NEOPLASMS OF THE BLOOD-LYMPH-VASCULAR SYSTEM WITH SPECIAL REFERENCE TO ENDOTHELIOMAS*

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The observation that tumors diagnosed hæmangiomas not infrequently recur after excision, and in some cases even metastasize until they kill the patient, together with the fact that benign hæmangiomas and so-called malignant endotheliomas often show morphologically indistinguishable areas, usually in the nature of partially differentiated blood-vessels, prompts the following generalizations.

1. Hæmangiomas and lymph-vascular angiomas, although usually benign, are potentially malignant endotheliomas.

2. There is an intermediate stage between the strictly benign and the actually malignant angiomas, represented by hæmangio-endotheliomas.

3. Malignant endotheliomas of the blood-lymph-vascular system exist as a pathologic entity.

My object in this paper is to present the data in support of these generalizations.

Endotheliomas will naturally demand considerable attention in the consideration of a group of tumors arising from an organ in which endothelium plays such a large part, as in the lining of the channels and spaces of the vascular and lymphatic systems. That such tumors arise from the blood-lymph-vascular system is in many instances evident from their study under the low power lens of the microscope, since certain areas are composed of tumor blood-vessels and vessels lined with endothelium.

I shall endeavor to show that there is a solid type of tumor in this group, relatively malignant, which can be seen to develop from, and to be composed of, blood-vascular tissue, which differentiates into endothelial lined channels and blood-vessels, indicating that the function of the adult cells is to line blood channels and lymph channels, and thereby show that the type cell is endothelium and the tumor is endothelioma.

Embryology.—It formerly was taught that endothelium was mesodermal in origin. However, it must be borne in mind that the mesoderm has its anlage in the primitive embryonic ectoderm during the early stages of development, extending laterally from the primitive streak and groove between ectoderm and endoderm. It is therefore logical to suppose that when endothelial tissue becomes malignant, it may in its reversion to embryonic type show morphologic characteristics of both epithelial tissue (carcinoma) and meso-

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dermal tissue (sarcoma). This possible bimorphism of endothelial cells might account for some confusion concerning malignant tumors of the pleura and pericardium. Reports of primary endothelioma and carcinoma of the pleura are common. Robertson,[33] in a recent review of the literature, while reporting four tumors of the pleura and one of the pericardium, has done much to clarify this subject, and in fact shows that endotheliomas or carcinomas of the pleura or pericardium are not primary. He demonstrates that such tumors are secondary carcinomas, usually from the lung, and that if a tumor is primary in the pleura, it must be sarcomatous. The term true endothelium is applied to that derived from the solid mesenchymal part of the mesoblast, in contra-distinction to the celomic or body cavity derivative of the mesoblast which gives rise to the endothelium of the pleura, pericardium, and peritoneum, and is really a mesothelium. The so-called endothelium of the cerebrospinal meninges will not be considered. Mallory[25] points out that it is not genetically identical with the endothelium, lining vascular and lymphatic channels, since it forms at a later period in embryonic development from the notochord.

It seems reasonable to believe that endothelium has in its very earliest development a contribution from both ectoderm and mesoderm, and there are but two important theories of origin of blood-lymph-vascular endothelium, the angioblast theory of His, and the theory of local origin. In the theory of His it is asserted that the so-called angioblast appearing early on the yolk sac gives rise to the endothelium of its blood-vessels which by their proliferation and down-growth invade and form the intra-embryonic vascular systems, also that all intra-embryonic endothelium of whatever nature arises from this preëxisting angioblastic endothelium of the yolk sac, or that there is never a local origin from mesenchymal tissue. In the theory of local origin, described by Reagan,[30] it is asserted that mesenchyme may, in practically any part of the body, change into blood-lymph-vascular tissue, and is not necessarily in direct descent from the yolk-sac endothelium of the angioblast. The theory further presumes that mesenchymal cells can by migration and alignment form vascular channels or cavities lined by endothelium, and that there are various embryonic regions where there is a first-hand production of vascular tissue, even to blood-cells themselves.

The "theory of local origin" is probably the most favored explanation of the origin of the vascular and lymphatic systems among competent anatomists and embryologists to-day. Sabin[35] supported the angioblastic theory of intra-embryonic lymphatic development. By injecting India ink into subcutaneous tissues of pig embryos, she showed to the satisfaction of many that all lymph-vessels budded off from the veins at four primary centres, and then invaded the skin, as well as the deeper tissues, by a process of centrifugal growth. Clark, Evans, and Minot also supported this view, and in fact, by 1912, this theory seemed generally accepted.

The theory of the development of endothelium *in loco* from mesenchyme dates from the work of Reichert, Goette, Felix, and more recently Rüchert

and Mollier, Maximow, Bonnet, and other European anatomists. Huntington and McClure until recently were its only sponsors in this country. Their series of convincing articles is summed up in Huntington's monograph which appeared in May, 1911. In 1912, Kampmeier demonstrated independent lymphatic endothelium anlagen in the thoracic duct of an injected pig embryo. Emmel, Reagan and Stockard stand as proponents of the theory of the local origin of endothelium. Soon even Sabin was led to accept in part the local origin theory by her studies of intra-embryonic blood-vessels and the formation of red blood-cells in living embryo chicks.

From now on the pendulum swings toward the theory of local origin, and McClure gives the present predominant opinion in the following words:

"While differences of opinion may still exist, as regards details of the process, both for the lymphatic and blood vascular systems, it is plain from this brief sketch that the general principle of the local genesis of intra-embryonic endothelium from mesenchyme, a theory so recently and so vigorously opposed by a large group of American anatomists, may now be regarded as an established fact." This statement has an important bearing on tumors of endothelium.

Problems of Classification.—Most tumors of blood-vessels and lymph-spaces have been easily recognized and correctly described and diagnosed as capillary or cavernous lymph-angiomas and hæmangiomas. When the cellular activity of these tumors becomes such that open spaces give place to solid masses and the compact areas are composed of endothelium-like tissue rather than fibrous tissue or epithelial cells, the classification and correct diagnosis become controversial. Invasion of adjacent tissues, local post-operative recurrence and metastasis further complicate the picture.

MacCallum says, "In practically no case has the origin of a tumor from endothelium been proved." But theoretically tumors of endothelium can occur in any part of the body, since that kind of tissue exists in or about all organs.

Most pathologists classify malignant tumors from the standpoint of the predominating cell, considering not only its structure, but also its embryonic origin, for when very malignant it loses all likeness to its adult functioning form.

Mallory [26] says, "The type cell is the one important element in every tumor." He goes on to show that histologic classification of slow-growing tumors is satisfactory, for they differentiate well, while with fast-growing ones embryology helps in recognizing types of cells and in explaining unusual situations of tumors. Ewing summarizes the problems of the classification of tumors as follows: "The generally accepted plan of classification and terminology which is based on histology, modified as much as possible by histogenesis, is a natural product which has become very firmly established and probably deserves to prevail against the varying prominence of embryology, chemistry, and etiology." A purely embryologic classification is not sufficient, as the origin of some parts of the body is not well understood. For instance, the Wolffian body may not be really mesoblastic; and again the adenomas,

and even so-called carcinoma of the kidney, instead of being classified as mesotheliomas, as they should if these organs are derived from mesothelium, are called epitheliomas. A strictly embryologic classification falls short in tumors such as malignant endotheliomas, which at times cannot be distinguished from carcinomas, or indeed, sarcomas by their histopathologic structure. Structure alone is insufficient as a criterion for classification of many tumors, for, as previously stated, highly malignant tumors, even from most dissimilar tissues, are indistinguishable.

A third great help in the classification of neoplasms, seldom mentioned in the past, is the knowledge and study of " reserve cells." The embryologic conception of three germ layers, as applied to tumors, while convenient in classifying neoplasms, is no longer necessary, and is in fact a mental hazard which keeps the more enlightened present-day conception of tumors from being accepted in practice. As MacCarty has shown in cancer of the breast that the membrana propria or " reserve cell " is the key to early carcinoma, so an attempt must be made to discover the embryologic " reserve cell " in studying tumors supposed to have arisen from vascular or lymphatic channels.

Endothelium.—Endothelium is spoken of as a primitive tissue, growing by " sprouting " as well as by mitotic division.[5] It is known that it comes from preëxisting endothelium. McClure [23] and others have demonstrated the mesenchyme cell to be the reserve cell of endothelium in the embryo.

It is usually stated that the specialization concomitant to the demand for function in adult organisms destroys the power of regeneration directly in proportion to the degree of specialization. In the adult, reproduction in such a tissue as endothelium is supposedly by direct division or sprouting, and occasionally by mitotic division, mesenchyme cells no longer being visible. This failure to find a " reserve cell " for endothelium in the adult has its exceptions. MacCallum describes connective tissue that has assumed the structure and function of endothelium in the repair of an infected wound of the neck of the adult dog. He explains this as a " kind of metaplasia, analogous to that which occurs in the first formation of endothelium." I have seen this same process in tumors of endothelial-lined spaces with adjacent areas showing solid masses of cells morphologically indistinguishable from endothelial cells. Considering these different cells as derived from mesenchyme, it is no wonder that they sometimes show in the adult a multiplicity of form, approaching in appearance, fibroblasts or fibrocytes here, epithelioblasts there, and again endotheliocytes in other places. This may be a manifestation of metaplasia, but might better be called an example of atavism since it is an inheritance from remote rather than immediate ancestors, from mesenchyme rather than fibroblasts.

If there is sufficient injury to destroy adult tissue of so-called mesoblastic origin, the mesenchymal primitive connective tissue responds to the demand for repair. This cell usually looks like a fibroblast, but may, and in fact ought, at times to resemble, in different environments and in different stages

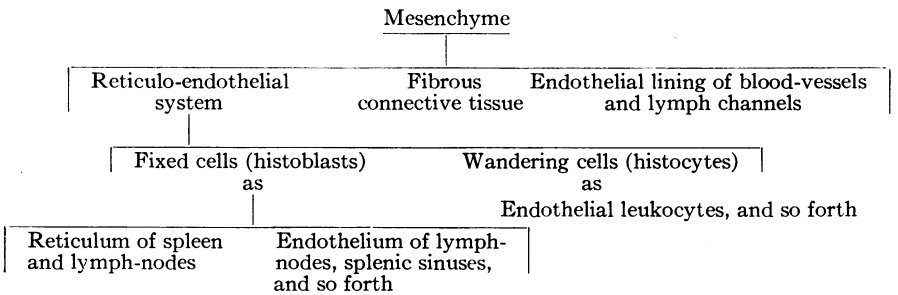
of repair, other different types of specific cells or tissues that arise from it, such as the following:

1. All the cells of the reticulo-endothelial system such as the reticular cells of splenic stroma and lymphatic tissue as well as the endothelial cells of the liver, lymph-gland and spleen sinuses, adrenal and hypophyseal capillaries (histoblast), fixed tissue cells, and the histocytes and wandering tissue cells such as the endothelial leukocyte series of cells.[1]

2. The connective-tissue series of cells which in adult form are called fibrocytes.

3. The endothelial cells lining blood-vessels and lymph-channels.

CELLS DERIVED FROM MESENCHYME



It is evident, therefore, that a certain polymorphism will be seen in tumor cells derived from the endothelial lining cells of the blood-lymph-vascular system, one of these so closely allied series of cells, so alike in function and origin. These tumors are therefore divided into three distinct groups, considering all endothelium-lined vessels as one, whether they contain blood or lymph: (1) angiomas, (2) angio-endotheliomas, and (3) endotheliomas.

The name endothelioma does not indicate its derivation from blood-channels or lymph-channels. The reasons for including it are brought out in the discussion. Suffice it to say that certain areas in the angio-endotheliomas, taken apart from the definitely vascular areas, simulate exactly morphologically the small group of tumors (Group 3), previously called endotheliomas, and seems to place the origin of the latter also in the lymph-blood channels.

Material Studied.—This report, while primarily a histopathologic study, includes a review of the clinical findings and end results of 290 cases of neoplasms at the Mayo Clinic, which were reported to have arisen in the blood-lymph-vascular system during the sixteen years from 1907 to 1922, inclusive. The material is only from the surgical pathologic laboratory and includes specimens removed at operation, but none of the many angiomas found in the internal organs at necropsy. The tissue was studied independently of all diagnoses, reports, or other data. Of the 290 cases on file ninety were discarded for various reasons; many specimens were lost; there was not sufficient material for proper study in other cases, and in some of the earlier ones the diagnoses were incorrect, especially in the endothelioma group.

The following tumors have been called endotheliomas in the past: mixed tumor of the parotid gland and palate, squamous-cell epithelioma, melanotic epithelioma, adamantinoma of the jaw, carcinoma of the appendix, metastatic epithelioma of the chest, neuroma, and benign xanthic tumor of the tendon sheath. Two very interesting tumors of the upper extremity with skin involvement were discarded, as they were probably Ewing's primary endotheliomas of bone. Another tumor, while resembling endothelioma, was thought at necropsy to be possibly of primary osteogenic origin, and was discarded. Follow-up letters were sent to all living patients not heard from within a year.

Tumors arising in celomic endothelium, such as those in the peritoneal cavity, pleura and pericardium, are not considered in this study, nor the so-called endotheliomas of the cerebrospinal meninges. Several tumors of the orbit were ruled out as probably of this origin.

On microscopic examination, the different specimens, with the exception of one type, arrange themselves into certain groups which conform very well to the classification already offered for such tumors. The one exceptional type of neoplasm is what has been variously named endothelioma, angiosarcoma, perithelioma, cylindroma, and so forth, fibrosarcoma, mixed-cell sarcoma, or not infrequently, carcinoma.

The neoplasms studied comprise three large groups: (1) angiomas, (2) angio-endotheliomas, and (3) endotheliomas. The term angioma is used to include tumors of both blood-vessels and lymph-vessels. For convenience of arrangement they are divided into ten main groups, according to their anatomic location (Table I).

TABLE I

Two Hundred Cases of Neoplasms of the Blood-lymph-vascular System, Showing Frequency of Occurrence of the Angioma, Angio-endothelioma and Endothelioma.

Location	Cases	Per cent. of total	Angioma		Angio-endothelioma		Endothelioma	
			Cases	Per cent.	Cases	Per cent.	Cases	Per cent.
Breast	7	3.5	6	85.7	1	14.3		
Extremities (upper)	28	14.0	22	78.5	5	17.9	1	3.6
Extremities (lower)	28	14.0	25	89.2	1	3.6	2	7.2
Gastro-intestinal tract	7	3.5	7	100.0				
Genito-urinary tract	20	10.0	19	94.7			1	5.3
Head and face	36	18.0	33	91.7			3	8.3
Lip	34	17.0	34	100.0				
Neck	11	5.5	11	100.0				
Tongue	16	8.0	16	100.0				
Trunk	13	6.5	10	76.9	2	15.4	1	7.7
Total	200	100.0	183	91.5	9	4.5	8	4.0

DESCRIPTION, TREATMENT AND RESULTS

Angiomas.—Angiomas are obviously benign, circumscribed tumors, often noticed at birth, occurring almost anywhere on the surface of the body, and occasionally in the internal organs. They cause great trouble only when congenital or in children of tender years, or when very extensive and so

situated that important structures are involved by direct extension of their growth. They are easily recognized grossly in the fresh condition by their reddish color and spongy, fibrous appearance. On section of such tumors, if cavernous in structure, the red color disappears with the outlet of the blood and serum, leaving a pale spider-web or honey-comb, relatively soft, mass of tissue. If they are large and contain blood from old hemorrhages or thrombosed blood cavities, dark red and blackish areas will be present, showing a deposit of laminated blood clot and hæmosiderin and hæmatoidin. Certain of these tumors, occurring in the skin, as so many do, contain true melanin, which does not, however, give a Prussian blue with potassium ferrocyanid solution, as do the iron-containing hæmosiderin crystals found in destroyed blood.

Under the microscope, a varied histologic picture is seen, with, as a rule, either blood spaces or fibrous tissue predominating, the arrangement of which has prompted the application of such descriptive adjectives as capillary, cavernous, villous, plexiform, and so forth. Obviously benign to the trained pathologist, these tumors at times show such cellular activity and so many histologic deviations from type that mistakes are not infrequently made in diagnosis. The absence of blood spaces in some, or the origin from lymph spaces almost totally unrecognizable in the fixed preparations, may lead to a diagnosis of fibroma, neurofibroma, or even sarcoma or endothelioma, when the tumor is growing quite rapidly. On the other hand, a relatively malignant angio-endothelioma may, because of its widespread differentiation into blood spaces and vessels, be called wrongly a benign angioma when it indeed is the immediate precursor of a malignant endothelioma. Other confusing pictures seen in those tumors arising at the body surface are due to reactions in the contiguous skin elements, such as squamous-cell epithelium, sweat glands and hair follicles. Marked hypertrophy of the squamous-cell layer is so frequent that the tumor may occasionally be mistaken for a squamous-cell epithelioma. Basal-cell epithelioma is also simulated by marked hypertrophy of the cells of hair follicles.

Among the rarer variations from the structure usually seen in angiomas may be mentioned phlebolith or psammona formation, foreign-body giant-cells simulating tubercle formation, and so forth (Table II).

The six sites of election for the angioma group, in order of numerical frequency, were: lip, head (including face), lower extremities, upper extremities, genito-urinary apparatus, and tongue. Of 149 (75.4 per cent.) of the total of 183 occurring in these situations, 62.3 per cent. were found in the lip, face and extremities. The average age of the patients when seeking treatment was thirty-five and two-tenths years; the youngest was ten weeks, and the oldest seventy-six years. Thirty-four angiomas (18.6 per cent.) were reported to be congenital. More than half the patients were female, 118 of 183 (63.9 per cent.). Only seventeen (9.3 per cent.) gave a family history of malignancy or "birth marks," and an equal number a history of injury. The average surface diameter of the lesions was 3.3 cm., the largest being

TABLE II

Detailed Clinical Data of the Angiomas

Situation	Patients								Tumors								Treatment				Result of treatment		Associated lesions
	Cases	Per cent. of total	Average age of patients, years	Age of youngest patient, years	Age of oldest patient, years	Males	Females	Family history of malignancy or birth-mark	Injury	Congenital cases	Average pre-operative, duration, years	Average size, cm.	Largest size, cm.	Smallest size, cm.	Multiple	With associated neoplasm	Previous	Excision	Excision and radium	Radium	Recurrent	Patients not cured	
Breast	6	3.3	45.5	27.00	45.5		6	1	1		9.0	1.0	1.2	0.30	6	1		6					Basal-cell epithelioma of chin.
Extremities (lower)	25	13.7	38.8	.58	60.0	6	19	1	1	9	11.1	3.3	7.0	2.00	1	4	2	23	2		4	*3	Three goitres; one adenofibroma of breast. *One toe amputated without cure.
Extremities (upper)	22	12.0	30.6	.20	66.0	4	18	1	3	6	12.4	2.6	18.0	0.50	4	2	8	*18	3	1	4	1	One squamous-cell epithelioma of forearm; one lipoma. *One amputation necessary.
Gastro-intestinal tract	7	3.8	44.6	22.00	67.0	2	5	1			3.0	7.1	15.0	2.00	2	2		7					One squamous-cell epithelioma of lip; one pelvic tumor.
Genito-urinary tract	19	10.4	41.2	19.00	76.0	5	14	2	1		3.8	4.0	10.0	0.50		3		*18		1	3		One uterine fibromyoma; two goitres. *Two excision and fulguration.
Head and face	33	18.0	30.3	.27	60.0	22	11	5	6	6	5.0	3.3	10.0	0.50	3	4	9	25	7	1	1	1	One goitre; one basal-cell epithelioma of cheek; one melano-epithelioma of ankle; one squamous-cell epithelioma of jaw.
Lip	34	18.6	38.1	.65	71.0	18	16	5	3	3	5.7	1.4	3.0	0.50	1	5	10	31	3		3		Two goitres; one lipoma; one squamous-cell epithelioma of lip; one leukoplakia of mouth.
Neck	11	6.0	22.2	.25	65.0	4	7			5	9.6	5.5	10.0	1.0	1		2	9	2		4		
Tongue	16	8.7	36.0	2.5	66.0	9	7	2	1	3	3.7	1.6	3.0	1.0		1	3	13	3		5		One squamous-cell epithelioma of lip.
Trunk	10	5.5	34.3	1.4	76.0	5	5		1	2	7.3	3.6	15.0	1.0		1		10					One uterine fibromyoma.
Total	183					75	108	18	17	34					18	23	34	160	20	3	24	5	
Averages			36.1			41	59.1 per cent.	9.8			7.06	3.34	9.22	.93							13.1 per cent.		

an angioma of the stomach, 15 cm. long, while the smallest was 3 mm. in diameter. Twelve cases were multiple. Thirty-four patients came with a history of previous treatment. The records show that the treatment of choice at the Mayo Clinic was knife excision, which was employed in 160 of the 183 cases. This was followed by applications of radium if the site and extent of the lesion did not permit complete excision. Radium was used alone in only three cases.

Angio-endotheliomas.—Angio-endotheliomas comprise a relatively small percentage of the total cases, but are the most important ones for study, as they appear to be a connecting link between the benign angioma and the malignant endothelioma. There were nine cases: six in the extremities, two in the trunk, and one in the breast.

Angio-endotheliomas do not differ grossly from angiomas, save that they are more irregular in outline and appear, as a rule, more solid in certain areas, and more meaty on section. The microscopic picture differs from that of the more circumscribed benign angiomas in two main respects. The first and most important difference is the presence of an occasional mitotic figure. The change from the benign to the malignant state is best indicated by this landmark. The malignant endotheliomas contain numerous mitotic figures. The second difference is that the cavernous or fibrous areas, characteristic of the angioma, give way in small areas to solid masses of larger, less differentiated cells whose structure, studied under the higher-powered lenses of the microscope, is seen to approach that of endothelial cells. These cells, however, continue to grow into numerous vessel-like channels in most areas, still suggesting that a capillary type of angioma is present. The reaction in surounding tissue is somewhat different, but the diagnosis should be based entirely on cytologic study. The differentiation into vessels, which in this case are tumor vessels, is analogous to the formation of keratin pearls in a relatively benign, although definitely malignant, squamous-cell epithelioma.

The repeated recurrence of angio-endotheliomas after apparently adequate excision prompted more careful study of them, until now a definite group can be recognized. These tumors are considered cytologically the forerunners of a definitely malignant tumor of endothelium. In order to indicate their pre-malignant or early transition stage, I have called them angio-endotheliomas. They are relatively benign, malignant tumors, their growth being checked by their differentiating into blood-vessels.

Five of the nine angio-endotheliomas appeared on the upper extremities. There was recurrence in four cases, metastasis in one, and two patients died, one of whom was a child of eleven with extensive involvement of the jaw and mouth.

On account of the small number in the series, and the similarity in the numbers of angio-endotheliomas and endotheliomas, groups 2 and 3 will be discussed together and analyzed in one table (Table III).

Endotheliomas.—The endotheliomas comprise a rare group of tumors lying morphologically midway between carcinomas and sarcomas, but are as

TABLE III

Detailed Clinical Data of Angio-endotheliomas and endotheliomas

Situation	Patients									Tumor			Treatment			Results				Remarks
	Number with angio-endothelioma	Number with endothelioma	Percentage of total	Average age, years	Age of youngest, years	Age of oldest, years	Males	Females	Injury	Family history of malignancy	Average pre-operative duration, years	Average size, cm.	Largest, cm.	Smallest, cm.	Previous	Excision	Excision and radium	Recurrence, angio-endothelioma	Recurrence, endothelioma	Metastasis, angio-endothelioma	Metastasis, endothelioma	Dead from angio-endothelioma	Dead from endothelioma	
Breast.....	1		5.9	38.0	38.0	38.0		1		0	1	5	5	5			1	1				1		
Extremities (lower)	1	2	17.6	31.3	24.0	53.0		3		0	6.3		*	2	2	2	1		2		1		1	*Extensive in foot and leg.
Extremities (upper)	5	1	35.4	32.8	26.0	45.0	3	3	1	0	5.3	2.6	13X8	1	3	4	2	3	1					
Genito-urinary tract.....		1	5.9	38.0	38.0	38.0		1		0					1	1			1					
Head and face.		3	17.6	14.7	11.0	17.0	1	2	1	0	.6	4.5	6	3	3		1	1	1	1		1		*Died from angina pectoris
Trunk.....	2	1	17.6	51.0	48.0	51.0	2	1	1	0			15	1		2	1		1			*1		
Total.....	9	8					6	11	3	0					9	9	6	5	6	1	1	3	1	
Average.....	52.9 per cent.	47.1 per cent.		34.3	30.8	40.3	35.3 per cent.	64.7 per cent.		0	3.3	4.0	8.6	2.4										

a rule relatively benign, as judged by their long duration and the tardiness and infrequency of metastasis.

There were eight cases of endothelioma, distributed as follows: extremities, three; head, three; and trunk and genito-urinary tract, one each. There was recurrence in six, metastasis in one, and death in one.

The gross appearance of endothelioma arising in the blood-lymph-vascular system in this series was quite similar to that of fibrosarcoma. Hemorrhagic and cystic areas are as a rule strangely lacking, and it is thought probable that this is one of the chief reasons why their origin from blood-lymph-vascular endothelium has been overlooked. The cut surface looks grayish in the fresh specimen, but is quite white and fibrous-appearing when it is fixed in formalin. It is fairly homogeneous, as a rule, without irregular lobulated areas, although fibrous tissue strands are seen.

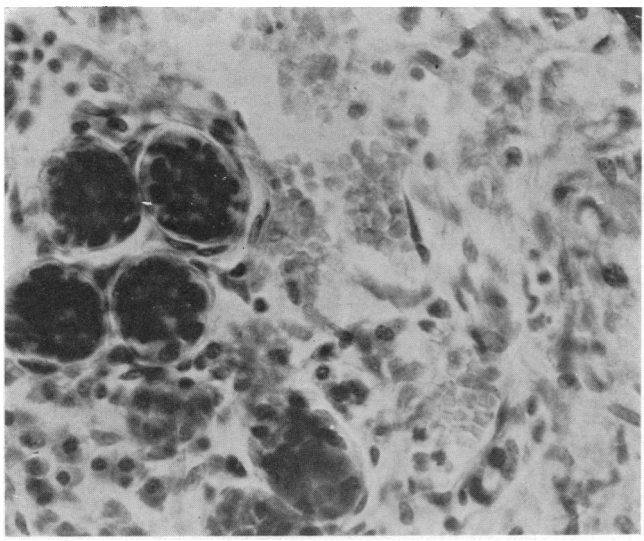


FIG. 1.—Malignant angio-endothelioma of breast showing red blood cells in the angiomatous spaces in the immediate vicinity of the most malignant part of the tumor. An example of differentiation into blood-vessels. (X 500.)

The microscopic section shows that the tumor is quite cellular with numerous mitotic figures and frequent invasion of fat and muscle. Morphologically the cell resembles endothelium, although it is more spheroidal in shape and larger, and the nuclei show hyperchromatosis. Differentiation into tumor blood-vessels is seen in some instances. There may be fairly large areas of fibrotic tissue and lymphocytic infiltration, and even hyalin formation. In some areas the similarity to the histologic picture of a certain stage of Hodgkin's disease is striking. The numerous mitotic figures in masses of rather undifferentiated cells signify malignancy, and the differentiation of certain of the tumor cells into blood-vessels indicates its endothelial type.

Angio-endothelioma and endothelioma are less common than angioma. The average age incidence is earlier, much earlier if the birth nævus is omitted, the predominant sex is female, the average pre-operative duration is shorter, treatment is less successful and recurrence more common (ten out of seventeen compared to twenty-four out of 183 cases). Metastasis and death, while not encountered in cases of angioma, followed both angio-endothelioma and endothelioma.

Very little difference is found between angio-endothelioma and endothelioma. It is important that the former be recognized as more than a simple angioma, so that it may be eradicated before it advances in malignancy and becomes an endothelioma. Important distinguishing clinical features are lacking and differential diagnosis is impossible, so that the burden of diagnosis is placed on the pathologist. His information, while of scientific importance in emphasizing the morphologic and cytologic truths shown by the tissue, should not influence the treatment of the two groups of tumor, for each should have early, wide surgical excision followed by prolonged radium treatment and frequent observation to prevent local recurrence, if possible. If such occurs, immediate further excision is required. Metastasis is rare from these tumors and occurs late.

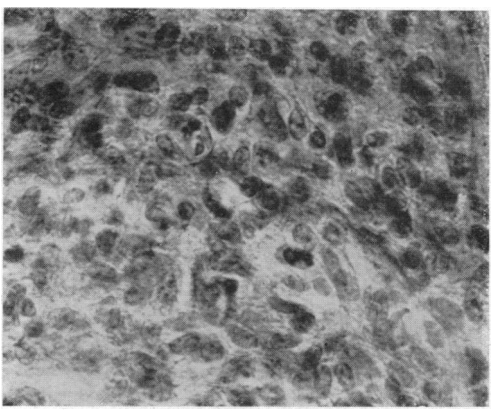


FIG. 2.—Same as Fig. 1, showing rapidly multiplying round and oval malignant cells with multiple examples of mitotic figures. (X 450.)

CASE REPORT I.—A woman, aged thirty-eight years, came to the Clinic May 29, 1921, complaining of tumor of the left breast slowly recurrent in the scar resulting from the simple amputation in 1917 for a "fibro-epithelial" tumor. The family and personal histories gave negative information, and there was no record of tuberculosis or malignant disease in the family.

She was a healthy looking, vigorous young woman with a good color. Nothing abnormal was found except an irregular, soft mass in the scar of the operation on the breast, with several bluish-red areas in the surrounding skin, and fibromyoma of the uterus. The Wassermann reaction was negative; the hæmoglobin was 70 per cent. (Dare); the erythrocytes numbered 4,080,000, and leucocytes 6100. The differential count and platelet count were within the normal bounds, and bleeding time was three minutes. A röntgenogram of the chest was negative.

The patient submitted to nine operations for recurrent tumors from April, 1921, to December 12, 1923, death occurring April 21, 1924, from general asthenia and absorption from growths. April 1, 1921, the tumor in the scar of the old incision was excised. The pathologic report was hæmangioma. Six months later the patient noted a recurrent local tumor, 7 by 7 cm., a lump in the right breast, about 10 cm. in diameter, and a small bluish tumor in the left deltoid region. A bluish nodule was found in the cervix uteri. August 16, 1922, the right breast was amputated and the glands excised. The pathologic report was hæmangio-endothelioma of the breast on an angioma; glands inflammatory. Radium was applied to the recurrent tumors in the left chest, the arm, and the cervix. April 2, 1923, the tumors in the left breast and left arm were excised. The pathologic report was hæmangio-endothelioma. July 11, the patient's general health was good in spite of the recurrence; more radium was applied. October 9, multiple nodules on the left chest and left arm, and one on the left back just above the iliac crest were excised. The pathologic report was again hæmangio-endothelioma (Figs. 1–6). December 12, nodules in the left chest, arm, back, and shoulder (twenty or more) were cauterized between the scars of the previous operations. April 21, 1924, the patient died from asthenia and "absorption."

Comment.—This case illustrates how a benign hæmangioma may become a locally malignant hæmangio-endothelioma, and eventually show the characteristics of malignant endothelioma, ending in metastasis and death.

Discussion.—Wagner,[38] in 1874, described a malignant tumor of the endothelium occurring in the pleura. His description of the tumor cells, apparently primary in the lymph channels, led subsequent observers to record similar cases as primary tumors of the pleura, and Eppinger called such a tumor "endothelioma." Since then various writers have reported and described tumors as of endothelial origin, but attention seems to have been focussed on the endothelium of serous membranes and bone, to the exclusion of the endothelium of the blood-lymph-vascular channels. Dermatologists have, from time to time, reported tumors involving the skin, whose cellular elements present the histologic characteristics of endothelial cells.[4] Kaufmann, as late as 1922, stated that endotheliomas belong histogenetically to the connective-tissue tumors. If my conception of the origin of endothelium is correct, endothelium does belong, histogenetically, to connective tissue. In the case of tumors of the blood-lymph-vascular channels it can apparently be recognized as a special form of connective tissue, and therefore the tumors are classified as endotheliomas. Ewing's well-known primary single or multiple endotheliomas of bone seemed to be established without cavil.

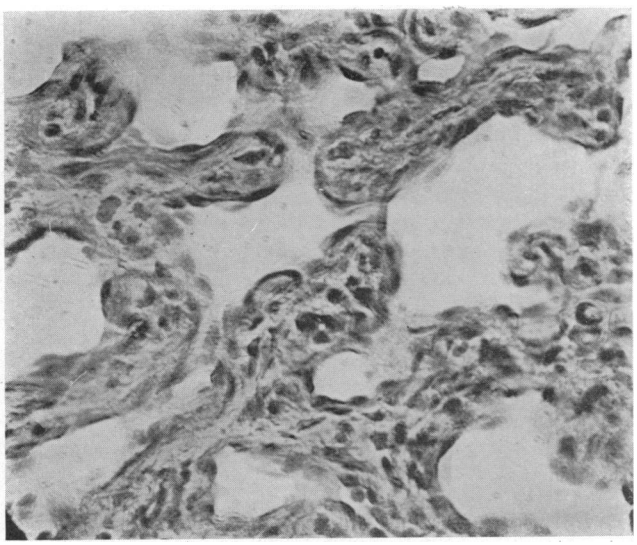


FIG. 3.—Differentiation into endothelium-lined channels and spaces. (X 500.)

It seems that there has been gradually increasing opposition to the conception of endothelioma as a distinct type of neoplasm. While fair so far as the serous membranes (celomic endothelium) are concerned, it would not seem justified by the study of the present series of tumors.

Since cells on becoming malignant lose or fail to acquire the characteristics by which they are known and classified in their completely differentiated state, it is necessary to investigate carefully the origin of the tissue under discussion, if it is not to be confused with other tissue or tumors when it becomes malignant.

Some malignant neoplasms are known to develop from a benign growth. A pigmented mole may become a melanotic epithelioma. Cancer of the

stomach is supposed to develop from simple gastric ulcer.[40] Leukoplakia sometimes becomes squamous-cell epithelioma.[29] Fibromas of the nasopharynx and other tissues show increasing degrees of malignancy, hastened and accelerated by repeated operations. A true conception of advanced growths is often best reached by a careful investigation and study of the earlier stages of their development.

In reviewing the development of a modern conception of growth and repair of tissues and a cytologic interpretation of tumor formation and malignancy, the contributions of Cohnheim, Hansemann, MacCarty and Broders should be considered and contrasted. In 1877, Cohnheim suggested in a lecture to a group of students that his "rest" theory or theory of the formation of *monstra per excessum* superfluous fingers, giant extremities, and so forth, by embryonic cell inclusion, might also apply in the great and wider field of true neoplasms. This hypothesis has been for almost half a century accepted as a fact, although never proved. Many pathologists to-day, however, believe that just as a fertilized ovum is totipotent as regards the cells and tissues of the adult organism which develops from it, so certain early segmentation cells are multipotent, and each cell then is the possessor of inherent potentialities for development into various forms, tissues or organs. This property of the cell would explain the *monstra per excessum* teratoma, mixed tumors, and so forth.

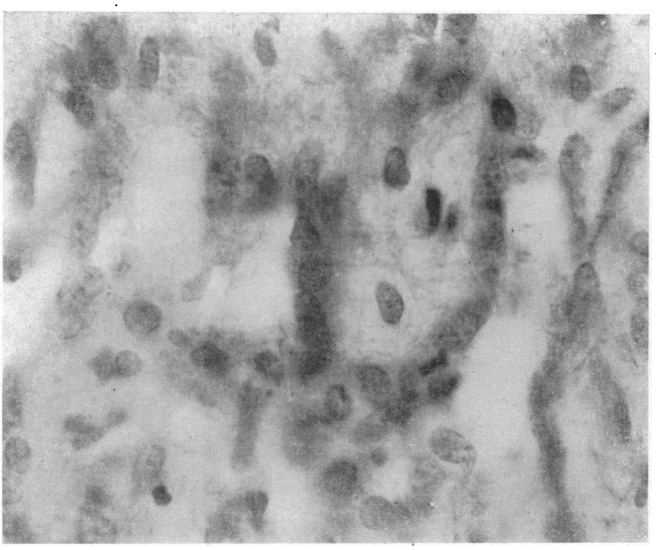


FIG. 4.—Angio-endothelioma showing endothelium-lined channels, malignant as indicated by mitosis. (X 1000.)

MacCarty[22] says the three fundamental biologic reactions in cases of neoplasia are hypertrophy, hyperplasia, and migration of the reserve cell on destruction of its overlying adult cell. He has called these reactions primary, secondary and tertiary cytoplasia. This work shows how nature has provided "reserve cells" in the mammary acinus to replace the destroyed adult cells. I believe endothelium has a reserve cell also. In the embryo it is clearly mesenchyme. In the adult it has not been identified. The terms, primary, secondary, and tertiary cytoplasia, do not represent degrees of malignancy, although they do express the biologic reactions which occur in the histogenesis or development of a malignant tumor.

Hansemann[14] wrote a great deal about the morphologic variation of tumors, but described them in terms of anaplasia and de-differentiation, and not in degrees of malignancy. He was intensely interested in the fact that malignant tumors, such as a carcinoma of the thyroid or of the liver, could, after metastasis to the brain or elsewhere, differentiate enough to perform their adult function as seen by the production of colloid and bile.[15] He quotes a report by von Eiselsberg who removed a carcinoma of the thyroid with resulting myxœdema. When later a metastatic tumor developed to a certain size the myxœdema was relieved only to return on excision of the tumor. It remained, however, for Broders in 1919 to apply this principle of cyto-differentiation, as he saw it in various types and parts of malignant neoplasms, to the grading of malignancy. It is mentioned here, as he shows in another tissue, protective epithelium, how the reserve cell is the key to the situation.

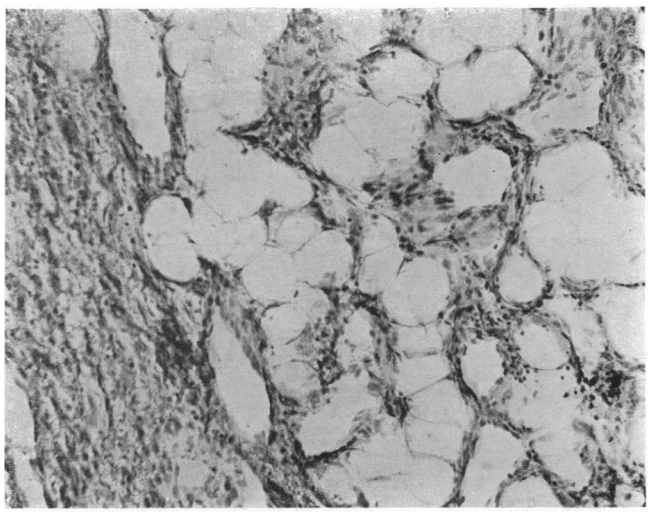


FIG. 5.—Angio-endothelioma showing invasion of fat by malignant process. (X 120.)

On the principle of differentiation by which he grades squamous-cell epitheliomas, it would seem possible to grade endotheliomas by an estimation of the amount of tumor blood-vessel formed. This has not proved of practical clinical value in this series of tumors, possibly because the malignant tumors appeared to be of a uniform degree of malignancy. Theoretically, and from the standpoint of cytology, however, it is possible to divide the malignant members of this group into grades according to the amount of differentiation into blood-vessels and connective tissue, frequency of mitosis, and the general tissue reaction. With the establishment of such a tumor as a malignant neoplasm of endothelium, the next step should be to determine toward what type of cell they differentiate, their degrees of differentiation, and then possibly the grade of malignancy.

The stratum germinativum of the skin as a forerunner of squamous epithelium and the fibroblast as the immediate progenitor of fibrous connective-tissue cells are good examples of reserve cells. Likewise, in the breast, when the secreting acinar cells are destroyed, they are replaced by cells from the so-called basement membrane. Reserve cells of breast acini are not seen in non-lactating, normal adult breasts.

The endothelial cell is very primitive and the usual reaction to injury is seen in replacement by direct division of preëxisting endothelial cells. The endothelial cell is more widely distributed throughout the body than almost any other kind, except perhaps the fibrous connective-tissue cell. It is possible then that the reserve cell of endothelium is identical with that of fibrous connective tissue, namely, the fibroblast, or that the primitive mesenchymal cell seen in the embryo as the forerunner of both is the reserve cell of endothelium, and that the mesenchymal cell lies invisible throughout the supporting structures of the body, ready to spring up into a malignant growth on adequate provocation, if the host has the proper hereditary tendency to tumor.

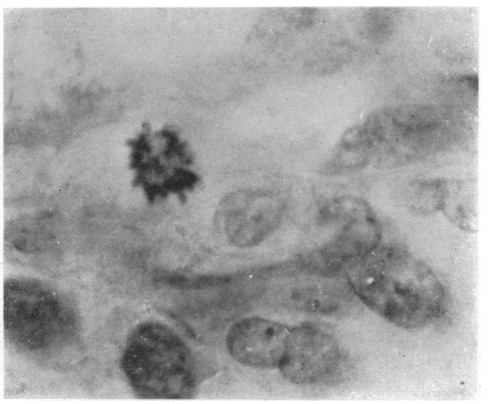


FIG. 6.—Angio-endothelioma superimposed on an angioma of the breast showing the highly malignant character of the growth. Large round and oval cells with irregular mitotic figure. (X 1500.)

If, in the case of the definitely malignant solid tumors of this series, arising from vascular tissue, the cells are too undifferentiated to be called endothelial cells, it is fair to suppose that they are genetically related cells, are surely not epithelial cells, often simulate fibroblasts, and because of their relation to vascular channels are most likely endothelioblasts. Almost invariably in some part of the neoplasm, perhaps in some cases so early in its development that it is not seen, there is definitely differentiated blood-vascular tissue.

SUMMARY

A histologic study of the neoplasms of the blood-lymph-vascular system of 290 patients treated at the Mayo Clinic in the sixteen years from 1907 to 1922, inclusive, shows 183 angiomas, nine angio-endotheliomas, and eight endotheliomas. Two hundred of the best preserved specimens, with full data and follow-up records, were selected for report. This simple classification seems adequate to meet all the clinical facts of the cases as well as all the known data from the standpoint of embryology, morphology, situation, and "reserve cell" diagnosis.

Endothelium in the embryo is derived from mesenchyme. In adult tissues, although not yet identified, the same mesenchymal cell lying invisible seems most likely to be the reserve cell of endothelium. Endothelium is closely linked with fibrous connective tissue in that mesenchyme is their common ancestor. This relationship does not preclude the existence of a specific tumor of endothelium, distinct from a fibrosarcoma.

The study of angiomas led to the recognition of the origin of the malignant tumors of this series from vascular endothelium. A case reported shows the change from benign to malignant in different stages. Specimens were

removed at operation during a period of three years, death finally occurring from metastasis and absorption from the growths.

The original hypotheses seem established as facts: blood-vascular and lymph-vascular angiomas, while usually benign, are potentially malignant endotheliomas; there is an intermediate stage between these two represented by the angio-endothelioma which is relatively benign but definitely malignant; and malignant endotheliomas of the blood-lymph-vascular system exist as a pathologic entity.

Just as a malignant tumor of the skin is recognized as a squamous-cell epithelioma by its differentiation into horny, protective epithelium, so may certain of the blood-lymph-vascular tumors be recognized as endotheliomas by their differentiation into tumor blood-vessels.

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