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ENDOTHELIOMA OF LYMPH NODES.*

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The question of the existence of an endothelial carcinoma of lymph nodes remained as an aftermath from the controversy over the connective tissue origin of cancer. After Waldeyer had succeeded in proving the exclusive epithelial derivation of cancer, cases of primary tumors of lymph nodes, apparently epithelial in nature, continued to be observed, but their true nature remained undetermined or was generally misconstrued. That all such growths could not be dismissed as simple carcinoma was held by many early observers who, however, did not venture to actively oppose the prevailing and orthodox opinion.

Zahn, in 1874, extricated himself from the dilemma by describing one of these tumors as "sarcoma alveolare epithelioides," and Birch-Hirschfeld later identified this case with one of his own as endothelioma. In France Colrat and Lepine described as primary carcinoma of lymph nodes a case which they suspected as originating from the endothelial cells. To Chambard belongs credit for actively maintaining the existence of a primary cancer of lymph nodes originating from endothelial cells. In 1880 he described a local form of the disease affecting one node or one chain, and a generalized form which was rapidly fatal. Again, in 1889, he insisted that no other primary tumor could be found in these cases. In 1881 Hoffmann and Schottelius definitely accepted the endothelial nature of

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their case, which they spoke of as a "granulation endothelioma." In 1895 Volkmann described a case which recurred in the neck after operation and produced fatal cachexia in one year. The tumor first appeared at the angle of the left maxilla; later, on the right side, and soon became adherent to surrounding tissues. The extirpated mass was composed of many fused nodes. The structure showed hyaline fibrous tissue inclosing sharply circumscribed groups of tumor cells in plexiform arrangement. The cells were polygonal, irregular, or elongated, with abundant cytoplasm and large nuclei. There seemed to be transitions between the endothelial lining cells and the tumor cells. The presence of many pearls, hornification and calcification, and the failure to mention a thorough search for a primary tumor, leaves a reasonable doubt regarding the origin of this case.

Recklinghausen in 1897 recognized the existence of endothelioma of lymph nodes and pointed out distinctions between this tumor and secondary carcinoma of lymph nodes. He observed involvement especially of pelvic and retroperitoneal nodes with extensive lymph stasis and the formation of dilated lymph sacs in the course of occluded vessels. Gallina reported one of these cases in detail in which the nodes contained many cell groups, some compact, some cystic, some forming pearls, while transition-forms from the normal endothelium of the lymph sinuses seemed to be conspicuous. Many of the nodes were extensively fibrosed, and from some the tumor had invaded the muscular tissue.

Kaufmann refers to the difficulty of distinguishing between secondary carcinoma and primary endothelioma of lymph nodes and refers to a case of the latter type. The tumor in the axilla of a woman of sixty-seven years reached the size of the fist, and became adherent to the skin and axillary vein. No other tumor could be found. The structure presented remnants of lymphoid tissue and was composed of alveolar groups of closely packed large polygonal vacuolated cells with lightly staining nuclei.

Ravenna discusses the history and position of endothelioma of lymph nodes in the light of the current scepticism concerning endotheliomas in general. He described a case in which many mesenteric and retroperitoneal nodes were enlarged to the size of a pigeon's egg, and the liver was much enlarged by invasion along the portal canals. Sections showed the lymph sinuses filled with neoplastic cells, arranged without order and divided into groups by very fine connective fibrils. The cells were oval, triangular or irregularly polygonal, with finely granular vacuolated cytoplasm and oval nuclei poor in chromatin. In some cells the nuclei were very large and a few exhibited karyokinesis. Degeneration, necrosis, and cell inclusions so common in cancer were missing. An important character was the appearance of the cells in broad masses in which the outlines of separate cells could hardly be distinguished. The intimate contact of the cells with each other and with the surrounding connective tissue seemed to distinguish the process from carcinoma.

Sguambati describes a tumor found in two lymph nodes of the axilla. No other tumor could be found. The structure was alveolar and the cells presented endothelial characters.

DaGradi and de Amicis describe and depict in detail the structure of an extensive endothelioma affecting the axillary, cervical, and mediastinal nodes, and involving the pleura, stomach wall, and adrenals. The patient was a man of thirty-four years, who without known cause began to suffer from enlargement of lymph nodes in one axilla, followed by edema of the arm. Later the cervical, pharyngeal, and mediastinal nodes were involved, the edema extended over the chest, a milky exudate appeared in the pleural cavity, cachexia developed, and the patient died from asphyxia.

The enlarged nodes were fused together, bound to the skin, and invaded the muscles. There was extensive diffuse invasion of the wall of the stomach, but the mucosa was normal. The tumor exhibited large and small alveoli surrounded by cords of lymphoid tissue. The cells were of various round or polyhedral forms, cytoplasm clear and hyaline, granular, or vacuolated. The nuclei were large and

vesicular. Concentric pearls and giant cells were observed, but no hornification. Transitions to normal endothelial cells could apparently be traced. The peculiar structure of the tumor, the endothelial characters of the cells, the clinical course and anatomical findings and the careful exclusion of any primary tumor in other organs, seemed to the authors to justify the diagnosis of endothelioma.

From these rather meager reports furnished by the available literature it is evident that endothelioma of lymph nodes occupies a very subordinate position in present day pathology. While its existence is admitted by leading authorities, its great rarity places it among pathological curiosities.

The present state of opinion is not favorable for the enlargement of the scope of this disease. Since the period, 1895–1900, when the diagnosis of endothelioma reached the height of sudden popularity the scope of endothelioma has been steadily narrowed. The histological criteria on which this tumor has often been identified have been subjected to searching criticism by Lubarsch, Ribbert, Borrmann and others, with the conclusion that there are no really definite features of neoplastic endothelial cells. The well-known endothelioma of the parotid has been placed in the group of epitheliomas through the work of Hinsberg and Krompecher.

Endothelioma of the skin, once a numerous class, has been decimated if not annihilated by Krompecher and Borrmann. A similar fate has threatened many so-called endotheliomas of the viscera. Ribbert accepts only the endothelioma of the dura mater and tumors arising from the lining cells of the great serous membranes. In the lymph nodes, to establish the endothelial origin of a tumor is particularly difficult. As Kaufmann remarks, there is always a strong probability that an epithelioid tumor of lymph nodes is secondary to a growth in neighboring glands or mucous membranes. It is seldom possible to thoroughly explore the mucous membranes drained by lymph nodes, especially those of the neck. There is the further

possibility that epithelioid tumors may arise from misplaced groups of epithelial cells in the lymph nodes. Moreover, the morphology of most of the suspected endotheliomas or lymph nodes is admittedly very similar to that of secondary carcinoma. With the possible exception of Ravenna's very careful analysis, the reports in the literature do not specify convincing distinctions between the structure of endothelioma and that of carcinoma. The clinical course and anatomical findings are suggestive rather than demonstrative of a specific process separable from carcinoma. The attempt to trace the derivation of tumor cells from normal endothelial cells of lymph nodes, however detailed the descriptions may be, convinces no one but the observer himself. Finally, no one observer has reported a sufficient number of these cases to establish the variations in morphology, the relation of the process to other forms of endothelial proliferation, the clinical scope of the disease, and to compel attention to this condition as an important and neglected field in oncology.

For many years I have been encountering tumors of lymph nodes in subjects presenting no other demonstrable tumor and with whom the subsequent course indicated that no other tumor existed, and in which the structure strongly suggested an endothelial origin. The observation of several tumors of this class within the past year which presented early stages and transitional forms between those previously observed has led to the conclusion that endothelioma of lymph nodes is a rather common neoplasm, that it is usually classed with lymphosarcoma on the one hand and with secondary carcinoma on the other, that the process differs in many histological, anatomical, and clinical features from secondary carcinoma, and that it is usually possible to recognize these features with considerable or complete certainty.

The following data are presented in support of these conclusions:

The case reports include first, two examples of extreme

endothelial hyperplasia, which is probably of inflammatory origin and nature. These cases are presented not only for their intrinsic interest but especially to emphasize the fact that lymphatic endothelium when subjected to inflammatory irritation is capable of very extensive hyperplasia.

Then follow examples of endothelial tumors associated with an infectious granuloma. Next are described probably primary tumors of lymph nodes similar to those reported in the literature. Finally, a group of primary axillary tumors is presented which are composed of large round or polyhedral cells, which may be associated with a granuloma resembling Hodgkin's, which resemble lymphosarcoma, and which are believed to originate chiefly from the reticulum cells of the lymph follicles.

CASE I. — Clinical Hodgkin's Disease. Extensive tumor-like hyperplasia of endothelial cells. (Figs. 3, 5.)

History: M., male, 32 years, previously in good health, first noticed enlarged nodes on both sides of neck about January, 1906. These increased slowly for some months, then more rapidly, involving supraclavicular and axillary nodes. Meantime the patient lost weight and strength. On June 18, 1907, he was examined by Dr John Rogers, who found very large masses of nodes on both sides of the neck and some smaller ones in the axillæ. One cervical node was removed for diagnosis. The condition was inoperable and the patient passed from notice. It was learned that he died anemic and cachectic, with progressive enlargement of superficial nodes, in April, 1908. Duration of disease, 27 months.

Microscopical structure: The material received consisted of a portion of a large node and one small contiguous node as large as a pea. Both show the same changes; the endothelial proliferation being more marked and diffuse in the smaller node. Sections show broad anastomosing bands of coherent endothelial cells, traversing the node and inclosing islands and strands of lymphoid tissue. These cells often form broad sheets, which grade insensibly into the lymphoid tissue. In places, they are sharply separated, from shrinkage in hardening. The outlines of the cells are very indistinct, the cytoplasm finely reticular, pale and vacuolated; the nuclei are large, distended with nuclear fluids, and contain one well marked nucleolus.

Mitotic figures are rare. Nuclear hyperchromatism appears in many cells, but the definite characters of a neoplasm are not conspicuous.

The lymphoid tissue contains many lymphocytes, a few plasma cells, but eosinophiles are missing. There are a few minute foci of necrotic cells. It is evident that the process is essentially that of an infectious granuloma.

Tubercle bacilli could not be demonstrated in sections and inoculation of guinea-pigs proved negative.

In this case one has to deal with a form of endothelial hyperplasia which approaches, if it does not reach, a neoplastic grade. The endothelial overgrowth resembles that occasionally observed in more typical Hodgkin's granuloma, but is much more active. Clinically the condition resembled Hodgkin's disease, but it presents notable structural variations from the usual type of Hodgkin's granuloma.

Like the succeeding cases it illustrates the association of an infectious granuloma with tumor-like hyperplasia of endothelium, and it furnishes an important transitional stage between inflammatory and neoplastic hyperplasia of endothelium.

CASE 2. — Tumor of lymphoid tissue of vault of pharynx. Neoplastic endothelial hyperplasia. Associated granuloma. (Figs. 1, 2.)

History: M. C., age 60. A robust active man without definite tuberculous antecedents, first noticed a swelling in vault of pharynx in February, 1912. The tumor grew slowly for six months, partially obstructing the posterior nares. In September, 1912, the growth had reached dimensions of 3 x 2 centimeters, and projected prominently behind the velum, being intimately connected with the mucous membrane and poorly circumscribed laterally. The surface was slightly eroded. There were no enlarged lymph nodes. The tumor was partially removed for diagnosis. At the present writing the remaining tumor continues to progress slowly without seriously affecting the patient's health, but with increasing obstruction to the nares.

The material received consisted of two globular masses of soft gray tissue covered by mucous membrane and resembling enlarged tonsils. On section the structure presents two main features in a somewhat remarkable association. There is, first, definite evidence of an infectious granuloma, in the form of well marked foci of necrosis surrounded by large epithelioid cells and giant cells of Langhans' type. These lesions strongly resemble miliary tubercles, but no tubercle bacilli could be demonstrated in them, and inoculation tests could not be practised, as the material was received in formalin. The outlying lymphoid tissue shows a few intact follicles, but chiefly disordered lymphocytes, plasma cells and a few eosinophiles.

The second feature consists of compact nodules and masses of coherent endothelial cells which stand out sharply from the surrounding tissue and in some respects resemble the structure of epithelioma. Further study,

however, reveals very intimate relations between these cell masses and both the granulomatous lesions and the lymphoid tissue. In many places the cell masses grade insensibly into the lymphoid tissue and the cells can be traced down to the endothelium of the lymphoid reticulum.

The endothelial nature is further indicated by the morphology of the cells which appear in sheets with very indistinct or indistinguishable cell borders, finely reticular and vacuolated cytoplasm and large vesicular and hyperchromatic nuclei.

The cell sheets exactly resemble those described in Case 1, but they appear in small foci. The most significant feature of these neoplastic cell groups is their relation to the granulomatous process. In many places the combined lesions appear as miliary tubercles in which, instead of necrotic centers, one finds hyperplastic endothelium surrounded by a zone of pale epithelioid cells and Langhans' giant cells. Occasionally the center of the cell mass is occupied by a necrotic focus.

This relation, which in my experience is unique, demonstrates that the proliferating endothelial cells have not invaded the granulomatous foci, but have arisen in situ. The most reasonable interpretation would attribute the endothelial hyperplasia to the same irritant which produces the granulomatous process. The epithelium of the mucosa is slightly eroded in places, but shows no hyperplasia or connection with the deeper cell masses.

In this case one has to deal with a peculiar combination of granuloma and excessive endothelial hyperplasia which seems to approach the neoplastic grade. That a true neoplasm exists cannot at present be demonstrated, and must await the clinical outcome of the disease. The morphology alone, the considerable bulk of the growth and its recrudescence after partial removal, strongly suggest that a self-perpetuating neoplasm exists. In fact the neoplastic structural features are so pronounced as to call for a critical separation of the process from epithelioma. This case, while resembling in some histological details Case 1, stands one step further along toward a true endothelial neoplasm arising on a granulomatous basis.

CASE 3. — Infectious granuloma of cervical lymph nodes. Hyperplastic miliary tubercles. Diffuse endothelial hyperplasia. Plexiform endothelioma. Perithelioma. Elimination of the granulomatous structure. (Figs. 6, 8.)

This case is remarkable for the association of an infectious granuloma possibly tuberculous with various degrees of endothelial hyperplasia reaching in some nodes a definite plexiform and perivascular endothelioma.

Clinical history: C. S., 40 years, policeman, admitted to New York Hospital September 12, 1907. Father died of tumors of neck after four operations. Sister died of cancer. Patient had a very severe attack of rheumatism in 1891. In 1902 he first noticed a swelling at angle of right lower jaw, and one year later a similar tumor appeared on left side. The tumor increased steadily and in 1904 several were removed. The patient was told they were tuberculous. In 1905 some tumors were removed from above left clavicle, and again, in 1906, several nodes were removed from both sides of neck.

On admission the well-nourished patient presented conglomerate masses of enlarged nodes on both sides of the neck, but complained of no pain or discomfort. No other region showed any involvement. By an extensive dissection all the glands in the neck were removed, the largest being the size of a walnut. For two weeks the temperature ran between 99°–101° F. Blood: September 13, 1907, lymphocytes, 12,000; polynuclears, 53 per cent; small lymphocytes, 41 per cent; large, 4 per cent; eosins, 2 per cent. He was then discharged.

Readmitted February 19, 1908, with a tumor below left ear which extended half way to clavicle. Operation removed a conglomerate mass of nodes as large as a hen's egg, and several small nodes. The subsequent history has not been traced.

Microscopical structure (1907 tumors).

(1.) The granulomatous process appears chiefly in the form of hyperplastic miliary tubercles composed of a central group of pale staining polygonal cells with or without necrosis, giant cells, and a broad peripheral zone of well-nourished endothelial cells mingled with lymphocytes. The giant cells are not of the typical Langhans' type but contain many large vesicular nuclei, peripherally arranged as in blastomycosis. Repeated search for tubercle bacilli was negative. Some nodes exhibit chiefly these lesions; others contain a few scattered tubercles merging into diffuse granulomatous tissue; still others are free from tubercles.

(2.) Tubercle-like lesions appear in which a central area resembling that of an ordinary miliary tubercle with beginning necrosis is surrounded by a broad zone of large hyperplastic endothelial cells of which the striking nuclear hyperchromatism indicates a beginning neoplastic process. These foci recall the curious tubercle-like formations of Case 2.

(3.) Diffuse granulomatous tissue occurs in somewhat isolated compact areas, surrounded by lymphoid tissue, and often assuming a convoluted aspect, inclosing sinuses filled with blood or granular cell detritus. This tissue is composed chiefly of endothelial cells and lymphocytes and is poorly nourished.

(4.) Areas similar to the foregoing, in their convoluted arrangement, including large sinuses, are composed of an outer zone of distinctly neoplastic endothelium including masses and strands of lymphoid tissue. There is every gradation in the size of the cells and hyperchromatism of the nuclei from the granulomatous areas to those which present features of a neoplasm. (Fig. 6.)

(5.) Certain fields present the structure of perithelioma, patent vessels filled with blood, sheathed by many atypical spindle or pavement cells with hyperchromatic vesicular nuclei. (Fig. 8.)

(6.) Figure 7 illustrates a structure which occurred in portions of the present and exclusively in three other cases of endothelioma of lymph nodes not here reported in detail. In these cases the tumor process consists in hyperplasia of endothelial cells inclosing large or small irregular sinuses.

Recurrent tumors of 1908: In these nodes the evidences of an infectious granuloma are entirely missing, while the tumor process is more pronounced. Most of the nodes are composed of convoluted masses of polygonal and fusiform cells with hyperchromatic nuclei, and inclosing dilated lymph channels. A peritheliomatous arrangement of the cells is frequent. Lymphoid tissue is limited to the periphery of the nodes or is missing.

In the smallest nodes there is lymphoid tissue with hyperplastic follicles receding before the advance of the tumor masses. In these early lesions one receives the impression that the process originates in each node and not by extension from primary foci.

In this case a process originally pronounced tuberculous recurs persistently over a period of six years and in the fourth recurrence the features of an infectious granuloma are completely eliminated, the structure presenting the appearance of a plexiform and perivascular endothelioma. Here there is no question of a primary tumor elsewhere, the process declaring itself as a progressive though well localized disease of the lymph nodes. Although no tubercle bacilli were demonstrated, some of the nodes of the third recurrence showed rather typical miliary tubercles. The relation of the virus to the apparently pure neoplasm of the fourth recurrence can only be surmised, but the lymphadenitis and apparent development of the lesion de novo in the small nodes indicates that it persisted in some form.

The chief importance of this case lies in its demonstration of transitional stages between the endothelial hyperplasia of an infectious granuloma and what according to all accepted criteria must be regarded as a specific endothelial neoplasm.

CASE 4. — Plexiform endothelioma of lymph nodes of neck. Recurrence after two years. (Fig. 7.)

Clinical history: E. T., age 46, German. Typhoid fever and pneumonia in 1906. In 1910 tumors as large as walnuts were removed from each side of the neck. No cause could be assigned for the growths, but a short time previously the patient stated that he had a hemorrhage from nose or mouth. In 1911 operation for varicose veins of leg and inguinal hernia. About five weeks before present examination he noticed a swelling on left side of neck, which did not notably increase. Admitted to Bellevue Hospital September 21, 1912, service of Dr. T. A. Smith, who removed the tumor and kindly placed the history at my disposal. The patient appeared well nourished; not anemic.

The teeth were in bad condition, the upper left teeth being entirely missing. Thorough inspection of the buccal and pharyngeal mucosa and transillumination of the antrum failed to show any abnormality. The lymph nodes on both sides of neck were moderately enlarged and one much enlarged node was found on the left side and removed. It measured 4 x 3 x 3 centimeters, was firm, opaque, and well encapsulated. The plexiform structure could be detected on gross section. Dr. Charles Norris kindly placed the material at my disposal.

Microscopical structure (Fig. 7): The tumor is composed of small islands, compact masses, and convoluted cords of tumor cells. The larger masses and cords inclose many dilated lymph sinuses lined by flattened cells and inclosing granular and homogeneous material. Lymphoid tissue remains in considerable amount and shows much fibrosis. The tumor cell masses are often sharply separated from the lymphoid tissue, but in many places merge insensibly into it. No transitional stages of hyperplastic endothelial cells of the lymphoid tissue into tumor cells can be traced.

The morphology of the cells varies greatly. Some are large and pavement-like, with clear staining cytoplasm and sharp cell borders; others appear as broad sheets of cytoplasm interspersed with large vesicular nuclei; others again form masses of spindle cells intermingled with lymphocytes. Sharp transitions from one to another type are observed. A few small groups of concentric cells appear forming minute pearls, and here the structure resembles epithelioma from a mucous surface.

On histological evidence alone the diagnosis of endothelioma seems doubtful, although certain notable cellular and architectural features of endothelioma are present. The general appearance is that of a metastatic tumor and not of a neoplasm arising in the node examined. The clinical history stands against a primary tumor of the mucous membrane, which ought to declare itself in two years. The

first appearance of the disease on both sides of the neck, its slow progress, and the reappearance of swelling in many nodes of both sides do not accord with the history of epithelioma. Until the final outcome of the condition is known, the exact nature of the tumor must be left in suspense.

CASE 5. — Probable infectious granuloma, associated with malignant plexiform and alveolar endothelioma. (Fig. 10.)

Clinical history: A. H., 45 years, bartender, admitted to New York Hospital November 30, 1904.

There was no personal or family history of syphilis or tuberculosis. Patient stated that five months previously he first noticed a tumor on the right side of the neck which grew slowly at first, later more rapidly. At the same time he began to lose weight and strength. On admission patient, who was pale and in reduced general state of health, presented a tumor as large as an orange on right side of neck, extending from mastoid, forward to hyoid bone, outlines irregular as of a congeries of smaller nodes, adherent to skin, firm, not tender. Many smaller nodes were traced, running in chains down to the clavicle. Examination failed to reveal any primary tumor in mouth or adjoining regions. By an extensive dissection the tumor was removed, together with portions of carotid arteries to which it was adherent. A few hours later the patient died suddenly with great dyspnea.

The specimen received for examination was an irregular ovoid tumor mass 9 x 5 x 4 centimeters. Attached to it are portions of the common, internal, and external carotid arteries. It is encapsulated, grayish on section and appears to be composed of several enlarged lymph nodes with several outlying smaller nodes.

Microscopical structure: The main tumor mass is composed of coherent sheets of pale staining endothelial cells arranged in cords, convoluted masses and diffuse areas, supported by bands of stroma in which are groups of lymphocytes.

The cytoplasm of the cells is remarkably clear, the outlines often indistinct, so that the hyperchromatic vesicular nuclei and nucleoli appear with unusual prominence. The capsule is thickened and fibrous, and there is considerable fibrous tissue in and about the nodes. In these fibrous areas the tumor cells appear in small alveolar groups. In the small outlying nodes the endothelial proliferation is less marked and more diffuse and fails to show the isolation of cell groups, characteristic of permeating carcinoma. On the contrary it is difficult to determine whether the process in the small nodes is granulomatous or neoplastic. Here there are ill-defined areas composed of endothelial cells with hyperchromatic nuclei, and similar cells form an irregular network traversing the lymphoid tissue, as in Case 1. Some focal lesions resemble miliary tubercles except that

the centers instead of being necrotic contain sheets of well-nourished endothelium with hyperchromatic nuclei. The lymphoid tissue is abundant and there are several hyperplastic lymph follicles. The capsule and surrounding tissue are rich in lymphocytes.

Finally, in other nodes are presented many transitional stages between those described above, demonstrating that the endothelial hyperplasia, first appearing as a part of a process probably granulomatous, passes rapidly into a type of overgrowth which is indistinguishable from that of a malignant neoplasm.

The value of this case in the present series is great, since it furnishes a transitional form between the plexiform endothelioma of preceding cases and a type of very puzzling primary tumors of lymph nodes of which the relation to endothelioma would otherwise appear uncertain.

CASE 6. — Primary alveolar endothelioma of cervical nodes associated with infectious granuloma, probably tuberculous. Local recurrence after excision. Extension to inguinal nodes. Death after two and one-half years.

Clinical history: L., male, 30 years. Grandfather died of rapid pulmonary phthisis. Patient lived six months in 1898 with a man who died with pulmonary tuberculosis. In college patient was devoted to athletics. In 1906 he first noticed enlarged nodes in lower right cervical region following a "cold." The enlargement persisted unchanged for two years, the nodes not increasing but becoming tender when he caught cold. August 15, 1908, the swelling began to increase rapidly, and on October 25 two nodes each as large as a walnut were removed from above clavicle near sternomastoid muscle. On microscopical examination the process was pronounced by two pathologists to be lymphosarcoma with caseous tuberculosis. November 13, 1908, two enlarged nodes appeared near the cicatrix. During 1909 the inguinal nodes became enlarged, five tumors varying in size from a large bean to a hen's egg appearing in the groins. The cervical nodes also increased in size, the patient gradually lost weight and strength and died February, 1911. No report concerning other nodes or the spleen.

Microscopical: Portions of the cervical nodes, hardened in formalin, were received for diagnosis. The complex features presented by the sections may be enumerated and described as follows: (1) There is considerable imperfect fibrosis in certain areas, which accords with the long duration of the disease. (2) Lymphoid tissue, diffuse and in the form of occasional hyperplastic lymph follicles persists in many portions of the nodes. (3) Diffuse endothelial cell proliferation is prominent in many areas. (4) Focal areas of endothelial proliferation resembling epithelioid tubercles with or without central necrosis and typical Langhans' giant

cells are occasionally observed. Prolonged search for tubercle bacilli was negative. (5) Cords, broad sheets, and sharply demarcated alveoli composed of pale pavement-like cells are the most prominent feature. The cell bodies are nearly stainless, often vacuolated; the cell borders indistinct, the nuclei large and vesicular. Some of the cell groups resemble secondary carcinoma. Other distinctly neoplastic cell groups grade insensibly into the proliferating endothelium of the lymphoid tissue; or these neoplastic cells lie in the centers of focal lesions resembling miliary tubercles with points of necrosis and peripheral Langhans' giant cells.

The entire picture gives the impression of an infectious granuloma with extensive endothelial proliferation in which some of the endothelial cells instead of degenerating have developed neoplastic qualities. This case resembles in its neoplastic features the one described by Da Gradi and Di Amicis, in which, however, no granulomatous process was observed.

CASE 7. — Malignant plexiform endothelioma of cervical lymph nodes. Invasion of tissues of neck as alveolar endothelioma. Compression of larynx, asphyxia. No metastases. (Fig. 11.)

Clinical history: C. L., male, 65 years. No signs of syphilis. Shortly after recovering from an attack of typhoid fever two years ago he noticed a painful mass at the angle of right inferior maxilla, which gradually increased in size. Six weeks ago a similar mass appeared on left side. On admission to Bellevue Hospital September, 1912, service of Dr. B. J. Lee, his chief complaint was dyspnea from pressure of large tumor mass on both sides of neck. The tonsils were found enormously enlarged, with the anterior faucal pillars stretched tightly over them. The lymph nodes in the neck are greatly enlarged and hard; those in the axillæ, groins, popliteal spaces and epitrochlear regions are moderately enlarged and hard. In the neck the skin is adherent. Spleen, not palpable, and abdomen free from masses. No primary tumor of mucous membranes could be demonstrated. Dyspnea steadily increased and he died a few hours after a tracheotomy. Autopsy was not permitted, but a node from the neck was removed for diagnosis. It was as large as a walnut and adherent to the main tumor mass, firmly encapsulated, sections showing light gray areas in smooth hard fibrous tissue.

Microscopical structure: The lymphoid structure is entirely replaced by tumor tissue which appears in the form of convoluted masses of large polyhedral cells inclosing wide sinuses filled with homogeneous material and desquamated cells. In many areas the cell masses are cut up into small groups by fibrous tissue. The cells are of the large pavement type with clear cytoplasm, large hyperchromatic vesicular nuclei, prominent nuclei, and occasional mitoses. Certain cells appear as hydropic areas in

which lie small pyknotic nuclei. In some areas the tumor masses are identical in appearance with that of the plexiform endotheliomas previously described. The periglandular fat and fibrous tissue is invaded by numerous small groups of cells. Lymphocytes appear in narrow bands and small foci. There is considerable new connective tissue.

Although a primary tumor of a mucous membrane could not be satisfactorily excluded, the history of the case, the size of the cervical masses, the involvement of distant nodes, and the histological picture of plexiform endothelioma seem to justify the interpretation of the case as a malignant endothelial tumor of lymph nodes belonging in the same group with the above plexiform endotheliomas.

CASE 8. — Systemic endothelioma of lymph nodes, involving peripancreatic, retroperitoneal, lumbar, bronchial, mediastinal, cervical, and axillary nodes. Extensions to diaphragm, thyroid, and adrenal. No metastases in liver, spleen, kidneys, lungs, breast, or bones. (Fig. 9.)

Through the kindness of Dr. Charles Norris I have been able to study the material from this case which has been fully reported by Flournoy (Trans. N.Y. Path. Soc., 1907, vii, 45) under the title "A Case of Generalized Tumor of Lymph Nodes," and with the diagnosis of endothelioma. A brief abstract may here be presented.

The patient, German, 45 years, almost aphonic on admission to Bellevue Hospital, December 31, 1906, gave an incoherent history of swelling in the neck and groin for two to five years, and of two operations on account of them. On admission he complained of weakness, dyspnea and edema of limbs. Large masses of nodes occupied both sides of neck from ear to clavicle and right axilla, with smaller tumors in left axilla and both groins, while the upper half of the abdomen was distended by an indefinite tumor mass. Urine and blood negative. With increasing dyspnea, weakness, and edema he died January 31, 1907.

Autopsy revealed large coherent masses of nodes in the neck, right axilla and groin, chest, and abdomen. The trachea and esophagus were embedded and compressed in a large tumor mass. The right lobe of thyroid was partly infiltrated. One mediastinal and two bronchial nodes were much enlarged, and there was a subcutaneous nodule near right nipple. The main abdominal mass, weighing 1,780 grams, surrounded the pancreas, which was not invaded, and enclosed and compressed the aorta and vena cava. The mesenteric nodes were not involved, but the mesentery was covered with many pin-point nodules which proved to be inflammatory. The left adrenal contained a few tumor nodules. Examination of all the organs and mucous membranes failed to reveal any point at which a primary epithelial tumor could have existed.

The hands and face presented the features of acromegaly, but the hypophysis was normal

The structure predominating throughout the large tumors and the smaller nodes is of an alveolar tumor, composed of large or small groups of cells supported by delicate connective tissue strands or broad bands of fibrous tissue. In the large tumor mass there are extensive masses of fibrous tissue in which the tumor cells are undergoing atrophy. In the small outlying nodes the process is very cellular and the cell groups large, but capsules are intact. A prominent feature is the presence of many spaces surrounded by tumor cells and containing homogeneous or granular material, or fat crystal beds. Many of the spaces are lined by flat cells and seem to be dilated lymph sinuses, others are filled with necrotic cell detritus Many of these spaces are large enough to yield a cystic appearance in the gross.

The cell forms vary greatly, being round, cylindrical, crescentic, and pavement-like in the small field. They readily assume a spindle form. The arrangement is likewise very irregular, being alveolar, or diffuse, and many broad sheets of cytoplasm are found in which cell borders are indistinct. Small distinct syncytial masses appear, and still smaller giant cells with multilobed nuclei are found.

Some groups of cells in concentric pearl formation are found in certain fields.

The cell cytoplasm stains faintly. Nuclei are vesicular and moderately hyperchromatic. In certain foci the cells have undergone fatty degeneration and these form areas resembling the granule cell areas in cerebral softening. All of these features are consistent with, or strongly suggest, the endothelial nature of the tumor cells.

All the nodes examined seem to show an invasion by tumor cells and not a development in situ. The original area in which this tumor developed was evidently lost in the early history of the case.

The clinical history, showing the early stages of the disease in widely distant areas, as neck and groin, and a remarkable limitation of the process to the lymphatic system, together with the peculiarities of cell form and grouping, many of which are characteristic of endothelial growths, seem sufficient grounds for the diagnosis of systemic endothelioma.

As Flournoy stated, this case closely resembles those described by Recklinghausen and detailed by Gallina.

CASE 9. — Primary tumor of lymph nodes of axilla. Excision, followed by local recurrence and splenomegaly.

Wood (Trans. N.Y. Path. Soc., 1912, xii, 54) has reported on the structure in this case, and through his kindness I have been able to study the sections. With Dr. Rogers I have had the opportunity to examine the patient at intervals.

Tumor of varying structure: (1) Loose large round cell "lymphosarcoma," (2) coherent sheets of endothelial cells, (3) Hodgkin's granuloma. (Figs. 13, 14.)

History: Mr. B., age 35. Without known injury or infection of any portion of arm, neck or shoulder, a tumor appeared in left axilla in September, 1911, and reached the size of a hen's egg by January 1, 1912. No pain, tenderness, fever, or other symptoms. Excision of tumor January 22, 1912, by Dr. John Rogers.

During the summer of 1912 there was some loss of strength, pain in left hypochrondrium and an acute febrile attack lasting two weeks, with pain in chest and dyspnea. October 1 the spleen, not previously palpable, was found to be enlarged, and its dimensions continue to increase, at present with some general anemia and weakness. December, 1912, the spleen continues to enlarge and the anemia increases. There is moderate leucocytosis; small lymphocytes, 16 per cent; large mononuclear cells, 20 per cent; polynuclear, 59 per cent; eosinophiles, 5 per cent. There are enlarged lymph nodes in both axillæ and in the supraclavicular regions.

Gross examination: The tumor removed is a rounded mass 5 centimeters in diameter, firm, encapsulated. Section shows several opaque whitish ill-defined nodules lying in a diffuse reddish gray tissue. It is evidently composed of enlarged lymph nodes.

Microscopical: The structure of the lesion in this case is of special interest, since it presents three different appearances in portions of the same or contiguous nodes.

(1) The main portion is occupied by a tissue composed of large round or polyhedral cells identical in appearance with those of Case 10. (2) In a small outlying node there are sheets of very large cells, similar to those in Case 11. (3) The remainder of the lesion is identical with that occurring in many cases of Hodgkin's granuloma, in which many pale endothelial cells, some with multilobed nuclei, lie among lymphocytes, plasma cells, eosinophile cells, and small irregular strands of reticular tissue. In one portion of the capsule there are two focal lesions closely resembling miliary tubercles.

In this case one has to deal with a systemic but somewhat localized disease of lymph nodes and spleen. The structure of the primary tumor is varied, showing areas resembling lymphosarcoma which clearly arise from the endothelial cells of the lymph node, and other portions which resemble Hodgkin's granuloma.

The association of these two histological processes in one node indicates that each represents more or less direct effects of the same cause. The further conclusion is suggested that when this same type of lymphosarcomatous structure is

observed alone, as in Case 10, a relation to Hodgkin's granuloma should be considered.

The interpretation of this case depends much on the character of the splenic process, which cannot now be determined. The gradual transformation of Hodgkin's granuloma into a sarcomatous process has now been recorded by several observers. The present case indicates that this transformation may occur early in the course of Hodgkin's disease.

The exact position of the case is a debatable question. That the process was originally granulomatous is indicated by the areas resembling Hodgkin's granuloma, by the focal lesions in the capsule, and probably also by the clinical course. The other areas seem to have quite a different significance. In them the extent of the hyperplasia and the nuclear hyperchromatism far exceed that observed in the ordinary case of tuberculosis or of Hodgkin's disease with large cell hyperplasia. The impression given by these areas is that of a malignant tumor. The appearance is identical with that pictured by Sternberg as lymphosarcoma or with that called by him alveolar sarcoma (Verh. d. Deutsche path. Gesell., 1912, Taf. 1, 2; Figs. 1 and 2). This impression is strengthened by the presence of numbers of the large cells in the peripheral lymph sinuses and in the blood vessels of the capsule. The study of the lesion as a whole justifies, at least, the conclusion that an infectious granuloma has here induced a process which has the morphological features of a neoplasm as well as the capacity to permeate blood and lymph vessels. That the process is completely autonomous cannot be claimed. The true significance of the case and its exact position are best revealed by comparison with the two succeeding cases in which neoplastic features are more pronounced.

CASE 10. — Endothelial sarcoma, "lymphosarcoma," of axillary nodes. (Fig. 15.)

Clinical history: Mr. P. B., age 67 years. About January, 1908, he noticed some enlarged nodes in left axilla. These grew slowly until October, 1910, when they began to increase rapidly, soon doubling in size.

Examination January 31, 1911, revealed a tumor mass, 6 x 8 centimeters, in left axilla, freely movable from skin and deeper structures. The mass appeared to be composed of several nodes more or less discrete, resembling the nodes of Hodgkin's disease. Excision of the mass was performed by Dr. Coley, February 1, 1911. It was composed of many discrete nodes from 1 to 3 centimeters in diameter, sufficiently attached to form one mass. They extended up as far as the clavicle and were removed by an extensive dissection. The patient received mixed toxins for six months.

November, 1912, the patient's physician reports him entirely well.

Microscopical: The lymphoid tissue is almost entirely replaced by tumor cells arranged in broad sheets traversed by occasional fine bands of reticular connective tissue. A few lymphocytes may accompany these strands which are remnants of the lymphoid tissue. Connective tissue growth is entirely missing. On the periphery of the node instant fixation has left the cell sheets continuous and the cell borders are difficult to distinguish.

Elsewhere shrinkage has left the cells loose, discrete, and rounded. The loose cells are opaque and acidophilic, the others clear, cytoplasm finely reticular and vacuolated. The nuclei are hyperchromatic. A few very large cells contain huge multilobed nuclei. Focal necroses and single necrotic cells are a feature. The blood and lymph sinuses are much widened and focal hemorrhages occur. The structure appears almost identical with that of Case 11, but the cells are smaller and more anaplastic.

In this case one has a form of multiple "round cell sarcoma" of the axillary lymph nodes. Since the dissection was extensive and probably complete the part played by the toxin treatment remains undeterminable, although other cases of this type proved fatal.

The structure is one that is ordinarily called lymphosarcoma, but its characteristic cell forms, the derivation of these cells from the endothelium of the reticulum which could readily be followed, and the resemblance of the process to sarcomas associated with Hodgkin's granuloma in which the large cells are admittedly of endothelial origin, all go to support the interpretation of the case as endothelial sarcoma.

CASE 11. — Clinical diagnosis: Axillary tumor.

Pathological diagnosis: "Hodgkin's endothelial sarcoma."

Summary: A single tumor, in an axillary node of a robust man, about 6 centimeters in diameter, encapsulated, soft, no visible necrosis. Second tumor appeared later below angle of scapula. Structure, diffuse growth of

large sheets of pale, rounded or polygonal cells with isolated cells and cell groups intimately incorporated in the structure of the node; traversed by cords of lymphoid tissue. Focal necroses. No connective tissue reaction. (Fig. 16.)

Clinical history: A. G. D., 48 years. One year ago noticed a lump size of a pea in left axilla. No pain in axilla or arm. Never any injury to arm. No disability. Never had cough or other pulmonary symptoms. General health always good except for frequent headaches. The mass has grown steadily and during the past months more rapidly.

Examination shows a large man, plethoric, general physical condition normal. In left axilla is a mass size of a small orange, firm, movable from skin and deeper parts, not tender, without local heat or swelling.

Operation by Dr. B. J. Lee, May 28, 1912; the mass was removed. There were several soft glands in axilla which were not removed. The excised tumor is spherical, 6 centimeters in diameter, well encapsulated. Section is firm, grayish white nodules separated by reddish streaks appearing throughout. No necrosis or hemorrhage. Since the operation a new tumor has appeared below the angle of scapula.

Microscopical: The lymphoid tissue is largely replaced by broad sheets of large clear polyhedral cells, traversed by cords of lymphoid tissue. Small groups of similar cells appear in many places, and many single large clear cells appear in the midst of lymphoid tissue as though springing from the endothelium of the reticulum. There are many foci of necrosis in the larger cell masses. The tumor cells are everywhere intimately connected with one another and on all sides they grade insensibly into the surrounding lymphoid tissue. The sharp demarcation and reactive fibrosis of secondary cancer are entirely missing. The cell borders are indistinct, some appearing almost as syncytial masses. The cytoplasm is very pale, finely reticular and vacuolated. Nuclei are vesicular, slightly hyperchromatic, with multiple small nucleoli. Mitoses infrequent. In imperfectly fixed areas the cells are loose, rounded, and suggest lymphosarcoma.

The clinical history of the case leaves no reasonable doubt that the tumor is primary in the lymph nodes. Careful study of the structure reveals essential differences from secondary carcinoma, and convinces us that the tumor arises from the endothelium of the lymphoid reticulum.

Three other cases of enlarged lymph nodes of cervical, supraclavicular, or axillary regions have been studied in this series, but detailed reports of them will be omitted. They show various grades of hyperplasia of large reticulum cells which connect the above axillary tumors by numerous transitional stages with the so-called "large cell hyperplasia" of lymph nodes. In one the structure resembles that observed in the spleen in the "epitheliome primitive" of Gaucher.

SUMMARY. — The foregoing cases represent several phases of the excessive growth of the endothelium of lymph nodes, beginning with a process which it is difficult to separate from an inflammatory hyperplasia and leading by a series of transitional cases to a malignant tumor of endothelium.

A peculiar form of diffuse endothelial hyperplasia which seems to approach a neoplastic grade is illustrated in Case 1, which ran the clinical course of Hodgkin's disease. Here the endothelial hyperplasia although very pronounced and far exceeding the large cell hyperplasia of tuberculous lymph nodes must still be regarded as essentially inflammatory in nature. Another peculiar tumor-like hyperplasia of endothelium intimately associated with an infectious granuloma is presented in Case 2. This tumor grew slowly in the lymphoid tissue of the upper pharyngeal tonsillar ring. Here the endothelial hyperplasia is even more distinctly neoplastic and yet so closely connected with granulomatous lesions that it seems impossible to decide whether it should be classed as neoplastic or inflammatory.

In Case 3 it was possible to follow for six years a condition of the lymph nodes which was originally granulomatous and probably tuberculous, which later appeared as combined granuloma and endothelioma, and which finally recurred in the form of a pure plexiform endothelioma without evidence of granuloma.

In Case 5 the same combination of a granulomatous lesion with endothelioma is observed and the apparent transitions of one process into the other may be traced in different nodes removed at the same operation. The neoplastic features in this case are very pronounced, the capsule of the node was extensively invaded, and the duration of the disease was short (six months). From these data the conclusion seems justified that an endothelial hyperplasia initiated by a granulomatous infection may very soon attain the momentum of a malignant tumor process.

In the preceding cases the hyperplastic endothelium was intimately connected with the lymphoid tissue and it was possible to trace the swollen and atypical tumor cells into

areas showing proliferating endothelium of the remaining lymphoid tissue. In these cases, therefore, the identification of the proliferating cells as endothelium whether inflammatory or neoplastic may be regarded as direct and positive.

In the next, Case 6, alveolar endothelioma with infectious granuloma, the groups of tumor cells are usually sharply separated from the lymphoid tissue, yet definitely neoplastic. From this observation the conclusion is drawn that endothelioma arising on a granulomatous basis may from the first assume the type of a pronounced atypical alveolar tumor.

Case 7 presents the structure of alveolar endothelioma of highly malignant type. Its very characteristic structure is a duplicate of that observed in preceding cases, but there is no evidence of any connection with an infectious irritant.

Case 8, reproduced from Flournoy's report and studied in the light of the present series, illustrates the most extensive development of a systemic alveolar endothelioma of lymph nodes. In many places the structure is identical with that of the last preceding case, and with portions of the tumor in Case 3.

A somewhat different type of endothelioma, resembling lymphosarcoma, is represented by Cases 9, 10, and 11. All of these were tumors of axillary lymph nodes.

In Case 9 the structure of the large nodes varies. In some the structure is that of Hodgkin's granuloma with excess of large endothelial cells, in others there is only diffuse overgrowth of endothelial cells, so that the structure resembles lymphosarcoma. The structure is identical with that observed in a case of Hodgkin's granuloma, terminating in sarcoma, reported by Welch, and studied in this laboratory, and it is very similar to that found in two cases of bulky mediastinal Hodgkin's tumors. These observations indicate that the process initiated by the virus of Hodgkin's disease may pass rapidly into a neoplastic process resembling lymphosarcoma.

In Case 10 an axillary tumor presents the structure of the sarcomatous portions of the preceding case, but without any

trace of granulomatous process. Since the structure is peculiar and highly characteristic in both cases and the clinical features are similar, these observations indicate that certain primary endothelial sarcomas of lymph nodes are an expression of much the same factors as are present in those cases of generalized Hodgkin's granuloma which terminate in sarcoma. For these cases I would suggest the term "Hodgkin's endothelial sarcoma;" and would offer the interpretation that they result from a rapid and markedly atypical overgrowth of lymphatic endothelium incited by the virus of Hodgkin's granuloma. Objection has already been raised against the use of the term "endothelial sarcoma," once used by Hansemann in another connection. Yet in this instance the tumors arise from recent mesoblastic derivatives commonly called endothelium, and these mesoblastic tendencies are somewhat conspicuous in the structure of the tumors, so that they pass under the name "lymphosarcoma." Other endotheliomas maintain the acquired pavement characters of the originating cells and on this account deserve unqualified recognition as typical endothelioma. For the former group a particular designation seems desirable, as "sarcomatoid endothelioma" or endothelial sarcoma. Diffuse edema of the node probably from lymph stasis seems to account for some of the histological peculiarities of this tumor. It is probable that this tumor is commonly called lymphosarcoma, but it is readily separated from tumors derived from lymphocytes.

In Case 11 one has another round or polygonal cell tumor of axillary lymph nodes. The structure differs from that of the preceding case only in the larger size of the cells. With these axillary tumors there appears to be a distinct tendency of the disease to become systemic, involving distant lymph nodes and the spleen.

These three axillary tumors, together with other cases not detailed in this report, seem to show that the so-called "large cell hyperplasia of lymph nodes" may reach a neoplastic grade and run the course of large cell lymphosarcoma.

Summary of clinical, gross anatomical, and microscopical features. — The tumors in the present series of cases represent both localized growths and systemic diseases. No uniform principle seems to have determined the systemic nature of the process, for in Case 1 one finds a widespread granuloma with certain neoplastic qualities; in Case 9 the systemic invasion of spleen and distant nodes follows eighteen months after the appearance of a single axillary tumor; while in Case 8 the systemic distribution appears to have resulted from extensive permeation of tumor cells exclusively in the lymphatic system. Thus the systemic character, while it is a notable clinical feature, is not of uniform pathogenesis and cannot be regarded as an essential character. This conclusion does not speak against a uniform etiology, for Hodgkin's disease exhibits exactly parallel variations in course.

The duration of the cases has varied from six months to six years, the former interval sufficing for a fatal result from removal of extensively invaded carotids and the latter period being recorded in a recurrent tumor of the neck. Both cases were associated with granuloma. The usual duration is about two and one-half years, as in Hodgkin's disease. Only one case seems to have recovered, and after removal of a local axillary tumor. The recovery indicates that in that particular form of tumor the disease may at first be strictly local. Another case of much the same type (Case 9), associated with granuloma, soon became generalized, possibly through the dissemination of the granulomatous virus. Several cases are still under observation. Localization improves the prognosis whether a granuloma is present or not. Histological signs of high malignancy have been present in both local (Case 4) and generalized processes (Case 8).

To summarize the observations on this point it may be said that tumor-like hyperplasia of endothelium and malignant endothelial tumors of lymph nodes may each appear as local or general diseases, and the generalization may result from a dissemination of a granulomatous virus or from progressive permeation of chains of nodes by tumor cells.

The degree of local aggressiveness of the tumors also varies greatly. As a rule these tumors show little tendency to destroy the capsules of the nodes but tend rather to extend widely through the lymph channels. Two factors may result in infraction of this rule, first the appearance of an associated granuloma which is locally destructive, and second, the existence of a highly malignant tumor process which, as in Case 4, destroys the capsule of the nodes before extending to other chains.

The general lack of local aggressive quality, however, distinguishes many endotheliomas from secondary carcinoma of lymph nodes. It is only the alveolar forms of endothelioma which present difficulty in the separation from secondary carcinoma and here the relatively long duration, late development of cachexia, and failure of a primary tumor to declare itself, deserve consideration from the clinical side. The usual absence of visceral metastases is another anatomical feature which distinguishes endothelioma, but it has not proven invariable. Yet the strict limitation to the lymphatic system with widespread lesions has sometimes been quite remarkable.

The minute histological characters of the process and the structure and relation of the cells, have formed one of the chief grounds for the interpretation of these cases as endothelioma.

With the exception of the alveolar tumors these cell characters are distinctive and in many instances practically unequivocal. As noted by Ravenna the tumor cells may form nearly diffuse sheets of cytoplasm in which cell borders are indistinct or indistinguishable, while the large vesicular nuclei with multiple nucleoli and delicate nuclear reticulum appear scattered at intervals. The cytoplasm may be nearly stainless or show a faint reticulum, but it is seldom definitely granular. The cell form is usually polygonal or pavement, in the plexiform type many cells may be spindle-shaped, in the axillary tumors rounded and polygonal, while in alveolar growths polygonal shapes predominate. Various degenerate cell forms may appear which are indications of an endothelial

nature. Thus one may find foci of cells distended with fat granules like the granule cells of cerebral softening. Hydropic vacuolation commonly contributes to the transparency of cell bodies. Giant cells are rare, but occurred in the axillary tumors. They are of the myeloid type with single multilobed nuclei and granular acidophilic cytoplasm. Thus the statement often encountered that there are no definite cell characters in endothelioma is true for some but not for all tumors of lymph nodes.

The intimate relation of the tumor cells to the lymphoid stroma often furnishes convincing evidence of their endothelial origin. In the tumors associated with granuloma, in the plexiform type, and in the axillary growths, the tumor cells grade insensibly although often sharply into large cells lying in and on the meshes of the reticulum. The nature of these cells of origin will be considered later. In the process cells of the lymphocyte class disappear or persist in narrow strands always sharply separated from the tumor cells. The lymphocyte nuclei remain compact and do not yield mitotic figures, whereas the endothelial nuclei are vesicular and often show mitotic figures.

The arrangement of the hyperplastic cells varies in different forms of the present tumors and these variations have formed the basis of the nomenclature employed.

According to this plan three histological varieties of endothelioma of lymph nodes are observed: (1) Diffuse, (2) plexiform or perivascular, and (3) alveolar.

(1.) The term diffuse, while not wholly exact, is applicable to those cases in which the cells appear in broad coherent sheets or syncytial masses. It has also been applied to the axillary tumors in which broad tumor areas are composed of rounded or polyhedral cells which are usually isolated and loose. This loosening of cells appears to be largely an artefact, since in such cases the polyhedral cells which have been promptly fixed appear in coherent sheets.

(2.) In the plexiform tumors the cells surround large irregular cavities filled with homogeneous material or cell detritus or leucocytes. Occasionally the cavities appear empty and lined by a continuous layer of flat cells resembling endothelium. I have interpreted these cavities as derivatives of the original lymph sinuses of the node, but am not convinced that this is their sole origin.

When the sinuses are highly developed the tumor cells cling to the arterioles of the septa, producing a characteristic perivascular arrangement which recalls the structure of perithelioma. In the plexiform and perivascular tumors the cells usually assume a spindle form but readily change to polygonal or pavement types.

(3.) The alveolar tumors present many difficulties of interpretation. Since it is seldom possible to trace the tumor cells to any structure of the original node, and since the cell groups often resemble those of secondary carcinoma, the diagnosis of this type of endothelioma requires full clinical and anatomical data and must often remain uncertain. Yet, it is just this type of tumor which has hitherto appeared in the literature and received considerable recognition as true endothelioma of lymph nodes. Moreover, the observations in Case 2 demonstrate that endothelial proliferation associated with granuloma may very early assume a form closely resembling alveolar endothelioma.

In this type of tumor the specific characters of endothelium are lost and the cells are polygonal or pavement-like with vesicular nuclei and clear or granular and opaque cell bodies. The occurrence of sheets of coherent cells with indistinct borders, the formation of minute concentric systems of cells or pearls without spines or keratin granules, are often observed and have been adduced as evidence of endothelial origin. These features are undoubtedly prominent in these tumors, but they seem suggestive rather than demonstrative of an endothelial origin. The intimate connection of tumor cells with tumor stroma, often urged as a ground for diagnosis, is usually missing in this group. The desmoplastic quality of many carcinomas is wanting, but a

notable tendency toward regression, degeneration and atrophy of tumor cells with secondary fibrosis and formation of cysts with fatty contents seem to distinguish some of these tumors from most secondary carcinomas.

Histogenesis: The term endothelioma has been applied to these tumors without a preliminary notice of the unsettled state of opinion regarding the nature of the cells from which the tumors are believed to spring.

Recklinghausen, employing silver impregnation, demonstrated pavement cells covering the reticulum of the cavernous and lymph sinuses. In the reticulum of the follicles he could not demonstrate this covering. By various methods of removing the included lymphocytes, Cornil and Ranvier, Bizzozero, Stohr, and others found the reticulum acellular, but covered with flat cell plates. On these observations, chiefly, is based the older view of the presence of an endothelial covering of the reticulum of lymph nodes.

Later, Baumgarten was able to demonstrate mitotic figures in fixed cells of the reticulum especially in the germ centers of follicles, and from these cells he derived the epithelioid cells of the miliary tubercle. He was unable to demonstrate the validity of Flemming's view that these same cells produce lymphocytes.

Ribbert concluded that there are both fixed reticulum cells and covering cells in lymph sinuses, cords, and follicles, and that the covering cells proliferate and become lymphocytes. Ribbert calls these cells endothelium.

Saxer finds that the reticulum is found throughout sinuses, cords, and follicles, that it is composed of anastomosing cells and cell processes without any specific covering cells. The reticulum cells he regards, from the embryological standpoint, as of connective tissue origin, and states that they are identical in nature with the capillary endothelium with which they are also directly continuous. Prenant and Bouin (1911) express the same views as Saxer, but call all the cells endothelial. They add the additional point that in the germ centers the reticulum cells may form a syncytium.

Further light on the origin and relation of these cells has been furnished by many embryological and comparative studies. Thus, Gulland shows that lymph nodes develop in embryonal connective tissue after the appearance of circulating lymphocytes. The first reticulum of the adult node he constructs through a multiplication of the lymph spaces of connective tissue, lined by modified connective tissue cells and eventually consisting only of these cells. The lymphocytes are deposited in this reticulum from the blood and lymph stream. Both Saxer and Gulland insist that the reticulum cells do not form lymphocytes and that the two series, reticulum cells and lymphocytes, remain rigidly distinct. That the reticulum cells are not so sharply separated from other mesoblastic derivatives is indicated by many studies, more recently by that of de Grot, which show that lymph nodes may be completely replaced by fat tissue or readily develop in this tissue.

These histological studies furnish essential data by which to interpret the origin and behavior of tumors of lymph nodes and of inflammatory processes that may precede them.

The uniform distribution of reticulum cells throughout the node and especially their presence in the follicles accords with the appearance of inflamed nodes in which a marked proliferation of these cells is commonly observed.

In the inflammatory hyperplasia of germ centers it is the reticulum cells which multiply by mitosis and replace lymphocytes and in the sinuses these cells proliferate and choke the sinuses. The common interpretation as endothelial, of the large cells which proliferate in granulomatous inflammation of lymph nodes, is fully justified and it is equally clear that tumors arising from these cells are properly called endotheliomas. It is of little moment whether the cells are called endothelial or otherwise. The important fact is that they originate from modified connective tissue cells in much the same manner as do the capillary endothelia and are modified chiefly by their acquired functions in lymph nodes. They may thus be expected to show a closer relation to fibroblasts than do vascular endothelia.

Many structural features of our tumors accord with the views expressed by Saxer and Gulland concerning the origin and distribution of the reticulum cells. The network of compact sheets of proliferating cells in Case 1 has been traced to the reticulum of the lymph node, and the lesser grades of proliferation of these cells in many granulomas can be clearly traced to the same origin. In the plexiform tumors the same participation of reticulum cells can again be traced and the labile form of the tumor cells, spindle and polyhedral, merely reflects the origin and function of the cells of origin. For the perivascular structure an origin chiefly from the lymph cords with preservation of the arterioles suggests itself. In alveolar endothelioma the pavement character of the cells suggests an origin from the endothelium of cavernous and lymph sinuses, and in some of the present cases (6 and 7) this origin seems directly indicated.

In all the diffuse, plexiform, perivascular, and alveolar endotheliomas no evidence was obtained that the reticulum of the germ centers is especially concerned in the tumor process, although several of these cases were traced from their earliest phases. On the other hand, in the axillary tumors, quite a different structure is observed which simulates a large cell lymphosarcoma.

In these tumors there is direct evidence of the special participation of the reticulum of the germ centers. In infectious lymphadenitis the follicular reticulum is regularly hyperplastic.

In Case 9 outlying follicles showed enormous hyperplasia which passed insensibly into a diffuse overgrowth of reticulum cells, and this same transition I have been able to trace in other cases of so-called lymphosarcoma.

In Case 10, with similar gross and clinical features, there is diffuse growth of cells derived from the reticulum of follicles, exactly similar to those of Case 9.

In some hyperplastic follicles unusually large endothelial cells predominate and the tumor in Case 11 seems to be stamped by this feature. The association of this tumor with an infectious granuloma of lymph nodes, in which

hyperplastic follicles are an early feature, accords with this view of the tumor's origin. Accordingly, from the data furnished by the present cases, I venture to draw the conclusion that the types of endothelioma of lymph nodes here designated as diffuse, plexiform, perivascular, and alveolar are derived chiefly from the endothelium of the cavernous and lymph sinuses and from the reticulum of the lymph cords, while other tumors with loosely packed large round or polyhedral cells, resembling lymphosarcoma, are derived chiefly, although probably not exclusively, from the reticulum cells of hyperplastic follicles.

From the studies of Saxer and Gulland and others there seems to be quite insecure ground for the assumption that small lymphocytes are derived from the reticulum cells of the lymph follicles. According to these observers the reticular endothelium and the small lymphocytes are entirely separate series.

The study of the present tumors and of the associated granulomatous processes leads to the same conclusion. Throughout these processes it is the reticulum cells alone which show mitotic figures and evidences of proliferation, while the small lymphocytes steadily diminish and disappear. The actively growing derivatives of the reticulum cells may often appear rounded, but as a rule they exhibit a persistent tendency to assume a polyhedral form. On the other hand, in true lymphosarcoma composed of small lymphocytes the cells are uniformly round, the tumors are highly malignant, and they differ essentially from the present group.

The question of the origin of so-called endothelial leucocytes from reticulum cells falls outside the present scope of this study. A competent discussion of this subject would lead directly into the extensive literature concerning the relations of lymphocytes to large mononuclear leucocytes and to endothelial cells. The limits of these cell groups have proved very difficult to define, and the present study is not designed as a contribution in that field. The endothelial derivatives in the present tumors are atypical neoplastic cells and, while they resemble the large lymphocytes and

large mononuclear cells of normal blood, this resemblance of tumor cells cannot apply directly to the origin of normal blood cells. It is obvious that if one identifies the large round cells of some of our tumors (here called endothelial sarcoma) with the large lymphocytes, the designation of these tumors as lymphosarcoma naturally follows.

Even thus, the necessity remains of recognizing a distinction between tumors composed of small lymphocytes and those containing large round cells of direct endothelial origin.

It remains to consider certain possibilities of error in the interpretation of the foregoing cases.

It is obvious that the task of tracing the derivation of neoplastic endothelium from simple hyperplastic cells is somewhat hazardous. Only the presence of the most definite and specific and histological criteria can render such a task successful. Yet it is just such criteria which have been relied upon in the identification as endothelial of those tumors which were associated with granuloma. Here, the minute characters of the tumor cells, their intimate relation to the lymphoid stroma, and the gradation into areas where the endothelial hyperplasia was less active may, I believe, be regarded as demonstrating beyond doubt the endothelial nature of the neoplasms.

Thus all the forms designated as perivascular and diffuse endothelioma must be considered as certainly of endothelial origin. It may here be added that the perivascular structure is not regarded as an indication of perithelial origin, but is merely a type of structure which is assumed in the interests of cell nutrition. Likewise for the three axillary tumors designated as Hodgkin's sarcoma, the endothelial origin seems to be beyond question, and attention may be specially directed to the necessity of separating this specific structure from the true lymphosarcomas.

In the case of the alveolar endotheliomas the evidence must be admitted to be somewhat less than conclusive. Here the cell characters approach those of certain epithelial

tumors, it is impossible to trace the tumor cells to any recognizable endothelium, and the cell groups are often sharply separated from the lymphoid stroma. In the advanced cases the original source of the tumor is lost, and the nodes available for examination have been invaded by extensions from other nodes.

The failure to find a primary tumor of a mucous surface or of any recognized form of epithelial misplacement is unsatisfactory evidence of the absence of such an origin of the growth.

In the absence of a very thorough post-mortem examination primary growths of the nasal sinuses, and especially of the antrum, may be overlooked. The inclusion of branchial epithelial cell nests appears as a definite possible origin of certain "endotheliomas" of cervical nodes. The history of endothelioma of the salivary and lachrymal glands suggests great caution in limiting the possibilities of epithelial inclusions in the cervical region and lymph nodes. Yet the history and structure of mixed tumors of the salivary glands, of branchiogenic carcinoma, and of carcinoma of the antrum, are distinctly different from those of the present cases called alveolar endothelioma of cervical lymph nodes.

Until it has been clearly shown that any one of the above primary epithelial tumors can duplicate the course and structure of endothelioma, it would seem justifiable to regard such cervical tumors as of endothelial origin without assuming such origin to be definitely proven.

Perhaps more important than the exact delimitation of the scope of endothelioma of lymph nodes is the demonstration furnished in the present cases of the frequent association of these tumors with an infectious granuloma. In fact certain endotheliomas of lymph nodes may be regarded as examples of a tumor process originated indirectly by a microörganism. These tumors belong in the irritation group, and they give no indication of an origin from misplaced or embryonal cells. For the acceptance of this view many previous observations on endothelioma have prepared the way. It has repeatedly been stated that endothelioma of the pleura propagates itself

over the pleura, pericardium, peritoneum, and lymph nodes, not by a permeation of tumor cells, but by a gradual extension of the tumor process over normal tissues, and that this extension depends on the diffusion of an irritant with the tumor growth. The tubercle bacillus has been regarded as the most probable irritant in these cases. In several of the present cases the endothelial tumor has been intimately associated with a granulomatous process. This granuloma has been interpreted as probably tuberculous, but in no case has the tubercle bacillus been demonstrable in sections and, unfortunately, few inoculations were made, so that the nature of the infectious agent remains in some doubt.

In some of the cases the granulomatous process resembled that of Hodgkin's disease. The possibility that the two processes were independent is negatived by the histological signs of immediate relations of the neoplastic cells to the phases of the granulomatous lesion. (See Figs. 1, 13, 14.)

It is somewhat difficult to formulate definite conceptions of the nature of the relation of an irritant to a neoplastic process, even in the most obvious instances in which that relation is generally accepted, as in pipe smokers cancer of the lip. Continued efforts at regeneration with hyperemia and overnutrition of cells suggest themselves as factors in bringing about a lawless overgrowth. The idea of a tissue predisposition is less definite and hardly applicable in lymph nodes. In those cases in which an endothelioma develops after a period of granulomatous inflammation it must be assumed that the special tendency of tubercle or Hodgkin's or other virus to cause the endothelial proliferation may in favorable, but as yet undefined, circumstances lead to excessive and neoplastic growth.

That this growth, once established, may progress of its own momentum without the continued presence of the parasite is an assumption which appears fully justified. In another connection I have considered other instances in which the tubercle bacillus or related microörganisms seem to act as etiological factors in tumor growth. (Harvey Lecture, 1907.)

In one of the present cases it was observed that the original granuloma was completely eliminated, while the tumor process appeared alone in the third recurrence. Experimental evidence in this field was long ago furnished by Jensen, whose transplantable sarcoma of the rat was originally produced by inoculations of an acid-fast tubercle-like organism isolated from an intestinal lesion of cattle. Jensen's failure to duplicate this experimental result diminishes but perhaps does not destroy its evidential value.

The present observations, therefore, seem to show that besides the gradual transformation of Hodgkin's granuloma into a sarcomatous or sarcomatoid process, previously described by various observers, localized granuloma of the lymph nodes may lead to regional tumors of endothelial origin, which progressively invade other lymph nodes and probably become independent of the original microörganism.

A further deduction from this study is that endothelial tumors of pronounced malignancy, and of identical structure with those observed with granuloma, may arise in the lymph nodes without apparent connection with granuloma. That such tumors are also the sequel of a granulomatous infection which is overlooked or early suppressed, can only be proven by data not yet supplied, but this explanation of the origin of such tumors seems highly probable.

Finally one group of the present cases, the axillary tumors, offers further basis for the generally accepted view that lymphosarcomas must be separated from other neoplasms, since they exhibit certain peculiar features which suggest a partly inflammatory nature and a parasitic cause. The same discrimination, and for the same reasons, may be made against many of the pure endotheliomas of lymph nodes.

To proceed further, and attempt to eliminate lymphosarcoma and endothelioma entirely from the category of tumors seems to me unjustifiable. It is by no means certain that the logical outcome of such a course would not be the elimination of the entire group of sarcomas.

There is a large number of processes, essentially neoplastic, which differ in etiology, pathological characters, clinical history, and therapeutic indications, and the more these specific peculiarities are studied the more conspicuous become the distinctions between these disease entities.

In view of these wide variations among processes belonging in the orthodox group of true tumors, and in view of the difficulty of constructing a rigid definition of neoplasms, it would seem best to retain in that category all conditions which consist essentially of lawless overgrowth of tissue cells.

From this point of view endothelioma of lymph nodes belongs among the tumors.

This conclusion, however, may well be qualified by emphasizing the distinctions which separate the present group of cases from other tumors. In the first place the ready response of endothelium to irritation indicates that an apparently excessive overgrowth of these cells has not the same value as a sign of autonomy as does an equal overgrowth of epithelium. In this respect endothelium belongs rather with lymphocytes. Secondly, experience shows that endothelioma is often associated with an infectious granuloma, a fact that suggests a close dependence of the overgrowth on the presence of an irritant. In most tumor processes no such relation has been observed. Third, the systemic character of some cases of endothelioma of lymph nodes reveals a mode of origin and dissemination which differs from that of some other tumors. Although some endotheliomas have a local origin and seem to disseminate by permeation into neighboring nodes, the remarkable limitation to the lymphatic system, even in extensive cases, appears not to be duplicated by the so-called true tumors. Fourth, the peculiar physiological relations of endothelium, their mesoblastic origin, their possible relations to mononuclear leucocytes, and their function as lining cells may account for many of the peculiarities which distinguish tumors derived from these cells from other neoplasms.

Therefore one may conceive of these tumors as belonging in a class by themselves, and constituting a disease sui generis.

GENERAL CONCLUSIONS.

1. Extreme grades of endothelial hyperplasia are not infrequently associated with and dependent upon granulomatous infection of lymph nodes, and these cases demonstrate the capacity of endothelium to respond to inflammatory irritation with extensive proliferation.

2. It some cases it is difficult or impossible to determine whether this overgrowth is simply inflammatory or independent of the irritant, autonomous, and neoplastic.

3. The long continued effects of a granulomatous infection may lead to neoplastic growth of lymphatic endothelium, and in the course of a granulomatous infection of lymph nodes, after repeated operations, the granulomatous element may be eliminated and the disease progress as a form of neoplasm.

4. Granulomatous infection of lymph nodes may very early give rise to excessive overgrowth of endothelium of distinctly anaplastic type, and with local aggressive properties.

5. Such malignant endotheliomas may arise without any evidences of an associated granuloma. It is possible to conceive that an original infectious focus may be overgrown and obscured by the neoplastic cells. No definite evidence of such an event has been secured, but it has been shown that one node of a chain may exhibit purely neoplastic overgrowth while others show chiefly granuloma.

6. Certain endotheliomas of lymph nodes designated as diffuse, plexiform, perivascular, or alveolar, are probably derived from the endothelium of lymph sinuses and lymph cords.

7. Certain primary tumors of lymph nodes, with or without associated granuloma, are probably derived from the

reticulum cells of the follicles. These tumors resemble lymphosarcoma with large cells, and may be distinguished from tumors of small lymphocytes.

8. Endothelioma of lymph nodes differs from other neoplasms in several particulars, and may be regarded as a disease sui generis, although, nevertheless, essentially neoplastic.

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DESCRIPTION OF PLATES.

PLATE I., FIG. 1. — (x 150.) Focal endothelial hyperplasia. Compact masses of endothelial cells with hyperchromatic nuclei surrounded by zones of pale staining endothelial cells. Case 2.

FIG. 2. — (x 230.) The same lesion with giant cell.

PLATE II., FIG. 3. — Diffuse endothelial hyperplasia in a case of clinical Hodgkin's disease. Case 1.

FIG. 4. — (x 150.) Portions of tumor, Case 3 (and others), showing proliferation of endothelial cells surrounding a dilated sinus.

PLATE III., FIG. 5. — The same as Fig. 3. Shows sheets of coherent endothelial cells with large vesicular hyperchromatic nuclei.

FIG. 6. — (x 100.) Plexiform arrangement of endothelial tumor cells surrounding vessels, sheathed with lymphocytes. Case 3.

FIG. 7. — (x 150.) Plexiform endothelioma. Case 7.

FIG. 8. — (x 150.) Portions of tumor, Case 3, showing more active growth of endothelium in perivascular arrangement.

FIG. 9. — (x 150.) Alveolar, plexiform, and perivascular endothelioma. Section from small abdominal node in case of generalized endothelioma of lymph nodes. Case 8.

FIG. 10. — (x 100.) Plexiform and perivascular endothelioma. Case 4.

PLATE IV., FIG. 11. — (x 230.) Diffuse portion of main tumor, Case 5. Rounded and polyhedral, isolated and coherent cells, extensively vacuolated.

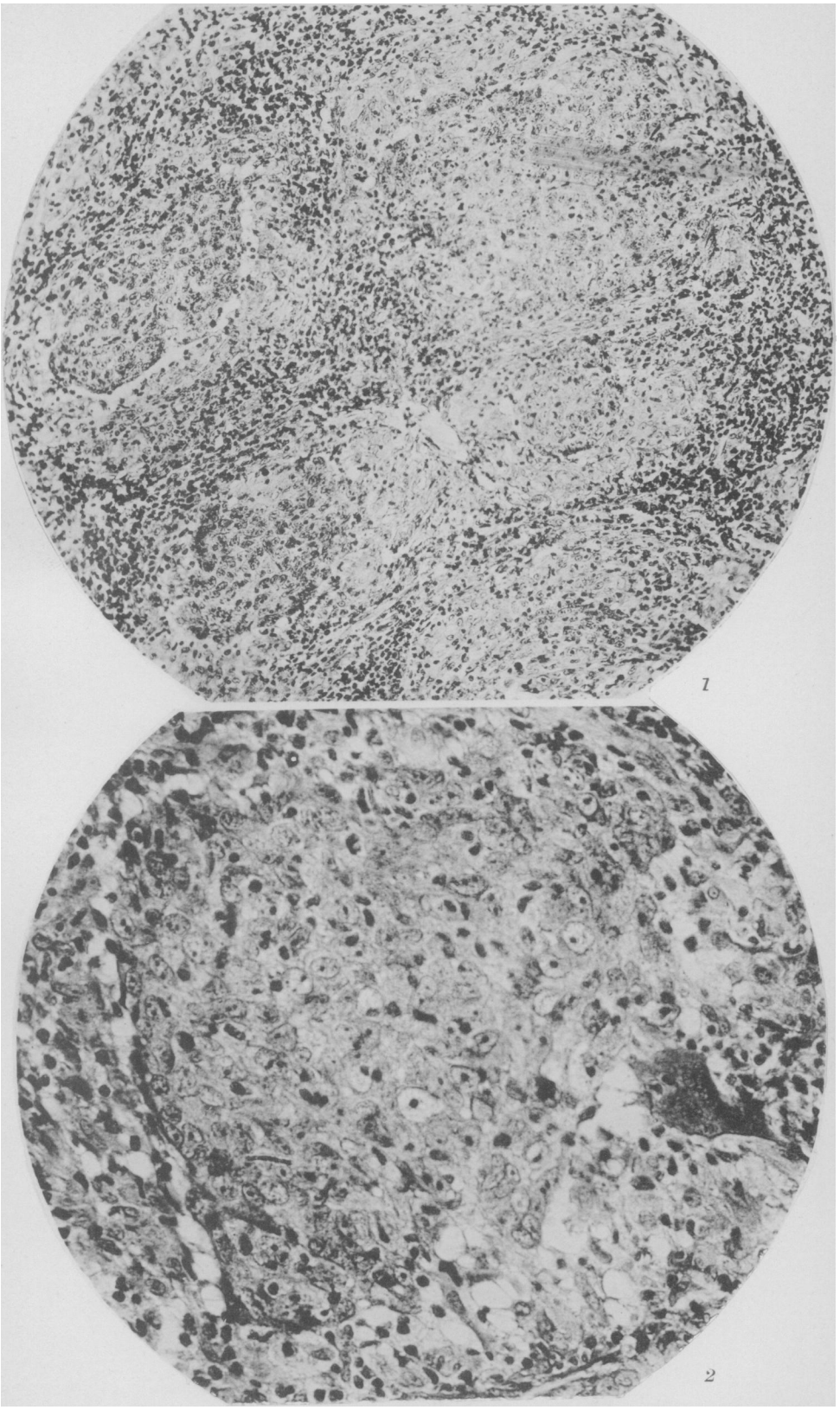
FIG. 12. — (x 230.) Structure of outlying small node in Case 5. The reticulum cells throughout the node show marked hyperplasia and nuclear hyperchromatism. Many areas resemble those of Case 1, Figs. 3, 5.

FIG. 13. — (x 150.) Granulomatous lesion resembling Hodgkin's, in portions of nodes, Case 9. Structure presents proliferating endothelial cells with hyperchromatic nuclei, plasma cells, lymphocytes, and eosinophiles.

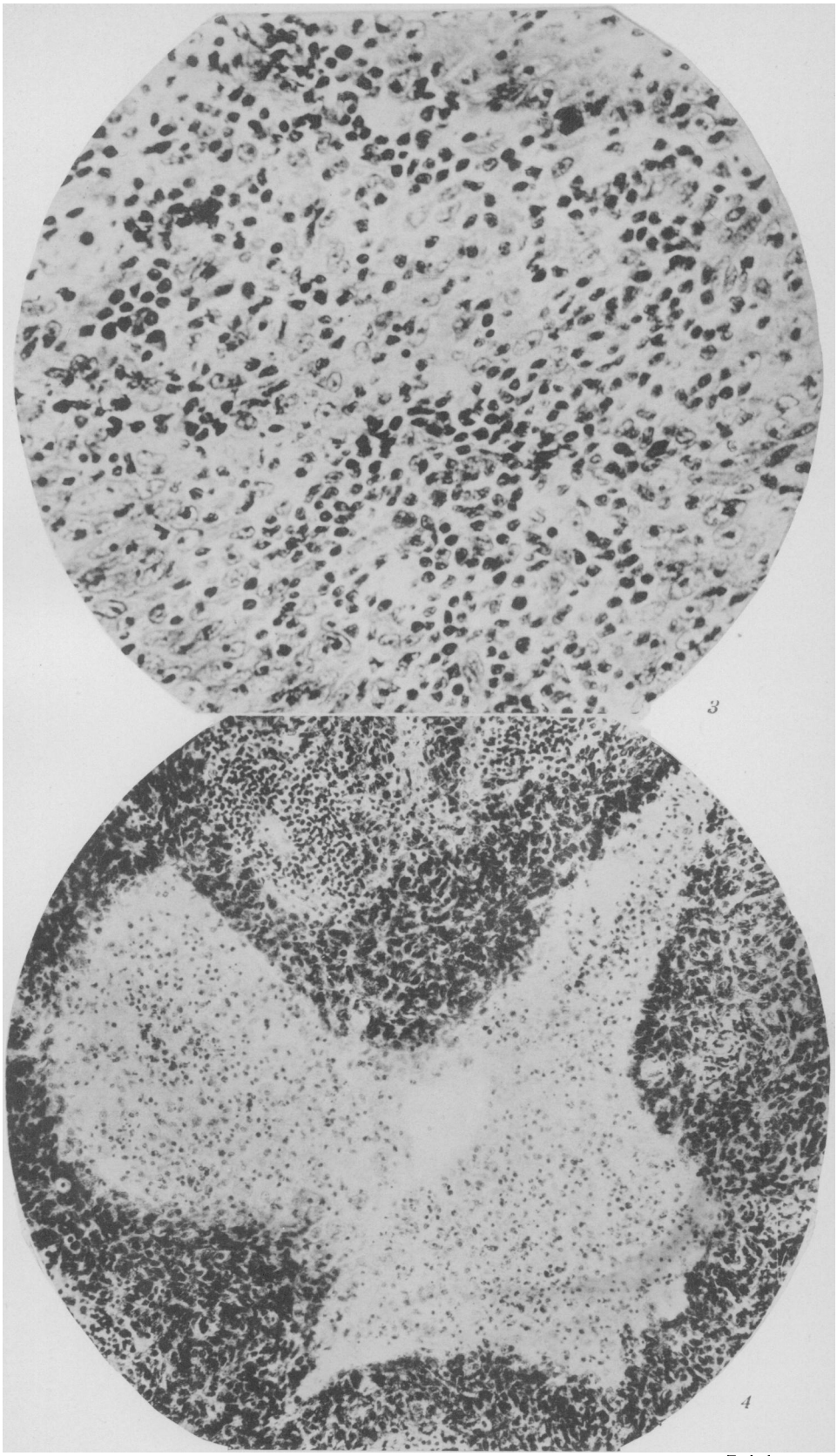
FIG. 14. — (x 150.) Other portions of same nodes, Case 9. Diffuse hyperplasia of large round and polyhedral cells which may be traced to the reticulum cells of the follicles.

FIG. 15. — (x 150.) Tumor of same nature as preceding case. Diffuse growth of rounded and polyhedral cells. No trace of lymphoid tissue. One giant cell. Case 10.

FIG. 16. — (x 150.) Very large round and polyhedral cells in tumor of axillary nodes. Case 11. Similar areas observed in Case 10.



Ewing Endothelioma



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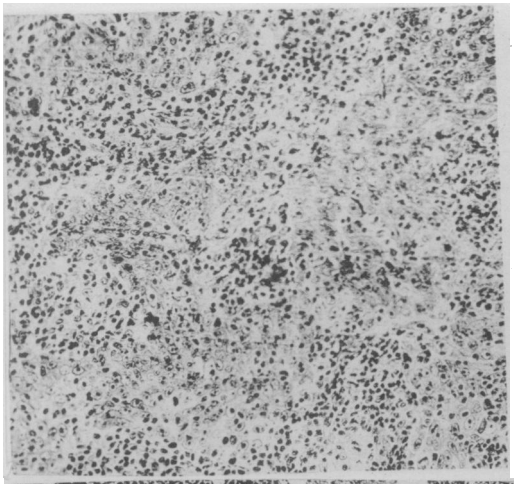

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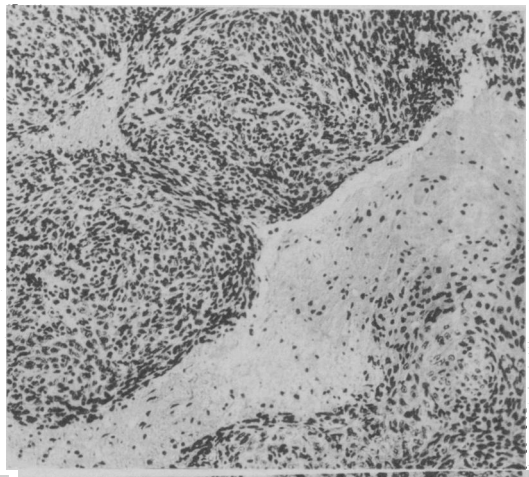

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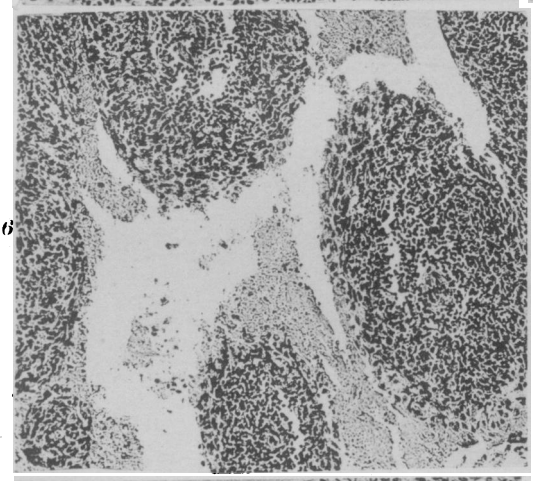

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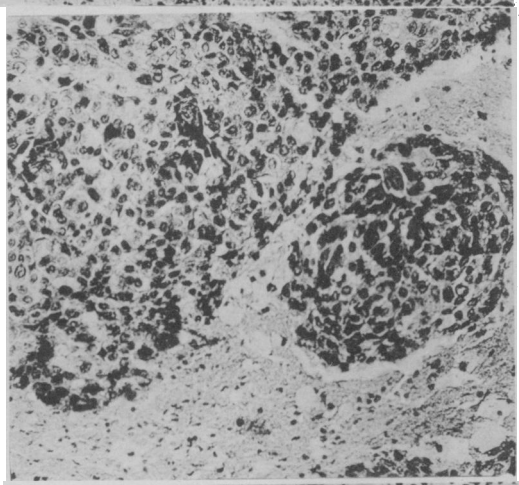

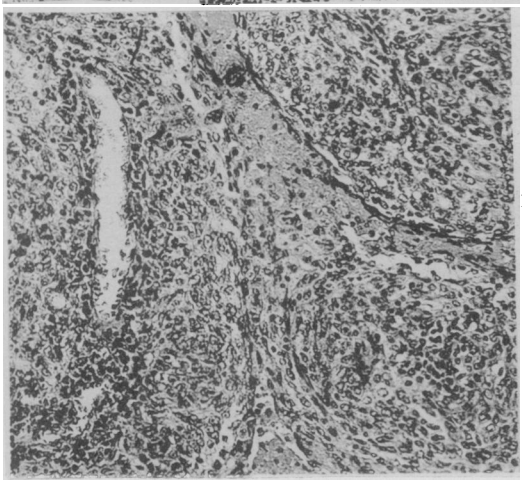

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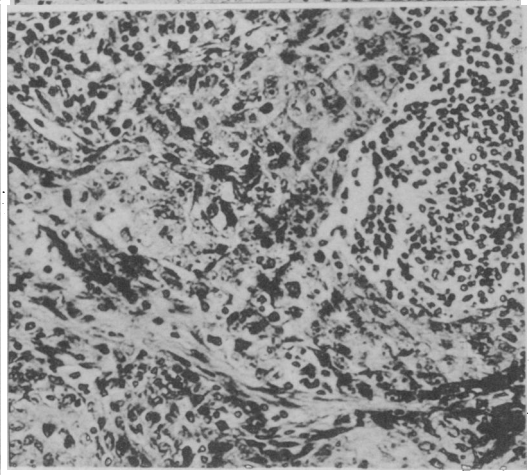

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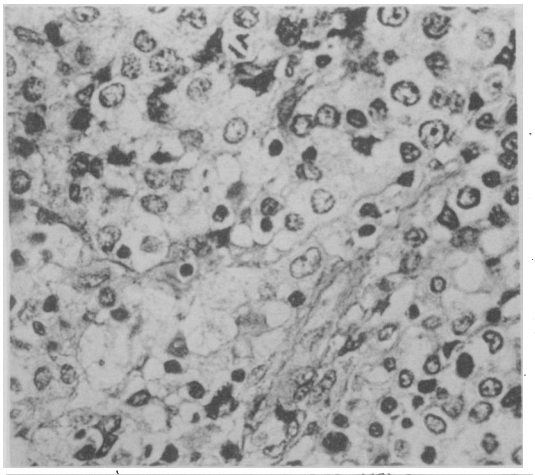

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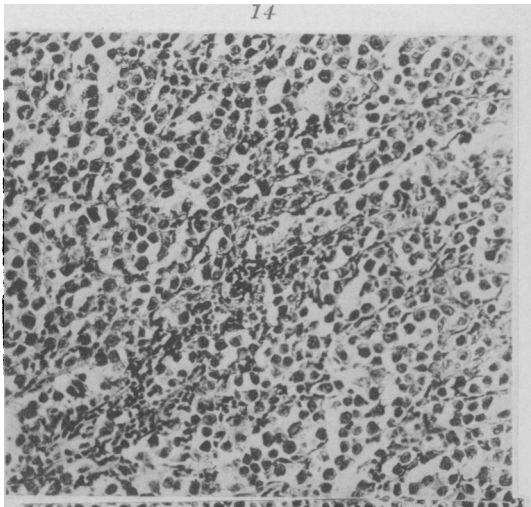

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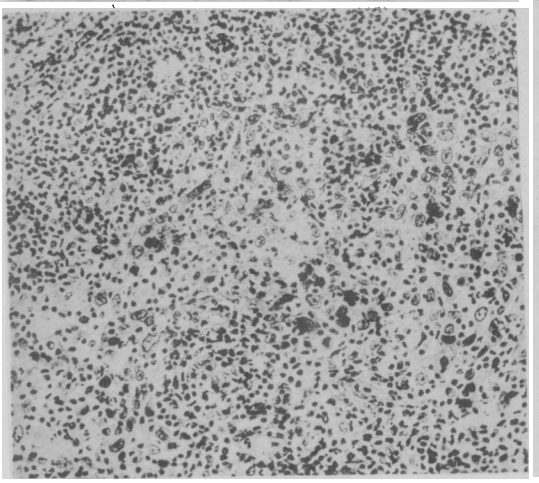

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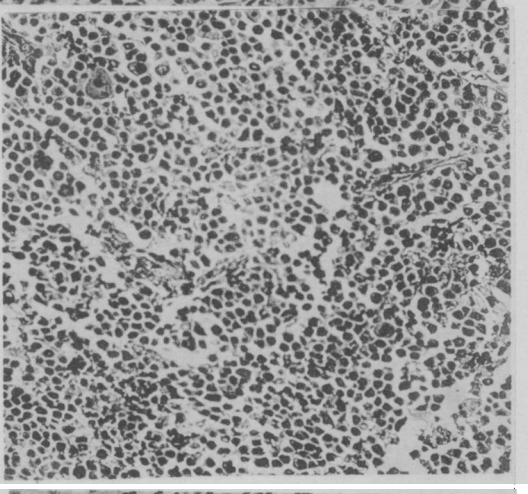

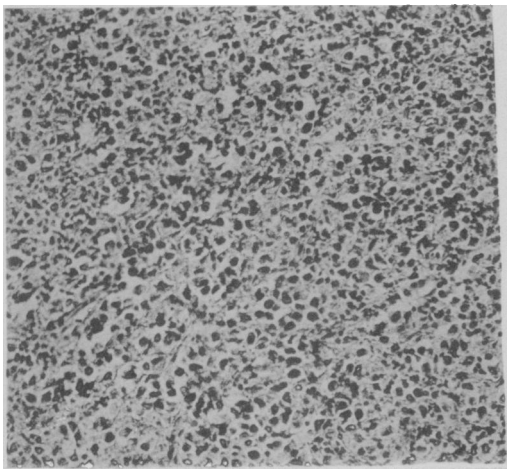

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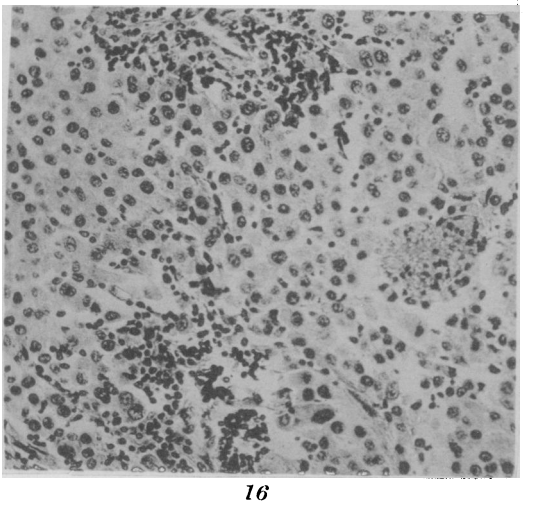

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