pulmonary lesions of Hodgkin's disease are typified in the four cases just recorded. The bronchi are conspicuously involved, and the entire substance of

1 The author is indebted to Dr. William Antopol for this case.
A. Case 4: Granulomatous pneumonia, early stage: low-power photomicrograph showing abundant exudate of fibrin and beginning granulomatous organization.

B. Case 4: Granulomatous pneumonia, early stage: slightly higher magnification showing granulomatous organization.

C. Case 4: Granulomatous pneumonia: higher magnification than B, showing complete granulomatous organization of exudate and beginning interstitial infiltration of alveolar septa.

D. Case 4: Granulomatous pneumonia: bronchiolc showing obliteration of lumen by fibrinous exudate undergoing granulomatous organization (bronchiolitis obliterans).

E. Lymphosarcoma: area of interstitial infiltration of alveoli. Note uneven spreading of alveolar septa producing the appearance of bending, also shedding and destruction of alveolar epithelium.
their walls provides the matrix for the evolution of the granuloma. Not infrequently the bronchi are transformed almost entirely into bulky structureless tubes of granuloma. The infiltration surrounds the accompanying branches of the pulmonary artery and invades their successive layers to a varying extent; at times the infiltration penetrates to the intima and narrows or obliterates the lumen, especially in arteries of small calibre (Fig. 2A). Judged by the far more extensive character of the bronchial involvement, the restricted involvement of the adjacent arteries (at least those of larger size) would seem to depend upon the more compact arrangement of their elastic and muscular layers. The term "pan-bronchitis," used by some authors (21), emphasizes the predominance of the bronchial involvement. As in the case of the lymph nodes, which become densely adherent as the lesion extends beyond their fibrous capsules (perilymphadenitis), the spread of the granuloma in the lung is not confined by the fibrous tissue sheath enclosing bronchus, pulmonary artery, lymphatics, and nerves, but continues into the surrounding alveolar parenchyma in the manner of a peribronchitis or peribronchial pneumonia. As in the four cases described, the combination of granulomatous bronchitis and peribronchitis, lymphadenitis and peri-lymphadenitis, may lead to the obliteration of a considerable part of the lung parenchyma, particularly about the hilum. This may reach an even greater magnitude when, as in Case 1 and Case 2, a large part of the mesial lung field is invaded on each side by a comparable "extracapsular" extension from the mediastinum across the contiguous pleural surfaces (pleurogenous spread) (Fig. 1A).

Significance of Alveolar Changes: A discussion of the alveolar changes in Hodgkin's disease raises questions closely bound with present-day concepts of the fundamental nature of this disease. It is safe to say that the majority of American and European observers (5–13) have reached a tentative accord that it is primarily of inflammatory rather than neoplastic nature. Moreover, it is now looked upon as a disease not necessarily confined to the lymphoid tissues but implicating the mesenchymatous elements of the body wherever existent. Favre (21) has ventured to suggest the possibility of a cytotropic virus with an affinity for mesenchyme upon the analogy of cytotropic virus diseases confined to epithelial structures. Because of their peculiar construction and intrinsic reactions, the pulmonary alveoli occupy a position of importance in the elucidation of some of these questions.

The growth of the Hodgkin's granuloma into the alveolar air spaces occurs in more than one way, as illustrated in the cases already described. In places the alveolar lumen is filled with granuloma tissue growing through the natural air passages; in other places the cells of the granuloma grow into masses of retracted fibrin strung from alveolus to alveolus—specific granulomatous organization (22) (Fig. 4A, b, c); elsewhere the masses of fibrin first become organized by fibroblasts of ordinary type and only subsequently assume the aspects of a specific granulation tissue (Fig. 2c).
It is particularly noteworthy that in the lung the granuloma tissue can be seen to grow in "pure" fashion, so to speak, within the alveolar air-spaces, unencumbered by stroma elements or other pre-existing tissue as found in other organs. The "pure" lesion reveals itself not as the product of a specific cell proliferation, but rather as a specific cell mixture of somewhat varied composition, including fibroblasts, histiocytes, and cells emigrated from the blood. Correspondingly the various stages of fibroblastic transformation and the ultimate dense cicatrization which such a lesion undergoes may be regarded, also, as probably "specific" phases of the lesion. Such findings are of significance in support of the view that the disease is primarily inflammatory in nature.

Comparison between Alveolar Lesions of Hodgkin's Disease and of Other Conditions: The infiltration of the alveolar septa in Hodgkin's disease is one of the outstanding characteristics of the pulmonary lesion; it has been described in some detail by a number of investigators (1, 21, 22). This feature was observed in each one of the cases in this series and typically in very pronounced degree (Fig. 3c). The widening of the alveolar septa at the expense of the lumina may progress to the point of complete obliteration of the latter or to their reduction to minute, epithelium-lined, rounded openings. Extensive areas of parenchyma may be transformed by this process alone into granuloma tissue which is solid except for isolated glandular structures representing the alveolar remnants. The peculiar facility of development of granulomatous interstitial alveolitis is approached in degree only by such frankly inflammatory processes as tuberculosis and actinomycosis. This is of particular interest in view of the fact that the interstitium of the alveolar septum is ordinarily impossible to demonstrate under normal conditions in the inflated lung. Its existence has actually been denied by an important observer (23). In early fetal life, however, the interstitial tissue constitutes the largest part of the growing lung. It appears as a loose jelly containing cells of mesodermal type; into this matrix the entodermal outgrowths of the primitive lung bud grow and ramify to form the primitive bronchi and alveoli. The persistence after birth of mesenchymal elements within the alveolar septum as autochthonous reacting cells in disease conditions must be inferred, not only from the findings in the above-mentioned conditions, but also from observations in simple acute inflammations of the lung, such as those produced by hemolytic streptococci. It is often possible to demonstrate individual alveolar septa showing edema separating the alveolar membrane from the engorged capillary. In the space thus formed leukocytes may be seen, tangled threads of fibrin, and a few pale-staining cells of histiocytic type (24). Paradoxically, a significant degree of edema of the alveolar septum is rarely possible to demonstrate in passive congestion of the capillaries in heart disease; even in cases of long duration it is very slight (25). These findings suggest the active participation of inflammation as such in the development of interstitial edema, possibly through some solvent action upon an intercellular
cement substance or upon the fibrillar reticulum which permits the separation of the basement membrane of the alveolar wall from the capillaries. Not infrequently the end-result of interstitial inflammation is seen in the form of interstitial fibrosis with loss of vascularity. The shape of such alveoli is often preserved, but their size reduced by the increased width of their fibrotic septa and by their retraction; they give the impression of being rigid and non-functioning. The walls of such alveoli are lined by a continuous carpet of low cuboidal epithelium of the type seen in the "gland-like formations" and quite distinct from bronchial epithelium. The case descriptions already given indicate how frequently many of these features are seen in the pulmonary lesions of Hodgkin's disease.

**Lymphosarcoma:** Infiltration of alveolar septa is not confined to inflammatory lesions. In cases of lymphosarcomatosis involving the lungs, bulky infiltrated alveolar septa may be seen resembling in some respects the analogous condition in Hodgkin's disease (Fig. 4). Inasmuch as the cells of Hodgkin's granuloma may at times lack the usual broad variations and accessory features which are characteristic, and instead tend to revert to a more uniform and more anaplastic character, such as is seen in immature (reticulum cell) lymphosarcoma (18), the need for criteria of differentiation is obvious. While it has not been possible to develop absolute criteria of differentiation between the two histologically, in at least one respect the alveolar infiltration of Hodgkin's disease, regardless of its cellular composition, may be called characteristic, namely its relation to the alveolar lining epithelium.² In

² The term "epithelium" is employed here to designate both the well known "alveolar phagocyte" and the cuboidal cells which line compressed or thickened non-functioning alveoli under a variety of conditions to form the "pseudoadenomatous" or "gland-like structures." The common origin of both types of cell seems probable from numerous evidences. Phagocytosis, for example, is observed not only in the desquamated large round cell but also in the smaller cells which form a continuous epithelium; intermediate stages are often demonstrable as, for example, in the outer wall of a chronic lung abscess in which cicatrization and healing go on side by side with acute inflammation; the phagocytic activity of the cells appears to be in direct proportion to the amount of their cytoplasm and degree of detachment from the alveolar wall.

Whether such epithelium is, embryologically speaking, of entodermal or of mesodermal origin is still much disputed. The chief evidence in favor of the mesodermal hypothesis is the actively phagocytic behavior of the lining cell, even while still in situ, but particularly after desquamation; likewise its tendency to form multinuclear conglomerates resembling foreign-body giant cells, at times of huge size. Phagocytosis, however, is not restricted to mesodermal derivatives, as pointed out by Cappell (26), but may be seen in epithelial organs undergoing atrophy (Guineyse-Pollissier, Wegelin), in "chronic mastitis," in certain tumors, in the central nervous system (Lubarsch), in tissue cultures (D. T. Smith, Lewis), and in the genital tract. Duthie (27) has recently shown active phagocytosis by bronchial epithelium to occur in mice exposed to dusty atmosphere, not only by cells desquamating singly or in groups, but by cells still in epithelial continuity.

In favor of the entodermal hypothesis is the obvious morphological fact of the existence of a definite cuboidal cell layer of unquestioned epithelial aspect making definite abrupt junction with the epithelium of the bronchioles under conditions leading to epithelial proliferation. The assertion (Fried, 28; Polleard, 29; Lang 30) that such epithelial gland-like structures are actually downgrowths from the bronchiolar epithelium fails to account for their very frequent occurrence in situations remote from bronchioli, such as the distal segment of the wall of the first subpleural alveoli in cases of pleural effusion or suppuration (24), or as a result of experimental chemical irritation of the pleura (Young, 31). Other evidences include
cases of lymphosarcoma with interstitial alveolar infiltration there is seen very little, if any, proliferation of alveolar epithelium; the septa appear to bulge and exhibit a tendency to exfoliation of whatever cells exist upon their surface, and generally appear naked of epithelium (Fig. 4e). In Hodgkin's disease, on the other hand, as in tuberculosis or actinomycosis, the infiltrated alveolar septa exhibit pronounced and active epithelial proliferation with abundant desquamation into the lumen, and with formation of a continuous lining of cuboidal cells whenever the septa have attained a certain degree of rigidity through cellular thickening or fibrosis (Fig. 2b, 3c). This fact fortifies considerably the point of view which identifies Hodgkin's disease, even when it appears most atypical histologically, with inflammation rather than neoplasia.

Non-specific Lesions: It should be clear from the four cases already described that not all the inflammatory and reparative phenomena encountered present the specific features of Hodgkin's granuloma. There is an abundant non-specific reaction in many areas which are quite free of obvious granuloma. This consists most often in "catarrhal alveolitis," i.e. exudation into the alveolar lumen of serum, a few leukocytes, and occasionally small amounts of fibrin and red blood cells. The alveolar lining cells undergo proliferation and are shed in large numbers into the lumen as "foam cells," which subsequently degenerate and liberate their contained cholesterol in the form of crystals. These changes have the aspect of an exceedingly mild irritative pneumonia; they do not lend themselves to definite etiological interpretation since, on the one hand, it is possible to regard them as resulting from the spilling into the alveoli of fluid exudate and detritus from bronchi which are the seat of infiltrations. On the other hand, it is possible that these changes are evoked by the virus of the disease itself or its toxins. In support of the latter view is the important fact that these non-specific the finding of certain "specific" lipid granules in such cells (and in the desquamating phagocytic cell) which are found otherwise only in the definitive alveolar endoderm of the fetus (Wenslaw, 32). Moreover, in the healing of pulmonary lesions these cells appear to possess one attribute only, that of forming epithelium; they never participate in the organization of fibrinous exudate, and definite proof is lacking that they enter into the formation of Langhans giant cells in tuberculosis, as suggested by Priol (28), or of the Sternberg-Reed giant cell, as suggested by Foulon (33). Furthermore, these cells are not seen within the interstitial space of the alveolar wall when the latter is widened by inflammation, but lie instead along its outer surface external to the basement membrane, where they apparently proliferate.

The work of Cappell (26), Seemann (19), Wenslaw (32), and others, indicates that the alveolar epithelium in the normal resting state is not a continuous lining, but exists as scattered cells singly or in small groups, the intervening capillaries being bare. Confirmatory evidence (Dogliotti, 34; Siracus, 35; personal observations) derived from the fetus reveals the loss of continuity between alveolar endodermal cells to begin during the fourth or fifth month, apparently as a result of evaginations of proliferating capillary loops into the potential lumen; epithelial continuity is maintained longest in the distal tip of the growing alveolus, viz. in that portion farthest from the bronchus. Whether separate or continuous, the endodermal cells of the fetal (uninflated) alveoli preserve certain morphological characters which permit them to be easily recognized during all stages before birth. Personal studies (unpublished) of the lungs of mature fetuses dying during birth have shown very active phagocytosis of aspirated meconium particles by these cells in a manner strikingly similar to that of the alveolar phagocyte of the mature lung.
changes occur close to areas of specific lesion without regard for bronchial pathways of conduction such as a purely spill-over reaction might be expected to follow. The same may be said for the areas of non-specific organizing pneumonia or of non-specific interstitial alveolitis, which may end in fibrosis without ever exhibiting the features of lymphohgranulomatosis, yet do not occur except in close anatomical proximity to granuloma nodules.

**Exudative Phase:** In connection with these mild forms of non-specific inflammation it is worthy of note that each of the cases described above exhibited, within the granulomatous lesions themselves, an abundance of those elements which characterize acute and subacute inflammation in general. Polynuclear leukocytes, eosinophiles, plasma cells, fibrin, and numerous fibroblasts were seen in varying amounts not only within the intra-pulmonic infiltrations but also within the involved lymph nodes. The non-specific acute inflammatory lesions, described in the preceding paragraph, together with inflammatory features of similar type within the specific granulomatous lesions, may both properly be included under the single descriptive term "exudative phase," signifying a definite phase of response of the host to the virus, similar to that seen in the evolution of tuberculosis, syphilis, and other infections.

In these cases, which in particular are marked by the richness of their exudative phase, certain relationships appear to exist between the degree of acute or subacute inflammation which is part of the lesions and the degree to which these lesions involve the alveoli. The relation of inflammation to the degree of permeability of the alveolar interstitium has already been discussed. In the case of Hodgkin's disease the most massive invasion of the interstitium of the alveolar septa is seen in cases such as the four described, in which the exudative phase is well defined. A similar relation seems to hold as well for the marked degree of peribronchitis, perilymphadenitis, and, in two cases, massive transpleural invasion of the lung from the mediastinum.

In the alveoli forming the frontier of granulomatous nodules it is common to see heavy skeins and clumps of fibrin clot almost filling the lumen. Extension into this fibrin of adjacent granuloma occurs in a regular manner in the form of a specific type of organization; in certain areas there is a preliminary stage of fibroblastic organization. The specific granulation tissue subsequently undergoes fibrosis, and the features of granuloma disappear as the process assumes more and more the aspects of ordinary fibrous scar tissue. The term "carnification" has been applied to this process by Ceelen and excellently described in detail by his pupil Fincke (22); they reserve the term "pseudo-carnification" for the fibrosis which follows in the wake of granuloma tissue which invades alveoli devoid of fibrinous exudate. Fibrin as such is not necessarily an evidence of primary inflammation in the ordinary sense, since it is frequent in association with metastatic carcinoma, lymphosarcoma, and other forms of neoplasia. Actually invasion of fibrin may be seen at times at the periphery of an area of
lymphosarcoma by the cells of the lymphosarcoma itself. In Hodgkin's disease, on the other hand, not only may fibrinous exudation be more abundant, depending on the degree of exudative component of the lesion, but it may be spread at times over a very wide area. The latter fact would seem to disprove the theory that the exudation of fibrin resulted merely from the locally destructive action of the lesion, as in the case of neoplasms, and would hint at the conveyance of some irritative agent somewhat beyond the immediate confines of the specific lesion. In all probability, then, the presence of fibrin is intrinsic to the disease as part of its exudative phase. It is not unlikely that fibrin occurs frequently in lesions developing elsewhere than in the lung, e.g. the lymph nodes (Foulon, 36), yet in no other organ but the lung is it possible to distinguish with such clarity either the very mild expression of the exudative phase of Hodgkin's disease, as seen in the catarrhal alveolitis, or the more intense fibrinous phase with its striking relation to the spread of the lesion, as seen in the granulomatous pneumonia.

The conservation and stimulation of alveolar epithelium, already discussed as a means of differentiation from lymphosarcoma, may be further adduced as evidence in general against the theory of Hodgkin's disease as a neoplasm and in favor of its classification with the infectious granulomas. Related to this is the rarity of an expansion tendency in nodules of granuloma in contrast to carcinoma; this may be appreciated even in the gross inspection of the lesions, which, as described in the protocols, may appear either as sharply circumscribed lesions with little or no atelectasis of the surrounding alveoli, or as imperfectly defined from these alveoli by a very gradual transition (Fig. 1b); in the zone of transition there may be seen various stages of alveolar septal thickening macroscopically. This is verified microscopically; atelectasis is a rare accompaniment of the lesions, and when it is present is most often explained rather by some special event, such as massive pleural effusion or bronchial occlusion affecting a large area uniformly.

**Case Report**

**Case 5:** E. T., a merchant of forty-nine, was admitted April 12, 1929, to the Mount Sinai Hospital under the care of Dr. Howard Lilienthal. The patient was Syrian by birth but had lived many years in Guatemala, Central America. He mentioned a past history of rheumatism at eighteen, two "chaneres" at twenty, and malaria at forty; otherwise he had been in excellent health and was always robust. For a number of years he had "bronchitis." Eighteen months before his admission to the hospital, a painless, hard lump appeared in the lower left parotid region, reaching the size of a pigeon's egg and then disappearing; the blood Wassermann test was negative. About nine months later he suddenly expectorated an unusually large quantity of sputum for a day. Cough and expectoration grew persistently worse, and about one month prior to admission were accompanied by fever and blood-streaking. At the time of admission the patient was somewhat short of breath, and, in addition, had occasional paroxysms of acute dyspnea and wheezing suggestive of asthma.

Physical examination indicated the existence of massive effusion within the right pleural cavity; this was verified by roentgen examination which showed, in addition, slight deviation of the heart and bronchi toward the right. This paradoxical shift of the
mediastinal structures toward the side of the effusion was again observed in a subsequent roentgen film. Compression of the right bronchus by tumor was diagnosed. Fluid was aspirated but the dyspnea was only slightly relieved. A catheter was therefore inserted into the right pleural cavity and permitted to drain. The fluid removed was clear, and centrifuged specimens contained cells resembling lymphocytes only. Despite the presence of the catheter drain, the patient grew constantly more dyspneic and had more frequent and more severe attacks of "asthma," during which he was described as "veritally gasping." Because of the gravity of his condition bronchoscopy could not be done. Thoracotomy was performed and a large amount of gelatinous clot removed from the pleura; through the opened chest wall the lung was seen to be thoroughly collapsed. An attempt to re-expand the lung by forced air pressure intratracheally failed completely. Following operation the temperature gradually rose, synopal attacks developed, and oxygen was needed continuously. Death occurred one week after operation. Autopsy was limited to examination of the thoracic contents.


Description of Lungs (Gross): The entire right lung is overlaid by a thick, tough sheet of fibrino-purulent exudate, thickest in its lower and lateral portions. The lobes are agglutinated to one another and to the chest wall. The right leaf of the diaphragm is very high. The entire right lung is shrunken, almost to one third its normal size, and is non-crepitant, with fleshy consistence. The left lung is free, voluminous, and somewhat congested superficially. Both lungs were injected through the trachea with sodium iodide solution and roentgenograms were made (Fig. 5A). By this means there is demonstrated a filling defect in the right main bronchus; the bronchial ramifications of the left lung appear normal.

When the trachea is opened the orifice of the right main bronchus is found plugged by a mass the size and approximate shape of a large peanut; its surface presents rudimentary lobulation and is covered by a smooth layer of mucous membrane (Fig. 5B). Its upper limit is rounded, projecting slightly into the trachea where it reaches the level of the carina. The entire length is 4 cm., the average width 2 cm., and the height of elevation above the surrounding bronchial mucosa 1 cm. The length of the base of attachment to the posterior bronchial wall is somewhat less than the total length, measuring 3.2 cm. The entire tumor is somewhat rubbery in consistence. Cut section shows it to be composed of uniform pale yellowish white solid tissue; the same tissue continues through the underlying bronchial wall into the adjacent lymph nodes, which are enlarged and infiltrated. Some of these nodes show yellowish areas of necrosis, but none is seen within the endobronchial tumor. The submucosa of the trachea above the tumor shows infiltration of slight extent. The bronchi distal to the tumor are somewhat dilated and their mucosa appears acutely inflamed.

The right lung, on cut section, appears airless. Within the hilum region is a broad, solid, yellowish white infiltration binding together the lymph nodes into a single mass the size of a hen's egg and continuing without interruption into the infiltrated lymph nodes in the adjacent mediastinum. From this mass short prolongations of infiltration extend outward along the bronchi which pass through it. The remainder of the lung contains granular, firm congested areas of bronchopneumonic character scattered within airless parenchyma.

Sections through the left lung show no abnormality except hypostatic congestion.

Description of Lungs (Microscopic): The customary balance between exudative and proliferative phases of lymphogranulomatosis is lacking. Instead, an exceedingly active and unrestrained reticulum-cell proliferation appears to dominate the histologic picture. It is seen probably in purest form in sections taken through the polypoid mass springing from the wall of the right main bronchus and occluding its lumen. Except for its rudimentary discontinuous epithelial lining, the entire mass is composed of tightly packed cells, typically in syncytial continuity, the cytoplasm scanty, basophilic, and finely granular, the nuclei large, round, vesicular, at times monstrous, with dense nucleoli,
delicate nuclear membrane, and very numerous mitoses, which are often of anomalous type (Fig. 5c). Scattered lymphocytes and polymuclear leukocytes are seen, and blood vessels are disproportionately few. Occasional small circumscribed areas of anemic necrosis are noted. In a few areas fibroblastic transformation is taking place and the cells are some-

![Fig. 5. Case 5](image)

A. Roentgenogram of unopened post-mortem specimen after intratracheal introduction of sodium iodide solution, demonstrating completeness of obstruction of right main bronchus.

B. Gross appearance of lung, showing polypoid mass obstructing right main bronchus.

C. Section of tissue composing polyp, showing active proliferation of cells of undifferentiated reticulum-cell type.

D. Section through base of polyp, showing lesion of older type with fibroblasts and giant cells.

what spread apart by delicate young collagen fibrils interweaving to form an irregular network. Multinuclear cells are few and small.

Sections taken from the depths of the hilar mass show an older stage of the lesion, evidenced by more widespread fibrosis; multinuclear cells are more numerous and larger, approaching the typical Sternberg-Reed type (Fig. 5d). Blood vessels are encountered in which the lumen is almost if not completely obliterated by granulomatous intimal pro-
liferation, and the outer coats diffusely infiltrated; veins are chiefly affected. The characteristic pan-bronchitis exists, also the distinctive alveolar septal infiltration and epithelial proliferation. The alveolar territory which, in turn, surrounds such foci shows albuminous and fibrinous exudation with beginning granulomatous organization of the nearest fibrin masses. The remainder of the parenchyma shows diffuse atelectasis, congestion, desquamative catarrh, and patchy fibrino-purulent bronchopneumonia (acute).

**Comment**

Massive polypoid growths obstructing the lumen of the large bronchi have not been reported, to our knowledge, in Hodgkin's disease, and the case herein described deserves particular distinction in this respect. Because of the strategic situation of the granulomatous polyp, obstructing the right main bronchus, the entire course of the disease in this case was governed by this unusual accident of growth rather than by the customary development of the lesions. The symptoms of bronchial obstruction, particularly the wheezing dyspnea and asthmatic paroxysms, developed and progressed with great rapidity and were undoubt-edly aggravated by the pleural effusion. Because of the comparatively short duration of bronchial obstruction, the clinical features of bronchiectatic disease were mild, and at autopsy only moderate dilatation of the peripheral bronchi was found; this is in conspicuous contrast with the observations in other obstructive states, particularly the very slowly growing adenomatous polyp of the bronchus (37). That the bronchial obstruction had become absolute is clear from the surgeon's account of the failure of the lung, observed through the thoracotomy incision, to become inflated when air under pressure was introduced into the upper air passages. This was confirmed once more by the post-mortem experiment with sodium iodide solution (Fig. 5).

**Varieties of Lymphogranulomatous Bronchitis:** While this case presents a peculiar and rare variety of bronchial involvement in Hodgkin's disease, a significant degree of bronchial involvement must nevertheless be reckoned among the most typical features of the disease as it affects the lung. The changes in the bronchi which affect their lumen, both as regards calibre and surface lining, show great variability. Commonly a certain degree of granulomatous infiltration of the mucosa and cylindrical widening of the lumen occurs merely as part of the so-called pan-bronchitis. This may appear to the pathologist as a simple chronic or acute bronchitis when the bronchi are opened at the autopsy table (38). Frequently, however, the specific nature of the bronchitis is suggested by plaque-like opacities in various parts of the mucosa or by elevated areas or bulky nodular outgrowths which narrow the lumen considerably (1). Complete occlusion of large bronchi, as in Case 4, has been recorded not infrequently (36, 39, 40).

Often the preliminary macroscopic diagnosis in cases showing much bronchial involvement has been carcinoma of the bronchus (42); lymphogranulomatosis was not suspected until sections were studied microscopically. In carcinoma of the bronchus, as is well known, the surface of the growth is often irregular, heaped up, knobby or granular,
HODGKIN’S DISEASE OF THE LUNG

with more or less surface ulceration; on the other hand, in some of the more rapidly disseminated forms the local growth may be flat or even actually submucosal for the most part, causing no more than a suspicious wrinkling of the surface, yet infiltrating widely the loose tissue of the bronchial wall and the peribronchial lymphatics. Obstruction of the lumen by carcinoma is due either to strictural contraction of the infiltrated wall, compression by external tumor masses, or irregular projection into the lumen of the tumor itself; obstruction by an actual polypoid projection of the tumor, however, is rare. In all the foregoing macroscopic respects, Hodgkin’s disease of the bronchus resembles carcinoma.

In certain instances the gross differentiation of Hodgkin’s disease of the bronchus and carcinoma may be possible if the following distinctions are kept in mind: in Hodgkin’s disease the elevated patches are part of a diffuse bronchitis and are accordingly much more often multiple and bilaterally situated than the plaques of carcinoma, which are typically single or closely grouped. Cases are on record in which the granulomatous involvement of the bronchi existed in the form of numerous plaques scattered along both bronchi and the lower trachea, some of considerable extent and causing much narrowing of the lumen and secondary bronchiectasis distally (41); in some cases the lesion presented as a “tumorous” outgrowth of homogeneous tissue within the lumen (1, 42). In some cases the entire bronchial mucosa was reddened and thickened, displaying numerous projecting nodules, and associated with much reduction in calibre of the entire bronchial tree (43). In Frankenberger’s (44) case there was marked narrowing of the trachea as well; in this case the granulomatous infiltration began 4 cm. below the vocal cords and extended into both bronchial divisions; the mucosa exhibited diffuse infiltration together with a number of nodular swellings and superficial ulcerations. In Hodgkin’s disease the individual patches in the bronchi tend to be less sharply circumscribed than those of carcinoma, at times appearing to fade at their edges by imperceptible degrees into the surrounding mucosa.

In occasional cases of Hodgkin’s disease of the lung the endobronchial spread predominates. More often, however, it is merely an expression of the completeness of its permeation of the entire structure of the bronchial wall. Polypoid projection into the bronchial lumen as seen in the case described above must be considered unique. Clinically the rôle of bronchoscopy in the diagnosis and treatment of suitable cases is still to be evaluated, e.g. in stricture of a bronchus such as observed clinically in Hurd’s case (45).

Case Report

Case 6: A. S., a bookkeeper aged twenty-seven, was admitted to the Medical Service of the Mount Sinai Hospital (service of Dr. E. Libman) Jan. 5, 1925. His chief symptom, backache, first appeared two years previously, associated with “sciatica”; since then he had been losing weight and strength despite cessation of pain. One year before admission pain recurred in the lower spine, associated with constricting pains in the abdominal wall. Anorexia became marked and there was a further loss of fifteen pounds.
Subsequently attacks of marked constipation occurred and occasional fever. Eight months before admission enlargement of the cervical lymph nodes appeared, followed by enlargement of the inguinal and axillary nodes. Biopsy revealed Hodgkin’s disease, and radiotherapy was given. One month before admission the spleen and all the superficial lymph nodes were enlarged. The blood showed hemoglobin 68 percent, red blood cells 3,200,000, white blood cells 12,200, polynuclears 80 percent, eosinophiles 2 percent, lymphocytes 13 percent, mononuclears 5 percent. The urinary sediment contained a moderate number of leukocytes. Roentgen examination of the chest showed enlarged bronchial lymph nodes which were considerably calcified; the mid-dorsal region of the spine showed moderate scoliosis. Radiotherapy was given with considerable benefit; the temperature, previously higher than 103°F, dropped to normal, and the patient gained twenty pounds in weight. Because of leukopenia (white blood cells 3,800), treatment was interrupted at the end of three weeks.

More than a year elapsed before the patient was re-admitted (May 25, 1926), complaining of weakness and loss of weight. Roentgen examination of the chest showed no change. Radiotherapy was resumed, and the patient remained in fairly good health for several months. Gradually weakness, loss of weight, and periodic fever compelled hospitalization and he was re-admitted May 30, 1927, almost in extremis. Pallor was marked and generalized anasarca existed. The blood showed hemoglobin 16 percent, red blood cells 1,380,000, white blood cells 6,800, polynuclears 82 percent, lymphocytes 16 percent, mononuclears 2 percent. Death occurred the following day.


Description of Lungs (Gross): Each pleural cavity contains about one liter of yellowish cloudy fluid. The right lung is loosely bound to the chest wall by numerous fibrous adhesions. The interlobar fissures are obliterated by adhesions. The right middle lobe and right lower lobe are almost completely consolidated by grayish white solid tissue disposed in innumerable rounded nodules separated by softer translucent tissue within which very little alveolar structure is recognizable. At the base of the lung these nodules are fused into one solid mass. The nodular infiltration extends to the surface of the involved lobes, and the pleura is studded with numerous rounded, firm nodules of the same character. The recognizable bronchi are greatly thickened by infiltration, and the regional hilar lymph nodes are enlarged and completely replaced by the same tissue. The left lung is adherent; the apex of the left upper lobe is capped by firm white tissue similar to that seen in the right lung. The trachea and bronchi contain creamy pus.

Description of Lungs (Microscopic): All the essential histologic features noted in the preceding cases are embodied in this case. The type and degree of spread of the granuloma within the lung are of the same order as exemplified in Cases 1 and 2. The nodules observed on gross inspection of the cut surface of the involved lobes are revealed microscopically as the cut section of bronchi and bronchioles showing an extreme degree of peribronchitis and peribronchial pneumonia to the exclusion of a large part of the intervening parenchyma (Fig. 6A). Not a single uninvolved bronchus or bronchiole is found in any of the sections taken from the involved lobes. Some of the bronchi in the involved areas are converted completely into thick tubes of granuloma; in others the change is less extreme and remnants of cartilage and of muscle may be identified. The mucosa is often denuded of epithelium and superficially infiltrated with numerous polynuclear leukocytes. Within the lumen are considerable numbers of polynuclear leukocytes and of granuloma cells, often necrotic and fused into amorphous shreds and masses of granular detritus stained blue with hematoxylin. Some of the smaller bronchi show healing infiltration; in a number of cases their entire supporting structure has been transformed into dense scar tissue, which also surrounds their associated blood vessels and includes along the periphery a number of partially obliterated alveoli. The lumen of such bronchi is somewhat diminished but is generally round and lined by well pre-
A. Granulomatous bronchopneumonia: extensive pan-bronchitis involving adventitia of accompanying artery and surrounding alveoli. Note catarrhal alveolar reaction and numerous cholesterol crystals resulting from degeneration of desquamated alveolar epithelial cells.

B. Healed bronchial lesion: replacement of granulomatous infiltration with scar tissue. Note hyperplastic bronchial epithelium. Active lesion present nearby (granulomatous bronchopneumonia).

C. Section showing alveolar rudiments within extensive lesion resulting from confluence of specific bronchopneumonic areas with areas of healing. Note gland-like appearance resulting from proliferation of alveolar epithelium (cf. Fig. 2d).
served tall columnar epithelium, often appearing hyperplastic, lying directly upon the dense fibrous tissue (Fig. 6b).

Interstitial granulomatous alveolitis accounts in greatest measure for the obliteration of parenchyma in and surrounding the nodules observed grossly. In addition many alveoli are filled with fibrin masses undergoing organization, either with ordinary fibroblasts or with cells characteristic of the granuloma. In the narrow spaces remaining between many adjacent nodules of solid infiltration may be seen various stages of involvement of the alveoli about to undergo obliteration; the catarrhal and fibrinous exudative reactions are well developed in their lumina and marked interstitial infiltration in their walls. The cuboidal epithelial cells lining the walls are retained until the lumen is completely obliterated. Even at this stage scattered groups of swollen epithelial cells with foamy cytoplasm persist within the granulomatous consolidation or become degenerated with liberation of cholesterol crystals (Fig. 6c).

COMMENT

This case is noteworthy for the fact that such pulmonary involvement as existed was asymmetrical, being confined largely to two lobes of the right lung, the right middle and right lower lobes. That this rather unusual situation had existed for a considerable length of time is indicated by the very nearly complete replacement of these lobes by granuloma and the abundance of fibrosis. As in the four cases first described, the marked extent of the peribronchial parenchymal involvement seems to stand in direct relation to the exuberance of exudative characters of all sorts within the specific lesions and beyond them, as described in the protocol.

CASE REPORT

CASE 7: L. B., a schoolboy of sixteen, was admitted to the Medical Service of the Mount Sinai Hospital (service of Dr. B. S. Oppenheimer), Oct. 26, 1928. At the age of eight a lymph node the size of a pea had been noticed in the right side of his neck; this grew slowly. At the age of fourteen, two years before admission to the hospital, there was an appreciable acceleration in the growth of the node, and five months before admission it had attained the size of an egg. It was removed and on examination showed Hodgkin’s disease. Radiotherapy was begun. For several weeks intermittent fever occurred in cycles of about two weeks, with fever-free intervals of a few days; cough with slight expectoration became persistent, frequently paroxysmal. On admission enlarged nodes were discovered in the right supraclavicular area; the spleen was enlarged. The blood showed hemoglobin 93 per cent, red blood cells 4,900,000, white blood cells 4,100, polymorphs 60 per cent, eosinophiles 1 per cent, lymphocytes 27 per cent, mononuclears 12 per cent. The Mantoux test (intra-dermal tuberculin test) was negative with old tuberculin and with avian tuberculin. Oscillating fever of 100° to 105° F. or higher continued. The hemoglobin sank rapidly to 32 per cent and the spleen became enormous. Roentgenographic examination of the chest was negative on two occasions. Death occurred seven weeks after admission.


Description of Lungs (Gross): There is no effusion in either pleural cavity. Both lungs are free, and resemble each other closely in all respects. The surface of the lung is pale and smooth. On section it has a yellowish red color, and crepitation is somewhat decreased. Many white, firm, discrete nodules are detected on close inspection, lying within the region of the lower border of the upper and lower lobes; on section these
appear homogeneous and yellowish white in color. Ill-defined yellowish areas are occasionally seen elsewhere in the lung, only slightly firmer than the intervening lung substance, which otherwise appears normal. The mucosa of the trachea and bronchi is pale. The tracheobronchial lymph nodes and paratracheal lymph nodes are moderately enlarged,

![Image of lung tissue](image)

**Fig. 7. Case 7**

A. Granulomatous interstitial bronchopneumonia of almost exclusively proliferative character. Note lack of exudative elements in surrounding alveoli.

B. Higher magnification of part of lesion seen in A. Note granulomatous interstitial infiltration of surrounding alveoli with proliferation of alveolar epithelium to form gland-like structures. Note, also, lack of desquamation of alveolar epithelium (alveolar phagocytes) as seen in exudative lesion.

soft, somewhat anthracotic, and infiltrated with homogeneous yellowish white tissue like that within the lung.

*Description of Lungs (Microscopic)*: The composition of the infiltrating tissue differs in certain respects from that seen in the preceding cases. The histologic analysis shows a predominance of reticulum cells of comparatively anaplastic type; the dominant cell type is a round or polygonal cell with conspicuously large vesicular nucleus and rather scanty acidophilic cytoplasm; the nucleus varies in shape and is often divided by fissures;
the nucleolus is often small or buried in coarse clumps of chromatin; mitosis is frequent. Fibroblasts are not frequent, and fibrous transformation, although present, is not a prominent feature. Polynuclear leukocytes and plasma cells are few. A few areas of characteristic lymphgranuloma of ordinary type are to be seen; the great majority of the infiltrations, however, show the composition described above, and are marked by the uniform character of the tissue and its lack of polymorphism.

The spread of granuloma longitudinally along the broncho-vascular sheaths is far more in evidence than its radial spread from these structures into the surrounding alveoli (Fig. 7A). The granulomatous pan-bronchitis is well developed, and there occur papillary ingrowths of granuloma tissue into the bronchial lumen, with superficial ulceration. The arteries are involved only slightly, and the changes that occur are almost entirely adventitial. The few lymphatic vessels still recognizable in these situations contain scattered free cells in their lumen which, for the most part, resemble closely the polygonal cells of the granuloma. Despite considerable granulomatous thickening of the bronchi and bronchioles, the line of separation from the surrounding parenchyma is sharply defined. For the most part the parenchyma shows no alterations whatever. Close inspection, however, reveals a fringe of alveolar infiltration surrounding the entire broncho-arterial mantle of granuloma. The involvement of these border alveoli is purely interstitial, the alveolar septa being widened by the same type of cell growth as found in the bronchial wall. The extent of interstitial alveolar infiltration is slight for the most part, yet occasional areas are noted (Fig. 7a) in which fairly marked and extensive interstitial thickening of the peribronchial alveoli is seen; their lumen is correspondingly narrowed, and is lined by a continuous layer of regular cuboidal cells, so that the appearance suggests glandular tissue.

The poverty in exudative characters of the lesion in this case has already been mentioned. There is a surprising lack of eosinophiles and other blood elements, even in the densest areas of infiltration. Only at points of superficial ulceration of infiltrated bronchial mucosa are leukocytes seen in any number. This tendency for the proliferative phenomena to overshadow completely the exudative manifestations of the disease is perhaps the outstanding feature of the case. This is expressed probably in its clearest manner in the changes affecting the alveoli. Instead of the marked engorgement of the capillaries and the outpouring of serum and fibrin into the air spaces seen in the other cases, the alveoli immediately adjacent to large nodules show only slight congestion and, as a rule, perfectly empty air spaces. Even more striking is the lack of epithelial desquamation which is so characteristic a feature of the other cases; instead, the alveoli, as already noted, are lined by orderly rows of cuboidal cells with compact scanty basophilic cytoplasm in contrast to the "stimulated" forms of alveolar epithelial cells with abundant acidophilic cytoplasm of the other cases. Fibrin is absent, and there is no suggestion of the "pneumonia lymphogranulomatosa."

**COMMENT**

**Proliferative Phase versus Blastoma:** In this case one is confronted with the difficulties of diagnosis seen in those cases of Hodgkin’s disease which lack the customary cellular pleomorphism, the prevailing cell type being an immature, actively growing cell of the reticulum-cell order. The individual cells for the most part appear to be of a low level of differentiation, not only in respect to their own cycle of maturation in the plane of the cell type which they represent, but also in showing so little variation phylogenetically (e.g. fibroblasts, lymphoblasts, giant cells), that it is difficult to distinguish the individual lesions from reticulum-cell lymphosarcoma. Histologically such equivocal lesions might best be designated "progressive reticulum-cell proliferation," in the sense of Klemperer (18), who has recently discussed this subject. However, occasional areas of typical Hodgkin’s disease are found in
certain regions showing fibroblasts with production of delicate collagen fibers and scattered foci of polymorphous character containing the usual cell types associated with the disease. One is reminded in some respects of Chiari’s (46) case, which was described in 1911 as resembling a blastomatous growth such as lymphosarcoma. One might be tempted to label it “Hodgkin’s sarcoma.” In this case, however, the designation “sarcoma” cannot be said to apply, since, in spite of the anaplastic character of the growing cells, in its manner of spread through the lung tissue the lesion exhibited none of the special characteristics of a neoplasm but conformed in a general way to the habit of growth peculiar to Hodgkin’s granuloma.

Histologically this case may be said to represent the purely proliferative phase of the disease. In contrast to the preceding cases, the parenchymal involvement occurs in a much restricted way, consisting of no more than a narrow fringe of purely interstitial alveolar infiltration of relatively slight extent about the infiltrated bronchi. In conformity with the other cases, the alveolar epithelium proliferates to the extent of forming a complete covering of the infiltrated alveolar septa in the form of a firmly attached layer of cuboidal cells similar to what is found in certain stages of tuberculosis and actinomycosis but not in lymphosarcoma.

The scantiness of its spread into the alveolar parenchyma draws attention again to the poverty in exudative characters of the lesion. Neither are the alveolar septa “loosened” to permit the development of more than a slight interstitial alveolar lesion, nor does fibrin occur in the air-spaces to stimulate granulomatous organization (granulomatous pneumonia); even serous exudate is lacking. Moreover, there is not seen the irritation-form of the alveolar epithelial cell, viz. the alveolar phagocyte and foam cell; not even within the lumen of the infiltrated alveoli do they occur. This case, then, if only in an indirect way, emphasizes the rôle of the exudative-irritant factors in the production of some of the more familiar morphological aspects of Hodgkin’s disease.

Case Report

Case 8: B. B., a male of fifty-one, was admitted June 27, 1932, to the Special Service for Chest Diseases (service of Dr. Harry Wessler) of the Mount Sinai Hospital. About two years previously he noticed the onset of occasional night sweats. Six months before admission he acquired a dry cough, which persisted; after about three months he began to expectorate small amounts of purulent sputum, greenish yellow in color and without odor. The night sweats increased, and appetite for food declined. When first examined, the patient was afebrile; he appeared a well built subject of stolid, hyposensitive type, slightly cyanosed but comfortable. In both lower lobes dullness and many crackling râles were observed. Roentgen examination (Fig. 8A) showed the presence of innumerable ill-defined shadows of pneumatic type throughout both lower lobes and the lower part of the right upper lobe; these shadows were densest nearest the diaphragm; there seemed very little tendency to fibrosis. Slight clubbing of the fingers was present, and an ill-defined abdominal mass, interpreted as an enlarged spleen. Smears of the sputum showed numerous Gram-positive cocci in chains and many bacilli; repeated examinations for tubercle bacilli were negative. The blood examination showed hemoglobin 78 per cent, white blood cells 13,400, polymorphs 76 per cent, lymphocytes 22 per cent, mononuclears
2 per cent. The Wassermann test was negative. Bronchoscopy proved negative. The symptoms improved and the patient was discharged at the end of two weeks.

During the succeeding four months the patient was observed frequently in the follow-up clinic. His cough and other symptoms gradually increased, and clubbing of the fingers became more pronounced. Successive roentgenograms showed spread of the infiltrations. The patient began to notice a sour taste in his sputum, reminding him of a paste he had once used in considerable amounts while employed in a paper box factory, shortly before he first became ill. The sputum was therefore cultured for fungi, but none were grown. The possibility of neoplastic disease (e.g. lymphosarcoma) was now considered seriously, and radiotherapy to both sides of the chest was instituted.

The patient was re-admitted to the hospital Nov. 3, 1932, somewhat weaker and paler and slightly feverish. His blood showed hemoglobin 55 per cent, white blood cells 7,000, polymonuclears 88 per cent, lymphocytes 10 per cent, eosinophiles 2 per cent; the polymonuclears showed considerable toxic granulation. The abdominal mass (spleen) seemed larger than before and irregular. The superficial lymph nodes were not enlarged. Bronchoscopy was repeated with negative results. Puncture of the lung yielded no evidence of tumor. The general condition did not alter materially and the temperature ranged between 100° and 101° F. for three weeks, when hyperpyrexia suddenly developed and death ensued.


Description of Lungs (Gross): The right pleural cavity is almost obliterated by adhesions and contains a small amount of encapsulated thin fluid; the left contains considerable clear, thin, brownish fluid. The left lung is almost entirely free of adhesions and is much heavier than normal. Upon its surface a number of depressed flat areas are seen; these are deeply congested and consist of rigid plaques of infiltration. Only scattered plaques involve the upper part of the lung, the largest being 5 cm. wide, and many being hardly more than circumscribed, thin, egg-shell stiffenings of the pleura. Nearer the base anteriorly they are very numerous, becoming confluent toward the free border of the lung and the interlobar fissure and forming a massive shell of dense infiltration. When the lung is artificially inflated it expands normally except where its surface is interrupted by the denser pleuro-pulmonic ("cortical") plaques. The lower parts of both lobes anteriorly are thereby prevented almost entirely from expanding, and their edges remain thin and sharp. The surface of the plaques is nodular, as a result of moderate irregular furrowing and linear retraction; in places patches of hyalin scar are present in the plaque or small clusters of hard pearly white nodular excrescences.

The extensively infiltrated lower anterior surface of the lung is coated by a delicate transparent fibrous membrane which is deeply congested and studded with innumerable tiny red tags; along the infiltrated edge of each lobe the latter form a row of minute polypi which are particularly prominent because of curious nodose and bead-like swellings within them; this is even more striking where they bridge the interlobar fissures as delicate adhesions.

On section (Fig. 8a) individual plaques are revealed as thick shells of solid, yellowish white pulmonary infiltration, some being several centimeters thick, others only a few millimeters. Adjacent plaques often extend into one another by means of narrow strips of infiltrating tissue lying almost entirely within the pleura. Many irregular wedge-shaped or sinuous stalactitic ingrowths project from the cortically situated plaques into the parenchyma. In the lowest part of the lung, beginning at its free border, the infiltration extends as a massive consolidation inward and almost reaches the hilum. Elsewhere within the deeper parts of the lung occasional large individual infiltrations are discovered similar to those in the periphery and invariably demonstrable as outgrowths of septal (and perivenous) infiltrations, to which they are tangent. Some of the larger bronchi and their satellite arteries are surrounded by infiltration which, however, is inconspicuous; where present, it is continuous with that of the hilar lymph nodes. The predominant localization of the infiltration is peripheral rather than hilar, forming the dense
CASE 8

A. Roentgenogram taken four and a half months before death, showing bilateral dense infiltrations of pneumonic character, most extensive in the lower part of each lung, especially in the peripheral portions. Note pleural thickening over right lung and marked interlobar infiltration.

B. Gross appearance of lung, showing massive consolidation of lobar character with predominant localization at periphery of lung.
pleural plaques already described, or related to interlobular fibrous septa which extend inward from the pleura (Fig. 9a).

Some of the thinner pleural plaques are composed of hyalin scar, entirely confined within the pleura; others show beginning extension of the infiltration into the lung, with formation of tiny subpleural nodules.

The infiltrating tissue in its typical form presents a smooth, yellowish white cut surface, delicately subdivided throughout by exceedingly fine gray lines, reminding one of glandular lobulated tissue, particularly of pancreas. Often the "lobular" subdivision is considerably exaggerated by intervening deposits of anthracotic pigment. Many of the individual infiltrations are abruptly limited by thin fibrous interlobular septa; the adjacent lobules appear entirely normal or exhibit infiltration in a different stage of development (see below). Very often the septum itself seems to conduct the infiltration deeply into the lung. As a rule, the completely developed infiltrations are sharply raised from the surrounding lung and fairly well circumscribed. The alveoli at the edge of such infiltrations, however, when examined closely, are distinctly patent, containing fluid or air or brownish translucent gelatinous material. In several places the alveolar walls are grossly thickened and their lumen is correspondingly reduced. It is often possible to demonstrate a gradual transition from areas of such partially infiltrated alveoli to areas of total solidification in which an occasional alveolar lumen may still be detected as a minute pin-point opening. Many large areas of such incomplete consolidation are seen, especially along the retracted lower lung border (Fig. 8a) in which the infiltrated parenchyma is still considerably alveolated, although progressing in patches gradually into complete homogeneous effacement of the alveolar architecture.

Within such infiltrations, fibrosis of recent development is frequent, best marked at the pleura, where it causes the superficial retraction already noted. In its gross aspects it appears in the form of streaks and bands of smooth resilient tissue, considerably congested, and somewhat transparent.

Except for the broad adhesions which almost completely obscure its surface, the right lung resembles the left. The same massive infiltration of its cortical region, especially of its lower portion, and the same details of finer structure of the infiltrations are noted as in the left lung. Both lungs are involved practically to the same extent.

The trachea and bronchi are everywhere congested, and contain considerable yellowish, soft, cheesy exudate; some of the smaller bronchi which pass through the more densely infiltrated areas are moderately dilated in an irregular manner; this is more evident in the inflated left lung. One of the smaller bronchi, which passes through an area of particularly dense infiltration in the right lower lobe, is almost completely obstructed at one point by a nodule 0.5 cm. in diameter projecting into its lumen but not penetrating its mucosa.

The lymph nodes at both hilar regions are very large, yet fairly discrete, and cause no apparent pressure deformity of adjacent structures; the tracheobronchial nodes are even more markedly enlarged; also the paratracheal lymph nodes on both sides and anteriorly. On section the nodes show dense infiltration, homogeneous except for moderate anthracosis.

Other Visceral Changes (Gross): The visceral pericardium overlying the great vessels is covered by a cluster of firm, yellowish gray nodules, the size of a pinhead. The parietal pleura covering the lower posterior portion of the pericardial sac exhibits several sharply defined, raised nodules 1 to 5 mm. wide; these are composed of the same homogeneous infiltration.

The lymph nodes of the porta hepatitis and peripancreatic region show slight enlargement, and on section show firm, shiny, fibrillar tissue replacing the normal structure.

The liver is greatly enlarged, weighing 2650 grams. Superficially and on section it appears uniformly congested, and has a yellowish tinge. The lobular architecture is well defined everywhere. The periportal areas occasionally exhibit grayish thickening. No distinctive nodular or diffuse infiltration is apparent.

The spleen weighs 1850 grams, being enormously enlarged. It is tense, but its consistence is somewhat flabby. On section the pulp scrapes off readily and appears diffusely congested. The malpighian follicles are not unduly conspicuous, and no infiltrations are observed anywhere.
A. Pneumonia granulomatosa (pleurogenous form of granulomatous interstitial pneumonia): section through subpleural plaque. Note polypous granulomatous pleuritis and extension of infiltration along interlobular septum (partly healed).

B. Pneumonia granulomatosa (pleurogenous form): section through bronchus illustrating spread of disease along interlobular septa (from pleura toward hilum) and freedom of bronchi from involvement except secondarily through contiguity.

C. Pneumonia granulomatosa (pleurogenous form): low-power photomicrograph through lower edge of lung, showing diffuse granulomatous infiltration with areas of fibrosis. Note marked bronchial dilatation (with hyperplastic epithelium) and emphysema of uninvolved or slightly involved alveoli; also marked pleural congestion.

D. Pneumonia granulomatosa: higher magnification of active lesion, showing fibrinous and leukocytic exudate in alveolar lumina and granulomatous infiltration of alveolar and vascular septa. Note proliferation of alveolar epithelium.
The kidneys are slightly enlarged, soft, and congested. The capsules strip easily; the outer surfaces exhibit a fine net of dilated capillaries and a few small whitish areas. Cut section shows no significant finding.

Within the substance of the third lumbar vertebra a grayish white nodule of homogeneous appearance, the size of a pea, is discovered.

The other viscera are without important changes.

**Description of Lungs (Microscopic):** The predominant cell type is slightly larger than the lymphocyte; its nucleus is compact, round, or elliptical; its cytoplasm is scanty and gives off a few small processes. Larger cells occur having the characteristics of the undifferentiated reticulum cell; fibroblasts are relatively few, and the stroma is scanty. Giant cells of the Sternberg-Reed type are present but exceedingly rare, and require prolonged search; they rarely attain the size seen in the other cases. In many areas healing has taken place in the form of well formed fibrous tissue, which is noteworthy for its abundance of dilated, thin-walled blood vessels, giving it an angiomatous appearance.

The parenchymal lesions assume the form seen as typical in the other cases. The advance of the granuloma within the lung tissue appears to meet with almost no resistance, and all pre-existing structures become completely permeated. Nevertheless, there is seen very little destruction of the underlying framework, despite the massive infiltration. Gland-like reversions of surrounded and narrowed alveoli persist in many parts of the infiltration, even within the depths of the lesion. The forefront of the lesion is seen to take possession of the alveoli by the characteristic interstitial infiltration of the alveolar septa (Fig. 9a, p). Their lining epithelium shows active proliferation in situ, in the form of a cuboidal-cell layer, and the lumen of these alveoli is often filled with desquamated epithelium (foam cells). In a number of areas the border alveoli also contain compact masses of fibrin clot undergoing granulomatous organization (pneumonia granulomatosa).

The small bronchi lying within areas of infiltration exhibit characteristic changes (pan-bronchitis granulomatosa); their lumen contains polymorphonuclear leukocytes and amorphous granular material, and in places their walls are denuded of epithelium and superficially infiltrated with leukocytes. The larger bronchi, on the other hand, show little or no involvement, particularly in sections taken from the hilar regions; occasionally areas of squamous metaplasia of their epithelium are seen (Fig. 9a).

Granulomatous lesions of blood vessels are common, chiefly the smaller, thin-walled veins. These are usually unrecognizable within large areas of infiltration except by elastic tissue stain, which simultaneously reveals the elastic framework of the obliterated alveoli, often surprisingly well preserved.

Fibrosis of considerable extent is frequent, especially in the more widely involved portions of the lower lobe and the lower part of the upper lobe (Fig. 9c). Bronchi formerly present in such areas are replaced by broad hollow spaces lined by continuous epithelium of tall columnar type, often somewhat hyperplastic, lying directly upon concentric lamellae of fibrous tissue. Occasional scattered areas of alveoli are noticed, generally markedly emphysematous. In addition, numerous alveolar remnants are seen overlain by fibrosis in all stages of infiltration; among the latter are patches of alveoli which at first glance appear normal, but on closer inspection show uniform interstitial thickening of slight or moderate degree by finely fibrillar scar tissue; their blood capillaries are largely obliterated, and their walls are lined by a continuous carpet of low cuboidal (“resting”) epithelium (Fig. 10a). As might be anticipated, fibrosis is particularly far advanced nearest the pleura corresponding to the apparent site of origin of most of the larger infiltrations. The angiomatoid proliferation of new blood vessels is best observed beneath and parallel to the pleura (Fig. 9c); this is true, also, of such thin plaques of pleural infiltration as show slight or no extension into the subjacent lung but have undergone almost complete fibrosis and often hyalinization.

The tiny beaded and polypoid tags of congested tissue observed on the pleural surface macroscopically are revealed as granulations possessing all the characters of the typical cellular stage of the lesion, including occasional multinuclear giant cells (Fig. 9a).

Intrapulmonic lymph nodes which drain areas of slight involvement show little or no change; nearer the hilum they show characteristic granulomatous infiltration. The
A. Case 8: Pneumonia granulomatosa: higher magnification of part of lesion seen in Fig. 9c, showing healed alveolar lesion with interstitial fibrosis and cuboidal-cell proliferation of alveolar epithelium. Note multinucleated giant cell in alveolar lumen originating from proliferation and desquamation of alveolar epithelium.

B. Case 8: Section through mediastinal lymph node. Note typical Sternberg-Reed giant cells and contrast morphology with that of multinucleated giant cell of epithelial origin seen in (A). Note also relative abundance of Sternberg-Reed giant cells in lymph node in contrast to lesions in parenchyma of lung.

C. Pulmonary actinomycosis in man (pleuropneumonia type): interstitial distribution of lesions as in Hodgkin’s disease of lung. Interlobular septa involved by direct continuity from pleural lesion.

D. Pulmonary actinomycosis in swine. Note tendency to formation of nodular proliferative lesions (“actinomycoma”) and predominance of interstitial localization of lesions.
massively enlarged lymph nodes of the mediastinal and tracheobronchial chains are completely transformed. Within the smaller nodes the earliest change is found; this consists in sinus catarrh of unusually marked degree, the sinuses being distended by masses of swollen, pale, acidophilic macrophages; the pulp cords are widened and their cells disposed in loose arrangement, consisting chiefly of plasma cells and polymorphonuclears (especially eosinophiles). In more advanced areas the differentiation between sinus and pulp cord is lost, the lymphatic tissue being replaced by a loose mesh of reticulum cells, plasma cells, and numerous young capillaries within a delicate loose fibrillar reticulum. More compact areas are also found, many showing active reticulum-cell proliferation with many multinuclear giant cells of typical Sternberg-Reed type, others showing considerable fibrosis. Giant cells are much more frequent in the infiltrated lymph nodes than in the intrapulmonic infiltrations (Fig. 10b).

Sections from other lymph nodes show essentially the same features.

Spleen: The enormous enlargement of the spleen is revealed microscopically to be the result of simple hyperplasia of its cellular elements. The most careful search made in numerous sections for nodules having the definitive structure of lymphogranuloma such as seen in the lung and lymph nodes is unsuccessful. Throughout the spleen is seen reticulum-cell proliferation within the pulp cords, and particularly in the peril follicular zones, where it is sometimes marked; the proliferated cells differ in no way from those seen in cases of chronic infection from various causes. In rare instances an area of fibrosis is discovered, apparently replacing an area of previous reticulum-cell proliferation. Giant cells of the Sternberg-Reed type are not seen. In addition to proliferated reticulum cells, the widened cords contain varying numbers of plasma cells, lymphocytes, erythrocytes, and polymorphonuclears; the last include many eosinophiles, and are very numerous in places. Swollen macrophages are frequent, occasionally multinuclear, containing vacuoles or inclusions of pigment, effete leukocytes, and erythrocytes. The malpighian follicles are somewhat reduced in size, but in a unit area their relative number seems very little if at all reduced, from which it seems justified to infer an absolute increase in their total number in view of the marked enlargement of the entire spleen. The follicles themselves show moderate reticulum-cell activity, but show no secondary follicle formation. The pulp sinuses show varying degrees of blood stasis.

Liver: There is considerable congestion of the liver, chiefly centro-lobular, with moderate parenchymal atrophy; the cells show little vacuolization. The Kupffer cells are very prominent and numerous. Many polymorphonuclear leukocytes lie in the widened sinusoids. Minute foci of plasma-cell infiltration are observed, chiefly in the perilobular (portal) areas; a few occur also within the lobules themselves; these foci are irregular and poorly circumscribed, and include occasional histiocytes and fibroblasts and a few eosinophiles.

Kidney: A few subcapsular deposits of plasma cells and eosinophiles are seen in the kidneys; also focal arteriolosclerotic atrophy and fibrosis.

Brain: In the brain is a rare perivascular focus of mononuclear or small round-cell infiltration.

Comment

This case is reported in some detail because of the singular distribution of the lesions of the disease. It is felt that one may rightfully use the term "primary lymphogranulomatosis of the lungs" in connection with this case in view of the clinical history and the autopsy findings. The known duration of the illness was approximately two years and a half. The first symptoms of consequence were cough and expectoration, and the positive physical findings were the extensive signs in both lungs, clubbing of the fingers, and enlargement of the spleen. Successive roentgenographic examinations of the chest showed infiltrations of pneumonic type in both lungs, which became progressively larger but without mediastinal involvement of significance. During the five months of observation no new findings developed, while those previously
noted increased in extent. At autopsy both lungs were infiltrated; the regional tracheobronchial lymph nodes were also affected, but only in proportion to the degree of pulmonary involvement; involvement of extra-thoracic organs was inconspicuous except in the case of the spleen, where it was atypical. The concentration of the pulmonary lesions along the peripheral portions of both lungs, with relative freedom of the hilar areas and bronchi, is one of the most distinctive features of the case. The sub-pleural tissues were considerably involved, yet the visceral pleura showed insignificant invasion. The condition must therefore be regarded as basically intrapulmonic; heavy plaques and wedges of solid infiltration formed an incomplete shell along the outer parts of the lungs, and in their lower portions extended much more deeply in the manner of a lobar consolidation. In the finer details of its spread within the parenchyma, however, the infiltration behaved characteristically.

The remarkable enlargement of the spleen (weight 1850 grams) does not negate the interpretation of primary pulmonary lymphogranulomatosis. The enlargement consisted in a diffuse hyperplasia of all the splenic elements, with no evidence whatever of the nodule formation which characterizes the usual type of splenic enlargement in Hodgkin’s disease. Little is known of this diffuse non-nodular type of splenic hyperplasia in Hodgkin’s disease; in two other cases of this disease seen in the Mount Sinai Hospital the autopsy showed a similar picture in the spleen, the weight in one case being over 1200 grams. In neither of these cases were the lungs involved significantly. In contrast to the classic porphyry spleen, in which most of the enlargement is due to “metastases,” in this type, to quote Foulon, the “virus of lymphogranuloma seems to fix directly in a diffuse manner upon the reticular or endothelial elements of the splenic parenchyma” (36). Jona and dalla Torre (47) describe a case in which the enlarged spleen showed the characteristics of inflammatory swelling without granulomatous invasion.

DISCUSSION AND SUMMARY

A. Interpretation of Hodgkin’s Disease Based on Morphogenesis of Pulmonary Lesion

In the lung parenchyma, because of its unique structure, it is often possible to observe the unfolding of the morphologic characters of disease in their simplest form. The particular features of the lung which are most significant in this respect are its interstitial tissue, its epithelium, and the air spaces which comprise most of its bulk. The morphological comparison of Hodgkin’s disease in the lung with certain infectious granulomas of known etiology (e.g. tuberculosis and actinomycosis) on the one hand, and with tumors (including lymphosarcoma) on the other hand, provides a method of some usefulness in the attempt to clarify the position of that disease.
Evidences of its Primary Inflammatory Character: Examination of the foregoing eight cases from this standpoint permits deductions which strongly support the view, held by many investigators, that Hodgkin's disease is a primary inflammatory reaction of granulomatous character rather than a neoplasm. The lesion in the lung, as seen in those cases, for example, appears to permeate with ease such resistant structures as the walls of arteries and such delicate structures as the walls of the alveoli; the direct result in either case is not mechanical compression and destruction but uniform infiltration, whereby the underlying framework is largely preserved; this is confirmed by elastic tissue stain. This and certain other evidences, which have been pointed out previously, indicate that merely the ingrowth of cellular elements of the disease, as in a tumor, is altogether inadequate to bring about the characteristic disease picture observed in the lung. These evidences favor the view rather that the spread of the disease is brought about by the diffusion of a virus or toxin, which constitutes the stimulus to an in loco proliferation of reacting autochthonous mesenchymal elements. On the same basis it is possible to account for the abundant lesions of entirely non-specific character which exist side by side with well defined specific lesions. As already described, these consist in catarrhal pneumonia and fibrinous exudation. The fibrin undergoes some form of organization (carnification), either by ordinary fibroblasts or by varying proportions of fibroblasts and of cells specific to the granulomatous lesions ("pneumonia granulomatosa"). The ultimate fate of such lesions is transformation into ordinary scar tissue. The particular anatomic relation which exists between the non-specific and the specific lesions suggests their common etiology. A decided contrast is seen between the non-specific exudative lesions of Hodgkin's disease and the inflammatory changes associated with certain neoplasms, which are brought about by their local destructive action.

Another verification of the inflammatory character of the disease is seen in its behavior toward bronchial and alveolar epithelium. In contrast to neoplastic infiltrations, which tend toward ulceration, the lesions of Hodgkin's disease are characterized by their tendency to conserve for the most part or to stimulate the epithelium of the infiltrated bronchi. A similar tendency is seen in relation to the alveoli. In the exudative phase of the disease the epithelial cells which line the infiltrated alveolar septa proliferate in large numbers and are shed into the lumen; they appear as mononuclear or multinuclear phagocytic cells with foamy cytoplasm and are similar to those seen in various types of pneumonia and in many portions of tuberculous or actinomycotic lesions in the lung. These cells, however, as already discussed, are never seen to participate in the formation of the granuloma (Fig. 3c, 10a, b), which is in accordance with the view that they are of entodermal origin. In the predominantly proliferative type of lesion (Fig. 7b), and also in the healing stages (Fig. 2n, 10a), they form a continuous row of cuboidal epithelium lining the infiltrated alveolar septa, often giving rise to the appearance of glandulae.
The solvent action of granulomatous infiltration on the collagenous fibrous support of the bronchial walls, as well as on that of the capsule of lymph nodes and of the subpleural tissue and interlobular septa, is consistent with its inflammatory nature; as already mentioned, it is particularly marked when the exudative phase is well developed, and may be related to its rapid spread. The same principle may be extended with plausibility to explain the noteworthy susceptibility of the alveolar septa to interstitial infiltration.

*Cavitation:* Necrosis of extensive intrapulmonic lesions with subsequent cavitation is well known (48–54), and roentgenologically may be indistinguishable from that of tuberculosis. The cavitation may be multilocular, as in one of the cases reported by Versé (51). Cases have been reported in which the entire wall of the cavity had become converted into dense fibrous scar tissue (36, 52a). Various speculations concerning the cause of the necroses have led to no definite conclusion; they have been attributed to vascular obliteration (22), radiotherapy (1), incidental bacterial contaminants (55), and the toxic agency of the virus of the disease itself (1).

**B. Comparative Features of the Hypothetical Virus**

Despite the fact that the identity of the virus of Hodgkin’s disease is unknown at the present time, it is possible to surmise a few general features of its pathogenic nature from a comparative study of other granulomatous diseases. It is especially valuable to compare the pulmonary form of Hodgkin’s disease with that of tuberculosis and of actinomycosis. All three diseases display varying degrees of productive and of exudative response, as well as necrosis and suppuration. In pulmonary tuberculosis the lesion is confined predominantly to the lung and lymph nodes, and the same is true of pulmonary Hodgkin’s disease. In actinomycosis of the lung the pleural localization of the disease is conspicuous, at times comprising its major expression, “primary actinomycosis of the pleura” (56), and a pleurogenous type of lung invasion is characteristic (Fig. 10c). One of the outstanding features of intrathoracic actinomycosis is its destructive invasion of the chest wall, much as in a malignant tumor. This form of invasion is rare in Hodgkin’s disease, although scattered instances of perforation of the sternum and external tumefaction with necrosis have been reported (57a, b, c, d). As in actinomycosis, the pleural involvement in Hodgkin’s disease is most often secondary to extension by contiguity from extensive infiltrations in neighboring structures (e.g. mediastinum). A primary pleurogenous form of Hodgkin’s disease of the lung, as exemplified in case 8, is exceedingly rare, and, as far as the accessible literature is concerned, has not been hitherto described.

In man actinomycosis, in contrast to Hodgkin’s disease and tuberculosis, rarely involves the lymph nodes. However, in certain animals, interestingly enough, the lesions of actinomycosis are predominantly proliferative, with nodule formation (“actinomycoma”) and with rela-
tively little destruction. In such animals the lymphatic system shows a not insignificant involvement (56). In the lungs of these animals the actinomyecotic proliferative lesions display much the same tendencies as those of Hodgkin’s disease in man, viz. a predilection for the interstitia of the lung, including the bronchi, the interlobular septa, and the walls of the alveoli (Fig. 10b). Similar tendencies are observed in tuberculosis affecting certain species, and exceptionally in human tuberculosis. In this connection it is worthy of mention that not only may human tuberculosis assume an atypical form in its primary and secondary stages (e.g. sclerosing giant-cell hyperplasia without caseation) (58), but may at times approach closely the form and development of Hodgkin’s disease; one of the best examples is the condition described by Wessler as “intrathoracic tuberculous lymphoma,” which is clinically indistinguishable from Hodgkin’s disease of the mediastinum, and, like the latter, is probably secondary to an undetected primary infect in the lung (59).

As already mentioned, the lesions of Hodgkin’s disease in man and of actinomyecosis in certain animals seek by preference the interstitial tissues of the lung; to some extent this is also the case in human actinomyecosis and tuberculosis. It is therefore justifiable to refer to these conditions as forms of interstitial pneumonia. In the majority of cases of Hodgkin’s disease of the lung the interstitial lesion predominates, and therefore may be properly designated lymphogranulomatous interstitial pneumonia. Like interstitial pneumonia in general (60), this is subdivided into two types, peribronchial and pleurogenous; this is in accordance with anatomical laws. The interstitial tissue of the lung is disposed in two separate systems, central and peripheral, the former comprising the walls and connective-tissue sheaths of the bronchi and their accompanying blood vessels (including the branches of the pulmonary artery) and extending outward from the hilum, the latter comprising the subpleural connective tissue and the interlobular septa arising therefrom (containing branches of the pulmonary vein) and extending inward toward the hilum, where both systems join. Both forms of distribution occur in Hodgkin’s disease; the peribronchial form is the rule, the pleurogenous form less frequent and almost invariably secondary to extension from other organs (as in cases 1 and 2). A primary pleurogenous form of lymphogranulomatous interstitial pneumonia, as in case 8, has not previously been described.

In Hodgkin’s disease of the lung, as in tuberculosis and actinomyecosis, the lesion seldom remains confined to the interstitial tissues, but in the majority of instances is complicated by a varying amount of “parenchymatous” involvement. This has already been discussed in relation to the various forms of alveolar reaction, non-specific as well as specific. In certain cases, however, the parenchymal lesion may be far more conspicuous than the interstitial lesion. When this occurs, one may speak properly of granulomatous lobar or lobular pneumonia; in Fincke’s (22) third case and in Déak’s (61) first case this had the aspects of a gelatinous pneumonia of acute type; in Versé’s (1) third
case the appearance suggested organizing pneumonia; in Weber's sixth case the parenchyma was replaced by solid reddish gray infiltration of lobar distribution (42); in MacCallum's (62) case the lobar involvement had progressed largely into the advanced fibrotic stage. Foulon (36) mentions a case of confluent lobular type of infiltration which included all stages. Frequently such massive lobar or sublobar lesions are associated with necrosis and cavitation (48, 49).

A specific bronchitis is observed in all three diseases, with catarrhal, ulcerative, cicatricial, and obliterator changes. Vascular lesions are also observed and are an important means of dissemination, especially in the case of veins from which a miliary actinomycosis, tuberculosis, or lymphogranulomatosis (63, 64) may arise respectively.

In view of the fact that in about 10 per cent of cases of Hodgkin's disease of the lung the primary lesion is pulmonary (Versé, 1), it is not altogether illogical to regard the lung actually as the portal of entry. Many investigators see in this a further analogy to tuberculosis.

Terplan (3) made use of the term "primary infect" in the same sense as the Ghon tubercle, which, together with the predominant involvement of the regional tracheobronchial lymph nodes, suggests the analogy to the "primary complex" of tuberculosis. Urchs (5) pursued the analogy still further, defining three stages based upon the Ranke concept of tuberculosis, (1) that of the primary infect, (2) the stage of generalization by lymphatic apparatus and blood stream, and (3) the tertiary stage, that of organ disease with spread via the bronchi. Terplan, however, in a recent contribution (65) stressed the rarity of clear-cut instances of primary lymphogranulomatous infect within the lung and felt that definite conclusions could not be drawn.

C. Classification

The classification of the various types of pulmonary lesion with their combinations presents a problem of unusual complexity and at the same time of great importance. The simplest gross anatomic grouping of the lesions is that of Ceelen and Rabinowitsch (66) into (1) generalized and (2) more localized. Versé contributed a useful classification based upon the anatomic and roentgenologic features of the lesions:

1. Mediastino-bronchial node formation with direct invasion of lung tissue.
   (a) By the hilum.
   (b) By the medial surface of the lung.

2. Mediastino-bronchial node formation and peribronchial and intrabronchial spread in the lungs.

3. More or less lobar (diffuse) lung infiltration with varying degrees of involvement of the broncho-mediastinal lymph nodes.

4. Confluent lobular (isolated circumscribed) focal formations in the lungs with involvement of lymph nodes as above.

5. Miliary dissemination (lympho-hematogenous) with involvement of lymph nodes as above (1).
The usefulness of this and other similar classifications is somewhat limited, and it is felt that sufficient justification exists to attempt a descriptive classification having as its basis the conception of Hodgkin's disease as a form of inflammation with a definite pathogenesis and employing a terminology which reflects this point of view. In the general classification of the various lesions two phases are distinguished, for which the customary designations "proliferative" and "exudative" are adequate, the majority of cases presenting a combination of both phases. The proliferative phase displays its most characteristic development within the interstitia of the lung; the exudative phase, which also occurs in the interstitia, where it is recognized with ease in some cases and with difficulty in others, attains its most pronounced morphological expression within the alveolar air-spaces. The various aspects of each phase, including certain non-specific lesions, have been discussed previously. Accordingly the following types of intra-pulmonic Hodgkin's disease are enumerated:

(1) Granulomatous pan-bronchitis and bronchopneumonia (peribronchial form of granulomatous interstitial pneumonia).
(2) Granulomatous pleurogenous pneumonia (pleurogenous form of granulomatous interstitial pneumonia).
   (a) Primary (rare) (Case 8).
   (b) Secondary (invasion from adjacent infiltrated structures, e.g. mediastinum).
(3) Exudative lobar and lobular pneumonia.
   (a) Acute (gelatinous pneumonia).
   (b) Subacute and chronic (organizing pneumonia).
(4) Miliary, submiliary, and multiple isolated nodular lesions (hematogenous, lymphogenous).

Note: The author acknowledges with gratitude the kind co-operation of Dr. H. Lilienthal and Dr. B. S. Oppenheimer, who permitted the use of their clinical records, and of Dr. L. Jaches for the use of the roentgenograms.

REFERENCES

2. Kraus, F.: Cited by Versé (1).
HODGKIN'S DISEASE OF THE LUNG


15. Cramer: Cited by Versé (1).


24. Personal observations.


35. Siracusa, V.: La questione del rivestimento dell'alveolo polmonare dal punto di vista istodocimastico, Arch. ital. di anat. e istol. pat. 2: 177, 1931.


40. CLAUß, W.: Cited by Versé (1).
41. FERRARI AND COMINOTTI: Cited by Ziegler (38).
42. WEBER, H.: Lungencyphogranulome, Beitr. z. path. Anat. u. z. allg. Path. 84: 1, 1930.
43. RIBBERT, H.: Cited by Versé (1).
44. FRANKENBERGER, O.: Cited by Verse (1).
50. DVORAK: Fall von Lymphogranulomatose, Fortschr. auf dem Geb. der Röntgenstrahlen 35: 1050, 1927.
52. (a) Lübarche, (b) Yamasaki, (c) Lenk, (d) Claus: Cited by Versé (1).
53. ZIEGLER (38): p. 171.
57. (a) TERPLAN AND MITTELBACH (54): Case 8, page 781.
(b) DRESSER, R.: Lymphoblastoma (Hodgkin's disease) of the sternum, Am. J. Roentgenol. 15: 525, 1926.
(c) PRUVOST, P., Mallet, L., AND HENRION: Forme thoracique de la maladie de Hodgkin avec tumeur fluctuante et ulcération, Paris méd. 1: 162, 1933.
(d) OLMER, J., AND LÉNA, D.: Les localisations sternales de la lymphogranulomatose maligne, Marseille-méd. 70: 368, 1933.
64. (a) SchOTTELIUS, (b) HELD, (c) RIBBERT, (d) SChLAGENHAUFER, (e) HECKER AND FISCHER, (f) KUHLMANN: Cited by Versé (1).
66. CELEN AND RABINOWITSC: Cited by Versé (1).