REPORT

of

Committee on Thesis

The undersigned, acting as a Committee of the Graduate School, have read the accompanying thesis submitted by Albert Compton Broders for the degree of Master of Science in Pathology. They approve it as a thesis meeting the requirements of the Graduate School of the University of Minnesota, and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science in Pathology.

Wm. Carpenter MacCarty.
Chairman

Louis B. Wilson

John A. Stokes

Moses Barron

S. E. Sweitzer

June 1920

THE UNIVERSITY OF MINNESOTA

GRADUATE SCHOOL

Report

of

Committee on Examination

This is to certify that we the undersigned, as a committee of the Graduate School, have given Albert Compton Broders final oral examination for the degree of Master of Science in Pathology. We recommend that the degree of Master of Science in Pathology be conferred upon the candidate.

Minneapolis, Minnesota

May 24 1920

Louis B. Wilson
Chairman

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THESIS

SQUAMOUS-CELL EPITHELIOMA OF THE SKIN.

A STUDY OF TWO HUNDRED AND FIFTY-SIX CASES.

Albert Compton Broders

Submitted to the Graduate Faculty of the University of Minnesota in partial fulfillment of the requirements for the Degree of Master of Science in Pathology

May, 1920

Squamous-cell Epithelioma of the Skin

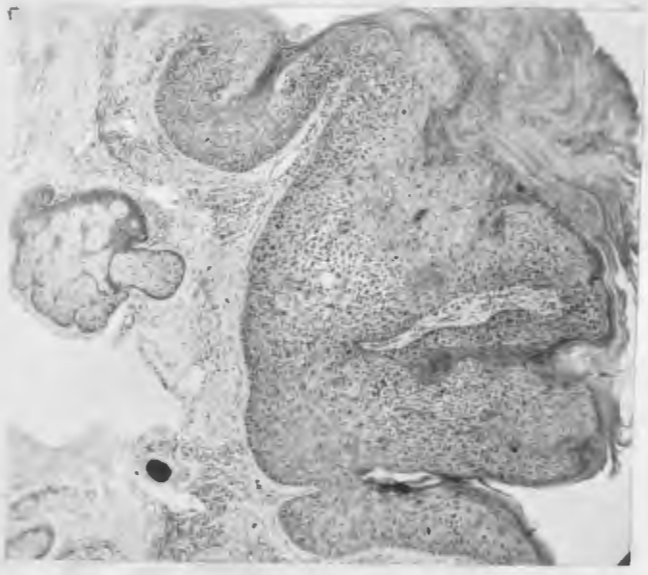
A study of two hundred and fifty-six cases

In the past, physicians have generally been inclined to use the term " skin cancer", which in the majority of instances is understood to be a basal-cell epithelioma or rodent ulcer; however, the squamous-cell epithelioma is also many times included under this broad and indistinguishable term. As a matter of fact, the term " skin cancer" should include four types of epitheliom, i.e., basal-cell, squamous-cell, melanotic epithelioma and non-melanotic melano epithelioma, varying in degree of malignancy as judged by their killing power in the proportion of approximately thirty-five for the first, sixty-five for the second, and ninety-five for the latter two types on the basis of one to one hundred. By "killing power" I mean the percentage of cases which died as the result of epithelioma. To know the type of "skin cancer" with which one is dealing is of prime importance from a standpoint of prognosis. Carcinomas which originate in the sweat and sebaceous glands should not come under the term "skin cancer" any more than carcinoma of the breast, as they originate from the germinal cells of specialized glands of skin origin.

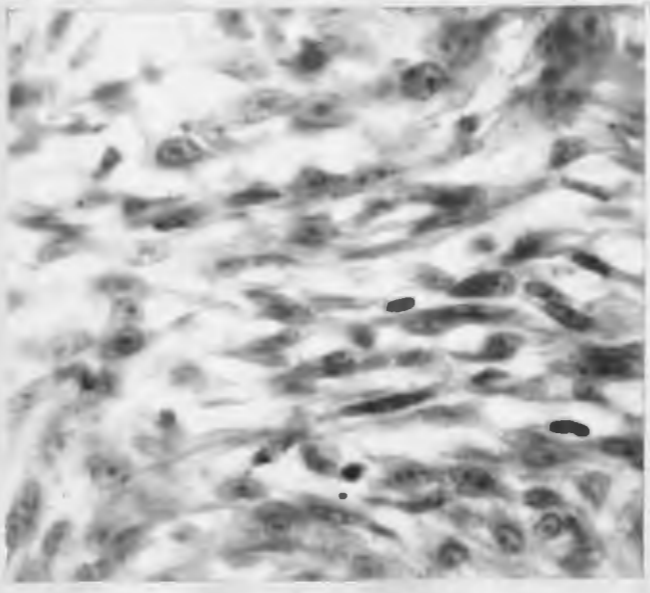
Polymorphism of Epithelial Cells

No cells of the body are more prone to change their form than are epithelial cells. One not infrequently sees cells in neoplasms, under the high power of the microscope, which bear a close resemblance to muscle-

cells and fibro-blasts but when they can be traced directly to the basal layer of the skin, how can one doubt their origin? (Fig. 2, 3, 4, 5,).



Low power of squamous-cell epithelioma of the skin, showing polymorphism of the cells.



High power of Fig. 2. Note the close renemblance to fibro-sarcoma.

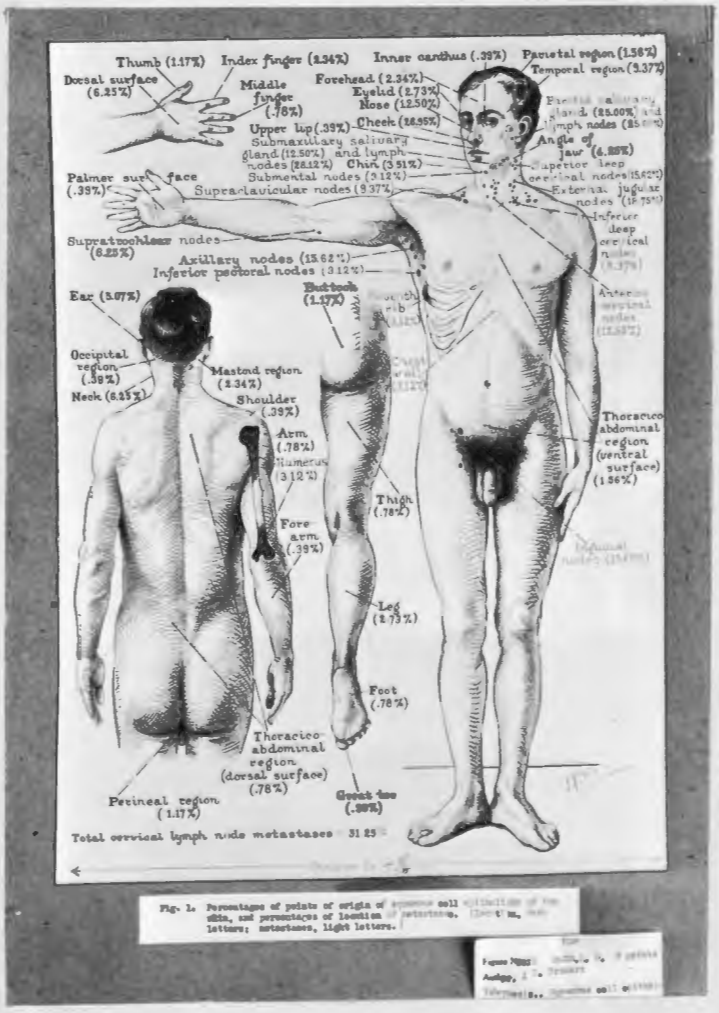
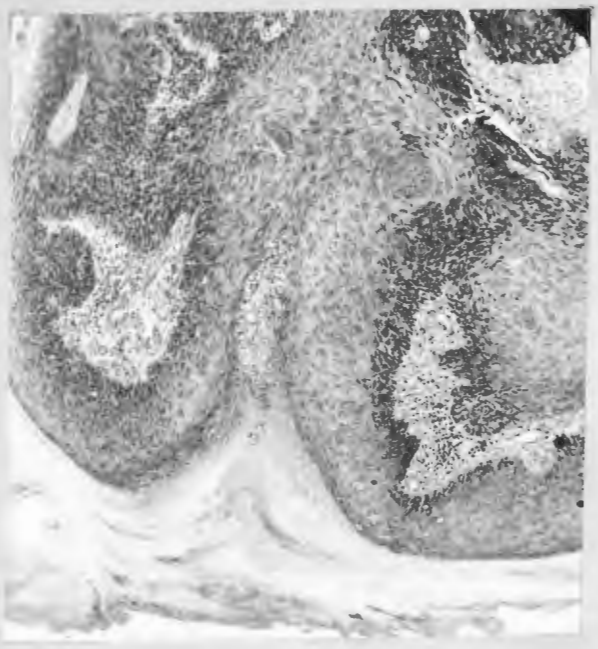
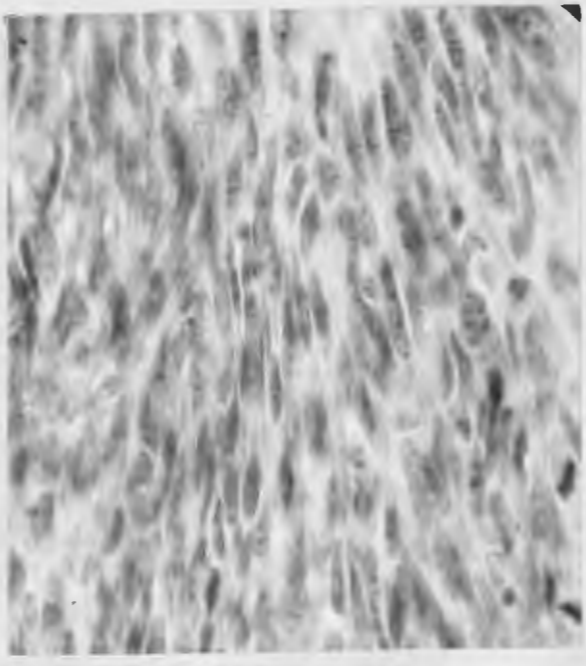


Fig. 1. Percentages of points of origin of [illegible] cell epithelioma of the skin, and percentages of localization of [illegible] metastases. [illegible] letters; metastases, light letters.



Low power of squamous cell epithelioma of the skin showing a marked polymorphism of the cells.



High power of Fig.4, showing an exact picture of myosarcoma.

Kettle, in his article, "Polymorphism of the Malignant Epithelial Cell", states, "That the malignant epithelial cell is capable of polymorphism is perfectly well recognized. The interchangeability of the acinus and the solid structure in adeno-carcinoma is familiar to every one, and the origin of a squamous-cell carcinoma from columnar epithelium has been reported on several occasions. Greater variations than these, however, are not, as a rule, considered possible. It is true Krompecher held that under certain conditions of growth and environment epithelial cells may assume a spindle form and may actually be converted into connective tissue elements, but his views have not found general acceptance, and the doctrin of the specific nature of cell-growth is not seriously questioned. Without going so far as to claim that the adult epithelial cell can actually become changed into a connective tissue cell, I am convinced that some carcinomata may possess such extreme powers of polymorphic growth that their cells, losing all trace of their epithelial origin, may become indistinguishable from connective tissue elements".

The view which Krompecher held seems rather "far-fetched" but when one considers the fact that the whole body is developed from the fertilized ovum, his theory is brought within the range of possibility. Squamous epithelium does not originate from columnar epithelium as the columnar cell is differentiated and cannot regenerate. What happens when a squamous cell epithelioma develops in an organ where columnar epithelium is normally found, the gall-bladder, for example, is this: The regenerative cells which, under ordinary circumstances, produce columnar epithelium, produce squamous epithelim instead. The same process takes place in an everted uterus when protective instead of columnar epithelium is needed.

Regeneration and Degeneration

Physicians habitually use the term "cancerous degeneration". To me, this term is wrong. MacCarty has often said, "Cancer is a regenerative and not a degenerative process". Cancers do degenerate as do other tissues. They are progressive,- some more so than others; as a matter of fact, some of them are so progressive that they cause the death of the whole body in a short time. By the enzyme activity of their cells, they may bring about death to part of their own cells and also to other cells. They may die as result of having their nourishment cut off; the same thing happens to other cells. Whatever affects the general metabolism of the body, affects the cancer. The cells of our bodies are subject to the two great processes of nature, namely, anabolic and katabolic; as is well known, the former builds up and the latter tears down. Nourishing diet, fresh air, sunshine and rest will help one rid himself of tuberculosis but this is not true with cancer as it is a part of one. When food is prepared and distributed to the normal cells it is also distributed to the cancer cells.

Why is chronic destruction of epithelial tissue often followed by cancer, for example, on ulcer of the lip? The destruction of the epithelial cells is a katabolic process and the regeneration by the cells of the germinal layer is an anabolic process. If the anabolic process wins, the ulcer is healed over by normal epithelium; if the katabolic process wins, the ulcer remains and continues to grow, but which one wins when cancer develops on the border of the ulcer? It seems to me that it might be called a compromise, the cancer having both regenera-

tive and destructive properties. Cancer cells are undifferentiated cells which have taken over new properties in addition to their regenerative ability, i.e., the power to invade and migrate, thereby infringing upon the rights of other cells, and, depending upon their degree of cellular activity, produce death of the whole organism. It seems to me that pernicious anemia, myelogenous leukemia, lymphatic leukemia, and in fact, all malignant neoplasias are regenerative-destructive processes, probably following, in the large majority of instances, excessive chronic destruction of differentiated cells, such as carcinoma following the chronic excessive destruction of epithelial cells, pernicious anemia following the chronic excessive destruction of red blood cells, lymphatic leukemia and lympho sarcoma following the chronic excessive destruction of lymphocytes, etc.

Maud Slye, in her work with mice, on,"The Relation of Pregnancy and Reproduction to Tumor Growth", concludes thus:

1. "Cancer and reproduction both being growth processes draw upon the same energy residuum and are made possible by the same food. Hence the food and energy used by one are withheld from the other .

2. " Therefore (a) if the female is sonstantly pregnant, energy and food are withheld from the tumor and it grows with extreme slowness. (b) If there is a hiatus between pregnancies, or a termination of pregnancy, the energy which was running into reproduction is released and diverted into tumor which grows very rapidly. (c) If tumor growth considerably antedates impregnation, the currents of energy are already being used for tumor growth and are with difficulty diverted for pregnancy, probably never wholly so.

3. "Hence, when a female is well advanced in tumor growth be-

fore impregnation there are rarely any offspring brought to birth. When offspring are delivered they are few, small, under-nourished, and rarely suckled(which in mice means there is no lactation).

4. "When tumor growth is not interfered with by pregnancy, it is (a) extremely rapid in mice which are young, well nourished, and vigorous; (b) less rapid in mice older or less vigorous or less nourished; (c) very slow in mice which are old, feeble, under-nourished, or afflicted with a destructive complicating disease".

The above conclusions of Miss Slye are ample proof that cancer is a regenerative- destructive process.

Cell Differentiation and Activity

In a recent paper on squamous-cell epithelioma of the lip, I brought out the fact that the more an epithelioma tends to differentiate, the lower the degree of malignancy.

I believe that this principle can be applied to malignant neoplasia in general. Very few melanotic or non-melanotic melano-epitheliomas show any tendency to differentiate, hence the high degree of malignancy, however, gland formations and squamous cells are sometimes found in these neoplasms.

The question has often been asked why the basal-cell epitheliona is of such a low degree of malignancy when it is made up of undifferentiated cells. The best answer I know to this question was suggested by J. Shelton Horsley when he said that basal-cell epitheliomas pass through a short cycle and differentiate into basal cells, while squamous-cell epitheliomas pass through a longer cycle in order to differentiate into squamous cells.

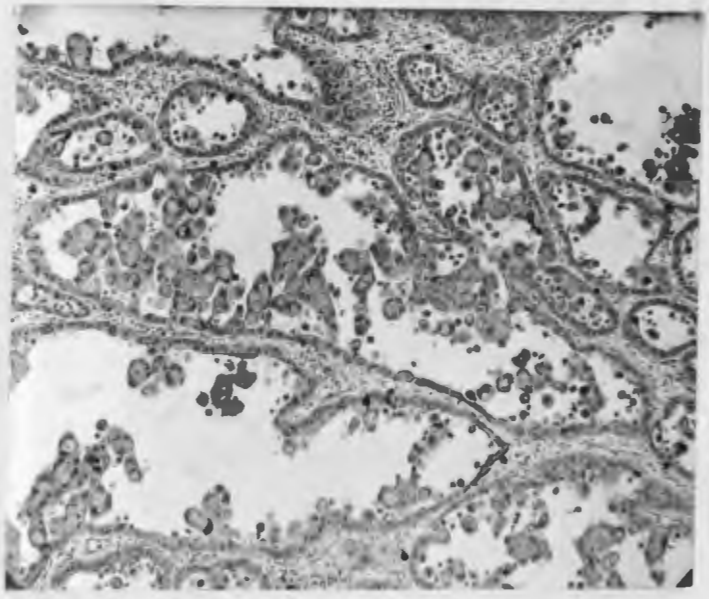
It is well known that the large majority of cells of a basal-cell epithelioma bear a close resemblance to the normal basal or regenerative cells of the epidermis; however, there are cells in this type of neoplasm which contain round nuclei with deeply staining single nucleoli ("one-eyed cells"); sometimes the nuclei are irregular in outline and contain more than one nucleolus or none. To me these cells show no differentiation whatever; they bear striking resemblance to the grade four squamous-cell epithelioma or the melanotic epithelioma. Whenever these cells predominate in a basal-cell epithelioma it is best to give a guarded prognosis because they are liable to infiltrate the surrounding tissues very rapidly. I see no reason why a basal-cell epithelioma with such active cells should not metastasize, and maybe they do but I have never seen it.

One not infrequently finds areas of squamous cells in a basal-cell epithelioma; this is due to the basal cells differentiating into squamous cells and from there on to complete differentiation into pearly bodies.

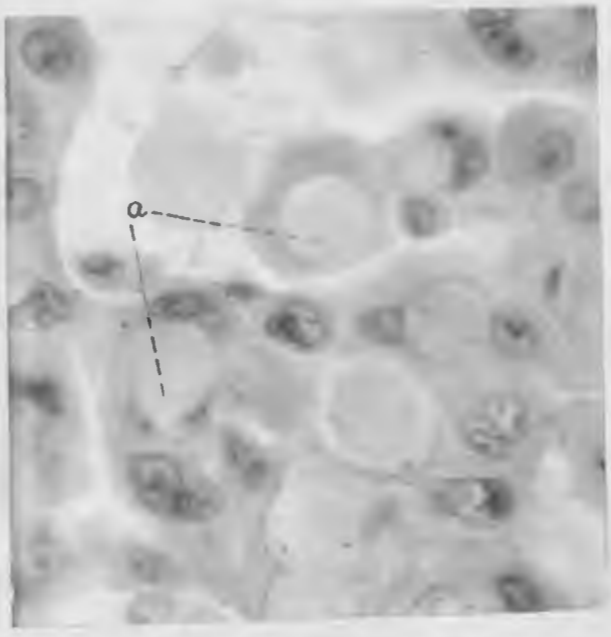
In presenting squamous-cell epithelioma of the skin, the same general plan will be followed as in squamous-cell epithelioma of the lip. The degree of cellular activity is graded on a one to four basis for the same reasons, namely, if the epithelioma shows a marked tendency to differentiate, that is if about three-fourths of its structure is differentiated epithelium and one-fourth undifferentiated, it is graded one; if the differentiated and undifferentiated epithelium are about equal, it is graded two; if the undifferentiated epithelium forms about three-fourths and the differentiated about one-fourth of the growth, it is graded three; if there is no tendency of the cells to differentiate it is graded four. As I said then, the number of mitotic figures and the number of cells with single large deeply staining nucle-

oli ("one-eyed cells") play an important part in the grading. After one has had some experience in the grading of epitheliomas, a picture for each class becomes fixed in the mind, thereby, making the grading rather easy. Not all cells with deeply staining nucleoli are malignant; however, when they are found in a neoplasm in large numbers it is best to think of the tumor as being malignant or pro-malignant. This cell is a regnerative cell, and, as malignant neoplasia is a regenerative-destructive process, their presence in malignant neoplasms is not out of order.

An endothelial leucocyte is also a "one-eyed cell" but it differs from the "one-eyed cell" of malignant neoplasia in that it lacks body, in other words it is like comparing Holstein with Jersey milk. Not all malignant cells have a single nucleolus, as some have more than one and others have none. As a rule the more malignant the neoplasm, the more irregular and ill-defined are its cell nuclei; however, exceptions to this are not infrequently seen. A pearly body in a lymph node is not itself cancer; neither are the large flat squamous cells with small nuclei which lie adjacent to it. The pearly body is a finished product which corresponds to the horny layer of the epidermis. The large flat squamous cell with a small nucleus is practically a finished product; the keratinization of this cell forms the basis of the pearly body. (See Figs. 6,7). The large flat squamous cell with the small nucleus and the pearly body are not cancer when found in a lymph node as they are incapable of regeneration. Cells which are incapable of regeneration are not cancer cells. Upon the foregoing reasoning, the basis of grading epitheliomas are formulated.



Low power of squamous-cell epithelioma of the skin, showing a number of cells undergoing keratinization.



High power of Fig. 5 showing (a) cells becoming keratinized.

I shall present the facts in this series of squamous-cell epitheliomas of the skin and make deductions from various standpoints similar to those which were made in the series of squamous-cell epithelioma of the lip. These epitheliomas are of the same nature and by comparison we are able to increase our knowledge.

Table I. Squamous-cell Epithelioma of the Skin

Two Hundred and Fifty-six cases(12.8 per cent of

Two thousand cases of General Epithelioma

Patients	256	
		Per cent
Males	205	(80.08)
Females	51	(19.92)
Age:		
Youngest patient		25
Oldest patient		88
Average age of patients		59.34
Occupation (males):		
Farmer		53.96
Laborer		11.11
Merchant		5.81
Railroader		4.23
Physician		3.17
Agent		2.11
Other occupations, 22 each below 2 per cent		19.57
Family history of malignancy		12.10
Previous lesion at site of cancer: Mole, wart, pimple, scab, ulcer, leukoplakia, crack, wen, blister, lump, etc		51.17
History of injury		23.82
(Burns, proportion of total injuries 24.59 per cent) (X-ray burns, proportion of total burns 20 per cent)		
		Years
Average duration of lesion		4.8
Longest duration of lesion		35
Shortest duration of lesion		.057
		Cm.
Greatest diameter		30
Average greatest diameter		3.854

Table 2. Location of the Lesion

	No.	Per Cent
Single lesion	247	96.48
Multiple lesions	9	3.51
Cheek		26.95
Nose		12.50
Temporal region		9.37
Neck		6.25
Hand (dorsal surface)		6.25
Ear		5.07
Angle of jaw		4.25
Chin		3.51
Eyelid		2.73
Leg		2.73
Forehead		2.34
Mastoid region		2.34
Index finger		2.34
Thoracico-abdominal region (ventral surface)		1.56
Parietal region		1.56
Thumb		1.17
Buttock		1.17
Perineal region		1.17
Thoracico-abdominal region (dorsal surface)		.78
Arm		.78
Middle finger		.78
Thigh		.78
Foot		.78
Inner canthus		.39
Occipital region		.39
Upper lip (near nose)		.39
Shoulder		.39
Forearm		.39
Hand (palmer surface)		.39
Great toe		.39

Table 3. Treatment elsewhere in Squamous-cell Epithelioma of the Skin

	Per cent
One or more treatments with acids(carbolic, chromic, hydrochloric, and nitric) alum (burnt) carbon dioxide, electricity, paste, potassium iodide, radium, roentgen ray, scarlet red and silver nitrate.... (Roentgen ray: proportion of total non-operative methods of treatment 50 per cent)	28.12
One or more operations.....	26.95
Operations without being treated with acids, alum, carbon dioxide, etc.....	19.53
Treatment with acids, alum, carbon dioxide, etc. without operation.....	20.70
Operation and treatment with acids, alum, carbon dioxide,etc..	40.23

Table 4. Patients operated on at the Mayo Clinic

	No.
Cases (92.18 per cent of 256)	236
1. Excision with knife immediately followed by cautery (one operation) (22.03 per cent of 236)	52
2. Excision with knife (one operation) (19.49 per cent of 236)	46
3. Block dissection of neck (unilateral) either alone or combined with other operations or methods of treatment before, at the same time, or after the block dissection was performed (3.81 per cent of 236)	9
4. Cautery (one operation)(3.38 per cent of 236)	8
5. Excision with cautery (one operation)(2.96 per cent of 236)	7
6. Excision with knife immediately followed by cautery (one operation) and later by skin graft (one operation) (2.96 per cent of 236)	7
7. Amputation of one or more fingers or thumb with removal of regional lymph nodes at the time of, or after amputation and either associated with or not associated with other operative or non-operative treatment before, at the time of, or after amputation (2.54 per cent of 236)	6
8. Amputation of thigh or leg with or without removal of regional lymph nodes and either associated or not associated with other operative or non-operative treatment before, at the time of, or after amputation (2.11 per cent of 236)	5
9. Amputation of arm, forearm, or hand with removal of regional lymph nodes before or at the time of amputation, and either associated or not associated with other operative or non-operative treatment before, at the time of, or after the amputation (2.11 per cent of 236)	5
10. Excision with knife immediately followed by cautery (one operation) and followed later by cautery (one operation) 1.69 per cent of 236	4
11. Cautery (two operations) (1.69 per cent of 236)	4
12. Block dissection of neck (bilateral) (two operations) accompanied by a complete evisceration of the left eye, excision of eyelids, and one supraclavicular lymph node preceded by three excisions with knife immediately followed by cautery (.423 per cent of 236)	1

Table 4. Patients operated on at the Mayo Clinic (con)

	No
13. Miscellaneous (various combinations of operations, radium, and roentgen rays)(34.74 per cent of 236).....	82
1. Inoperable (6.25 per cent of 256).....	16
2. Refused operation after diagnosis had been made (1.56 per cent of 256).....	4
1. Cases in which no lymph nodes or salivary glands were removed (77.96 per cent of 236).....	184
2. Cases in which lymph nodes or salivary glands were removed (one or more groups). (22.03 per cent of 236)	52

Table 5. Removal of Lymph Nodes and Salivary Glands

	Per cent
Submaxillary lymph nodes.....	44.23
Submaxillary salivary glands	44.23
External jugular nodes.....	38.46
Superior deep cervical nodes	28.84
Anterior cervical nodes	23.07
Inferior deep cervical nodes	23.07
Total cervical lymph nodes removed ..... 40.38 per cent	
Parotid salivary gland.....	19.21
Paratid lymph nodes	17.30
Submental nodes	17.30
Axillary nodes	17.30
Inguinal nodes	11.53
Supratrochlear nodes	5.76
Supraclavicular lymph nodes	5.76
Chest wall.....	1.92

Table 6. Pathologic Findings in Cases in which Lymph Nodes and Salivary Glands were Removed Metastases

	No.	Per Cent
No metastasis found	20	38.46
Metastasis found	32	61.53
Inguinal lymph nodes alone (one side)	5	15.62
Axillary lymph nodes alone (one side)	3	9.37
Parotid salivary gland and lymph nodes (one side)	5	15.62
Submaxillary lymph nodes alone (one side)	2	6.25
Submaxillary salivary gland and lymph nodes (one side)	2	6.25
Right and left external jugular, submental, left submaxillary and supraclavicular lymph nodes	1	3.12
External jugular, anterior cervical, superior and inferior deep cervical lymph nodes (one side)	1	3.12
Supratrochlear and axillary lymph nodes, lower and upper end of humerus, chest wall including seventh rib, axillary line (one side)	1	3.12
Miscellaneous (submaxillary lymph nodes and salivary glands, parotid lymph nodes and salivary glands, cervical, supraclavicular, supratrochlear, axillary, and inferior pectoral lymph nodes, alone or in various combinations (one side)	12	37.50

Table 7. Metastases (Total Involvement)

	No.	Per Cent
Submaxillary lymph nodes	9	28.12
Parotid lymph nodes	8	25.00
Parotid salivary gland	8	25.00
External jugular lymph nodes	6	18.75
Superior deep cervical lymph nodes	5	15.62
Axillary lymph nodes	5	15.62
Inguinal lymph nodes	5	15.62
Submaxillary salivary gland	4	12.50
Anterior cervical lymph nodes	4	12.50
Inferior deep cervical lymph nodes	3	9.37
Supraclavicular lymph nodes	3	9.37
Supratrochlear lymph nodes	2	6.25
Submental lymph nodes	1	3.12
Inferior pectoral lymph nodes	1	3.12
Chest wall	1	3.12
Lower and upper end of humerus	1	3.12
Seventh rib, axillary line	1	3.12

Total cervical lymph node involvement 31.25 per cent

Table 8, Grade of Two Hundred and Fifty-six cases on a Basis of One to Four According to Cellular Activity

	No.	Per Cent
Grade 1	21	8.20
Grade 2	178	69.53
Grade 3	44	17.18
Grade 4	13	5.07

Duration and Size of Epithelioma According to Grade

	Grade 1	Grade 2	Grade 3	Grade 4
	Years	Years	Years	Years
Longest duration	20.00	35.00	10.00	20.00
Shortest duration	.08	.05	.16	.10
Average duration	4.76	5.36	3.02	3.30
	Cm.	Cm.	Cm.	Cm.
Largest size	4.30	30.00	14.00	15.00
Smallest size	.50	.30	1.20	.60
Average size	2.09	5.70	4.61	5.40

Inoperable Epithelioma According to Grade

Grade 1	Grade 2	Grade 3	Grade 4
0	11	4	1

Refused Operation After Diagnosis had been made According to Grade

0	3	1	0

Table 9, Results

General Ultimate Results

Patients traced (operable,141; inoperable, 5; refused operation, 1) (57.42 per cent of total)	147
Patients operated upon	141
Patients dead (51.77 per cent)	73
Patients alive(48.22 per cent)	68
Good results(no recurrence) (82.35 per cent of 68)	56
Fair result (slight recurrence) (13.23 per cent of 68)	9
Poor result (no improvement) (4.41 per cent of 68	3

Duration of Life since last or only Operation According to Result

	Good result	Fair result	Poor result
	Years	Years	Years
Longest	13.16	12.05	5.23
Shortest	4.31	5.50	.15
Average	7.44	8.78	3.28

Table 9 (con).

Mortality

Deaths (13.74 per cent of 147)	79
Deaths of patients with operable epithelioma (92.40 per cent of 79)	73
Deaths of patients with inoperable epithelioma (6.32 per cent of 79)	5
Deaths of patients who refused operation after diagnosis had been made (1.26 per cent of 79)	1

Cause of Death of Patients Operated on: Data from Relative, Home Physician, or Pathologic Records of the Clinic.

	No.	Per Cent
Known cause	58	
Epithelioma	38	65.51
Old age	4	6.89
Heart Disease	4	6.89
Paralysis	3	5.17
Pneumonia	2	3.44
Arteriosclerosis	1	1.72
Acute gastritis	1	1.72
Carcinoma of pancreas	1	1.72
General Infection	1	1.72
Carcinoma of prostate and pneumonia	1	1.72
Influenza	1	1.72
Tuberculosis	1	1.72
Unknown	15	

Cause of Death of Patients who died in the Mayo Clinic (all operable)

Epithelioma and pneumonia (1.28 years after operation)	1
Carcinoma of prostate and pneumonia (.47 years after operation)	1
Epithelioma and shock (.027 years after operation)	1
Total (1.27 per cent of 236)	3
Actual operative mortality (.42 per cent of 236)	1

.able 10, Patients Operated on Treated with Pastes, Plasters, Acids, etc;

Before Entering the Clinic

	Grade 1	Grade 2	Grade 3	Grade 4
Patients concerning whom information has been received				36
Patients living (58.33 per cent of 36)				21
Patients living, good result	2 (10.52% of 19)	14 (73.68% of 19)	3 (15.79% of 19)	
Patients living, fair result	1 (100% of 1)			
Patients living, poor result			1 (100% of 1)	
Patients dead	15(41.66% of 36)			
Cause unknown	1			
Good result	1 (100% of 1)			
Poor result	9 (69.23% of 13)	3 (23.07% of 13)	1(7.69% of 13)	

Total results

Total good result(patient recovered from epithelioma and is living or recovered from epithelioma and died from other cause)	57.14% of 35
Total fair result(patient living with slight recurrence)	2.85% of 35
Total poor result(patient living with no improvement or died from epithelioma)	40.00% of 35

Table 11, Patients Operated on Not Treated with Pastes, Plasters, Acids, etc.,

Before Entering the Clinic

	Grade 1	Grade 2	Grade 3	Grade 4
Patients concerning whom information has been received				104
Patients living (44.23% of 104)				46
Patients living, good result	4(11.11% of 36)	27 (75% of 36)	5 (13.88% of 36)	
Patients living, fair result	2(25.00% of 8)	5 (62.50% of 8)	1(12.50% of 8)	
Patients living, poor result		2 (100% of 2)		
Patients dead,	(55.76% of 104)			58
Cause unknown	2	10	2	
Good result	6(31.57% of 19)	11(57.89% of 19)	2(10.52% of 19)	
Poor result		11(44.00% of 25)	8(32.00% of 25)	6(24.00% of 25)

Table 11.(Con) Total Results

Total good result(patient recovered from epithelioma and is living, or recovered from epithelioma and died from other cause)..... 61.11% of 90
Total fair result (patient living with slight recurrence)..... 8.88% of 90
Total poor result (patient living with no improvement or died from epithelioma..... 30.00% of 90

Table 12. Patients with Metastasis Operated on in which Regional Lymph Nodes or Salivary Glands were Removed.

Patients concerning whom no information was received..... 13(40.62% of 32)
Patients concerning whom information was received..... 19(59.37% of 32)
Patients living ..... 2(10.52% of 19)

	Grade 2	Grade 3
Patients living, good result.....	1 (100% of 1)	
Patients living, fair result.....		1 (100% of 1)

In the patient who reported a good result and in the one who reported a fair result, the parotid lymph nodes and salivary glands on only one side were involved.

Patients dead..... 17(89.47% of 19)

	Grade 2	Grade 3	Grade 4
Cause unknown	2.....	2.....	
Poor result	4(30.76% of 13)	4(30.76% of 13)....	5(38.46% of 13)

Total Results

Total good result (patient recovered from epithelioma)..... 1(6.66% of 15)
Total fair result (patient living with slight recurrence)..... 1(6.66% of 15)
Total poor result (patient died from epithelioma)..... 13(86.66% " 15)

Cause of Death

Epithelioma..... 13(100% of 13)

Table 13. Patients Without Metastasis Operated on in which Regional Lymph Nodes Or Salivary Glands were removed

Patients concerning whom no information was received				10 (50.00% of 20)
Patients concerning whom information was received				10 (50.00% of 20)
Patients living				6 (60.00% of 10)
	Grade 1	Grade 2	Grade 3	
Patients living, good results	2 (33.33% of 6)	3 (50.00% of 6)	1 (16.66% of 6)	4 (40.00% of 10)
Patients dead				
Cause unknown		1		
Good result		1 (100.00% of 1)		
Poor result		2 (100.00% of 2)		

Total Results

Total good results (patient recovered from epithelioma and is living or recovered from epithelioma and died from other cause	7 (77.77% of 9)
Total poor results (patient died from epithelioma	2 (22.22% of 9)

Cause of Death

Epithelioma	2 (66.66% of 3)
Heart disease	1 (33.33% of 3)

Table 14. Patients Operated on in whom no Regional Lymph Nodes or Salivary Glands Were Removed

	Grade 1	Grade 2	Grade 3	Grade 4	
Patients concerning whom no information was received					74
Patients concerning whom information was received					111
Patients living (53.15% of 111)					59
Patients living, good result	5 (10.41% of 48)	36 (75.00% of 48)	7 (14.58% of 48)		
Patients living, fair result	1 (12.50% of 8)	7 (87.50% of 8)			
Patients living, poor result		2 (66.66% of 3)	1 (33.33% of 3)		
Patients dead (46.84% of 111)					52
Cause unknown	2	8			
Good result	7 (36.84% of 19)	10 (52.63% of 19)	2 (10.52% of 19)		
Poor result		14 (60.86% of 23)	7 (30.43% of 23)	2 (8.69% of 23)	

Total Results

Total good result (patient recovered from epithelioma and is living or recovered from epithelioma and died from other cause)	67(66.33% of 101)
Total fair result (patient living with slight recurrence)	8(7.92% of 101
Total poor result (patient living with no improvement or died from epithelioma)	26(25.74% of 101)

Cause of Death

Epithelioma	23(54.76% of 42)
Old age	4(9.52% of 42)
Paralysis	3(7.14% of 42)
Heart Disease	3(7.14% of 42)
Pneumonia	2(4.76% of 42)
Acute gastritis	1(2.38% of 42)
Arteriosclerosis	1(2.38% of 42)
Carcinoma of pancreas	1(2.38% of 42)
Carcinoma of prostate and pneumonia	1(2.38% of 42)
General infection	1(2.38% of 42)
Influenza	1(2.38% of 42)
Tuberculosis	1(2.38% of 42)

Table 15. Patients with and without Metastasis operated on and also those Patients in whom no regional Lymph Nodes or Salivary Glands were removed

	Grade 1	Grade 2	Grade 3	Grade 4
Patients with metastasis		11(34.37% of 32)	12(37.50% of 32)	9(28.12% of 32)
Patients without metastasis	2(10% of 20).	14(70.00% of 20)	4(20.00% of 20)	
Patients who had no regional lymph nodes or salivary glands removed	19(10.32% of 184)	139(75.54% of 184)	23(12.50% of 184)	3(1.63% of 184)

Duration of Lesion before Examination at Clinic

	Years		Years
Longest duration(patient with metastasis)	15.00	Patient without metastasis	20.00
Shortest duration(patient with metastasis)	.10	Patient without metastasis	.08
Average duration (patient with metastasis)	2.67	Patient without metastasis	5.03

Patients in whom no Regional Lymph Nodes nor Salivary Glands were removed

Longest duration	35.00
Shortest duration	.05
Average duration	4.78

Size of Lesion at the Time of Examination at the Clinic

	Cm.		Cm.
Largest size(patient with metastasis	30.00	Patient without metastasis	15.00
Smallest size(patient with metastasis)	1.5	Patient without metastasis	1.5
Average size(patient with metastasis)	6.3	Patient without metastasis	4.15

Patients in Whom no Regional Lymph Nodes nor Salivary Glands were Removed

Largest size	30.00
Smallest size	.3
Average size	3.08

Table 16. Duration of Life after Operation of Patients with Metastasis According to Grade

	Grade 2
Good Result	
Number of Patients	1
	Years
Longest duration	4.8
Fair result	
Number of patients	1
	Years
Longest duration	11.8

Duration of Life after Operation of Patients of all Grades

	Good Result	Fair Result
	Years	Years
Longest duration	4.80	11.80

	Grade 2	Grade 3	Grade 4
Number of patients	4	3	5
	Years	Years	Years
Longest duration	1.28	.50	2.96
Shortest duration	.15	.31	.027
Average duration	.68	.41	1.58

Duration of Life after Operation of all Patients with Metastasis who are dead

	Years
Longest duration	2.96
Shortest duration	.027
Average duration	.98

Table 17. Duration of Life after Operation of Patients without Metastasis

According to Grade

Good result	Grade 1	Grade 2	Grade 3
Number of patients	2	3	1
	Years	Years	Years
Longest duration	7.26	7.97	8.90
Shortest duration	6.01	6.33	
Average duration	6.63	7.18	

Duration of Life of Patients of all Grades

	Good Result
	Years
Longest duration	8.90
Shortest duration	6.01
Average duration	7.29

Duration of Life after Operation of Patients without Metastasis who are dead

Good result (patient did not die from epithelioma)	Grade 2
Number of patients	1
	Years
Longest duration	.37

Poor result (patient died from epithelioma)

	Grade 2
Number of patients	1
	Years
Longest duration	1.33

Duration of Life after Operation of all Patients without Metastasis who have died

	Years
Longest duration	1.33
Shortest duration	.37
Average duration	.85

Table 18. Duration of Life after Operation in Patients, in Whom no Regional Lymph Nodes or Salivary Glands were removed, According to Grade

Good result	Grade 1	Grade 2	Grade 3
Number of patients	5	37	7
	Years	Years	Years
Longest duration	6.49	13.14	10.88
Shortest duration	4.93	4.31	6.04
Average duration	5.70	7.74	7.59
Fair result	Grade 1	Grade 2	
Number of patients	1	7	
	Years	Years	
Longest duration	1.59	12.50	
Shortest duration		5.50	
Average duration		8.38	
Poor result		Grade 2	Grade 3
Number of patients		2	1
		Years	Years
Longest duration		5.23	.15
Shortest duration		4.46	
Average duration		4.84	

Duration of Life of Patients of all Grades

	Good result	Fair result	Poor result
	Years	Years	Years
Longest duration	13.14	12.50	5.23
Shortest duration	4.31	1.59	.15
Average duration	7.51	8.40	3.73

Duration of Life after Operation of Patients in whom no Regional Lymph Nodes or Salivary Glands were Removed who have died

Good result (patients did not die from epithelioma)

	Grade 1	Grade 2	Grade 3
Number of patients	6	10	2
	Years	Years	Years
Longest duration	8.16	9.02	6.40
Shortest duration	.43	.26	5.34
Average duration	3.96	3.55	5.87

Table 18(con).

Poor result	Grade 2	Grade 3	Grade 4
Number of patients	13	7	2
	Years	Years	Years
Longest duration	3.61	1.95	.98
Shortest duration	.26	.05	.58
Average duration	1.45	.93	.78

Duration of Life after Operation of Patients of all Grades

	Good result	Poor result
	Years	Years
Longest duration	9.02	3.61
Shortest duration	.26	.05
Average duration	3.92	1.22

Duration of Life after Operation of all Patients in whom no Regional Lymph Nodes or Salivary Glands were removed who have died

	Years
Longest duration	9.02
Shortest duration	.05
Average duration	2.45

Table 19, Results Following Operation According to Grade

	Grade 1	Grade 2	Grade 3	Grade 4
Information received from patients operated on	16(76.19% of 21)	92(56.09% of 164)	26(66.66% of 39)	7(58.33% of 12)
Patients living	8(50.00% of 16)	50(54.34% of 92)	10(38.46% of 26)	
Patients living, good result	7(87.50% of 8)	41(82.00% of 50)	8(80.00% of 10)	
Patients living, fair result	1(12.50% of 8)	7(14.00% of 50)	1(10.00% of 10)	
Patients living, poor result		2(4.00% of 50)	1(10.00% of 10)	
Patients dead	8(50.00% of 16)	42(45.65% of 92)	16(61.53% of 26)	7(100% of 7)
Good result	6(100% of 6)	12(38.70% of 31)	2(14.28% of 14)	
Poor result	.....	19(61.29% of 31)	12(85.71% of 14)	7(100% of 7)
Not stated	2	11.....	2.....	
Total good result (patient recovered from epithelioma and is living or recovered from epithelioma and died from other cause).....	13(92.85% of 14)	53(65.43% of 81)	10(41.66% of 24)	
Total fair result(patient living with slight recurrence	1(7.14% of 14)	7(8.64% of 81)	1(4.16% of 24)	
Total poor result(patient living with no improvement or died from epithelioma).....		21(25.92% of 81)	13(54.16% of 24)	7(100% of 7)
Total result not stated.....	2.....	11	2.....	.....

CONCLUSIONS

1. The term "skin cancer" should be discarded as it is indefinite.

2. One should know the killing power of a cancer because it is necessary knowledge when giving a prognosis.

3. The use of the term "cancerous degeneration" should be discontinued.

4. Cancer is a regenerative-destructive process, resulting from the interaction of anabolic and katabolic processes in the majority of instances.

5. Malignant neoplasia probably follows, in most cases, the chronic excessive destruction of differentiated cells.

6. As a rule, the more marked the differentiation in a squamous-cell epithelioma, the lower the degree of malignancy.

7. Pearly bodies and large flat squamous-cells with small nuclei are not cancer; cancer is regenerative or undifferentiated cells.

8. The 255 cases of squamous-cell epithelioma of the skin in this series represent 12.8 per cent of 2,000 cases of general epithelioma.

9. Squamous-cell epithelioma of the skin occurs more often in males than in females; the proportion is 4 to 1. It occurs in patients past middle life; their average age is 59.34 years.

10. It occurs most often in farmers; they represent 53.96 per cent of the male cases.

11. The site of the cancer was preceded by either a mole, wart, pimple, scab, ulcer, leukoplakia, crack, wen, blister, or lump in 51.17 per cent of the cases.

12. There was a history of injury in 23.82 per cent of the cases; burns represented 24.59 per cent of the injuries, and x-ray burns represented 20.00 per cent of the burns.

13. The average duration of the lesion is 4.8 years while the average

greatest diameter is 3.85 cm.

14. Seventy-eight and four hundredths per cent of all the lesions occur above the clavicle.

15. Twenty-eight and twelve hundredths per cent of the patients were treated with acids, paste or plaster, etc., before they entered the clinic.

16. Twenty-six and ninety-five hundredths per cent were operated on before they entered the clinic.

17. Ninety-two and eighteen hundredths per cent of the patients were operated on at the clinic.

18. No regional lymph nodes nor salivary glands were removed in 77.96 per cent of the cases.

19. Of the 22.03 per cent of the cases in which the regional lymph nodes or salivary glands were removed, metastasis was demonstrated in 61.53 per cent.

20. The cervical lymph nodes were involved in 31.25 per cent; submaxillary lymph nodes in 28.12 per cent; the parotid lymph nodes in 25.00 per cent; the parotid salivary gland in 25.00 per cent, and the axillary and inguinal lymph nodes, each 15.62 per cent.

21. In a division of the epitheliomas according to cellular activity, on a basis of one to four, Grade one represents 8.20 per cent; Grade two, 69.53 per cent; Grade three, 17.18 per cent, and Grade four, 5.07 per cent.

22. The average duration of the lesion according to grade is longest in Grade two, 5.36 years, and shortest in Grade three, 3.02 years.

23. The average size of the lesion according to grade is largest in Grade four, 5.4 cm., and smallest in Grade one, 2.09 cm.

24. Of the patients operated on and traced, 51.77 per cent are dead and 48.22 per cent are alive.

25. Of the living patients, 82.35 per cent report a good result, having been free from the disease on an average of 7.44 years.

26. Of the patients operated on who have died, concerning whom information has been received, 65.51 per cent died from epithelioma.

27. Three, or 1.27 per cent, of the patients who were operated on died in the clinic, while the actual operative mortality was only 0.42 per cent.

28. The patients who were treated with pastes, plasters, etc., before entering the clinic did not get such total good results as those who werenot so treated; 57.14 per cent in the former and 61.11 per cent in the latter; the total poor results were 40.00 per cent in the former and 30.00 per cent in the latter.

29. Of the patients with metastasis, 10.52 per cent are living and 89.47 per cent are dead.

30. Of the two patients living who had metastasis, one reports a good result and one a fair result. In these patients the parotid lymph nodes and salivary gland on only one side were involved.

31. No patient with cervical lymph nodes or more than one group of any lymph nodes involved has been reported living.

32. Of the patients reported dead who had metastasis, 100.00 per cent died from epithelioma.

33. Of the patients operated on in whom no metastasis was demonstrated, 60.00 per cent are living, and 40.00 per cent are dead; of the living 100.00 per cent report a good result.

34. Of the patients reported dead who did not have metastasis, 66.66 per cent died from epithelioma.

35. Of the patients operated on in whom no regional lymph nodes or salivary glands were removed, 53.15 per cent are living and 46.84 per cent are dead; of the living, 81.35 per cent report a good result.

36. Of the patients reported dead in whom no regional lymph nodes or salivary glands were removed, 54.76 per cent died from epithelioma.

37. The total good results for the patients with metastasis are 6.66 per cent; without metastasis, 77.77 per cent; and those in whom no regional lymph nodes or salivary glands were removed, 56.33 per cent.

38. The total poor results for the patients with metastasis are 86.66 per cent; without metastasis, 22.22 per cent; and those in whom no regional lymph nodes or salivary glands were removed, 25.74 per cent.

39. The average duration of the lesion in the patients with metastasis is 2.57 years; without metastasis, 5.03 years; and those in whom no regional lymph nodes or salivary glands were removed, 4.78 years.

40. The average size of the lesion in the patients with metastasis is 5.3 cm.; without metastasis, 4.15 cm.; and those in whom no regional lymph nodes or salivary glands were removed, 3.08 cm.

41. Among the known causes of death, deaths from epithelioma were as follows: None of Grade one; 61.29 per cent of Grade two; 55.71 per cent of Grade three, and 100.00 per cent of Grade four.

42. The total good result for Grade one is 92.85 per cent; Grade two, 65.43 per cent; Grade three, 41.66 per cent; and none for Grade four.

43. The total poor result for Grade one is none; Grade two, 25.92 per cent; Grade three, 54.16 per cent; and Grade four, 100.00 per cent.

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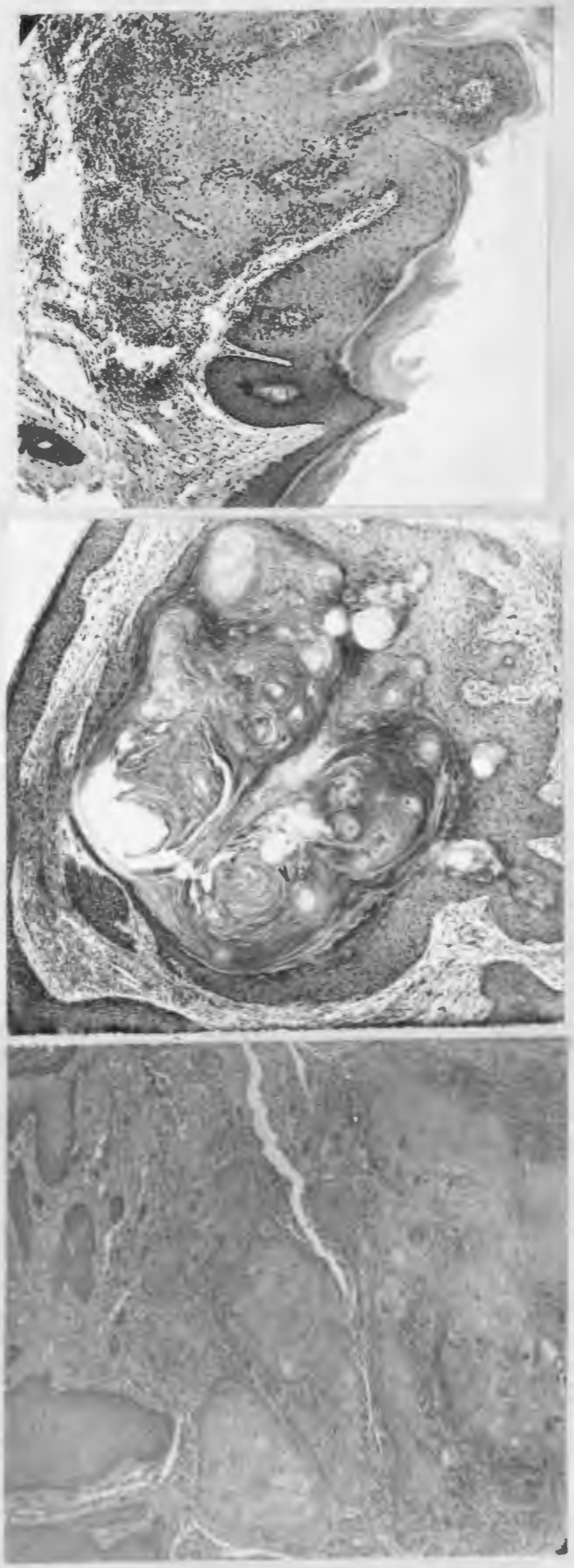
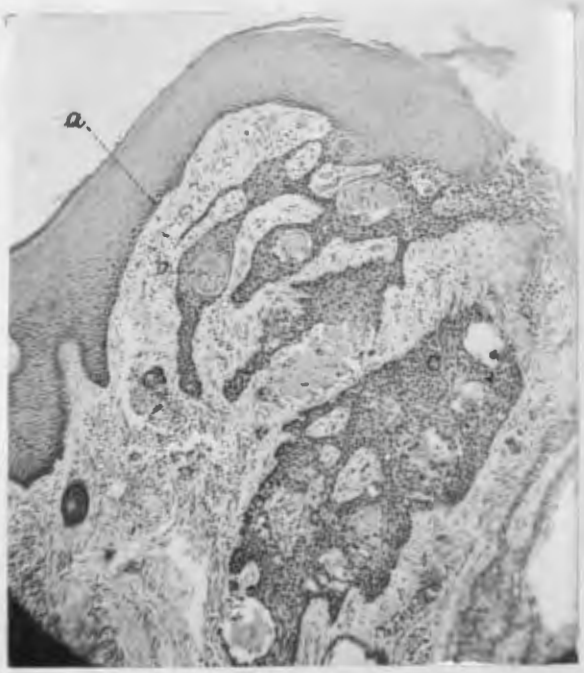
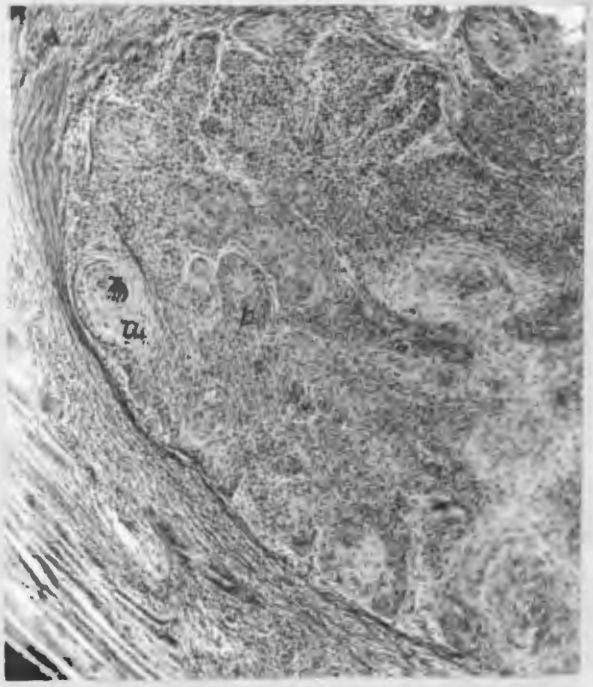


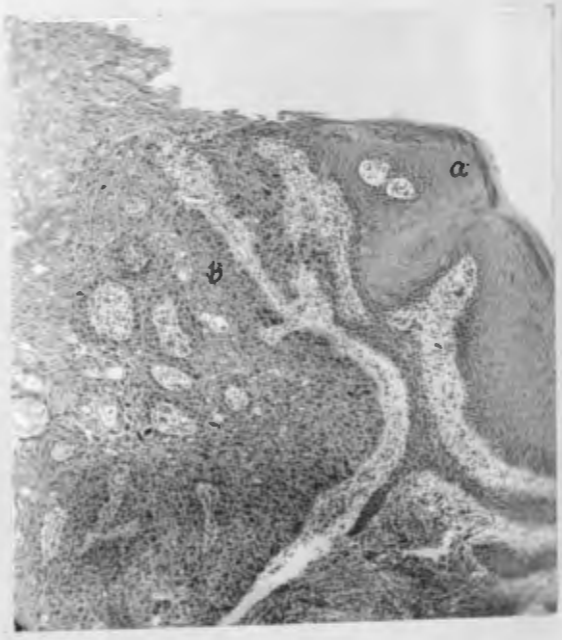
Grade 1 epitheliomas



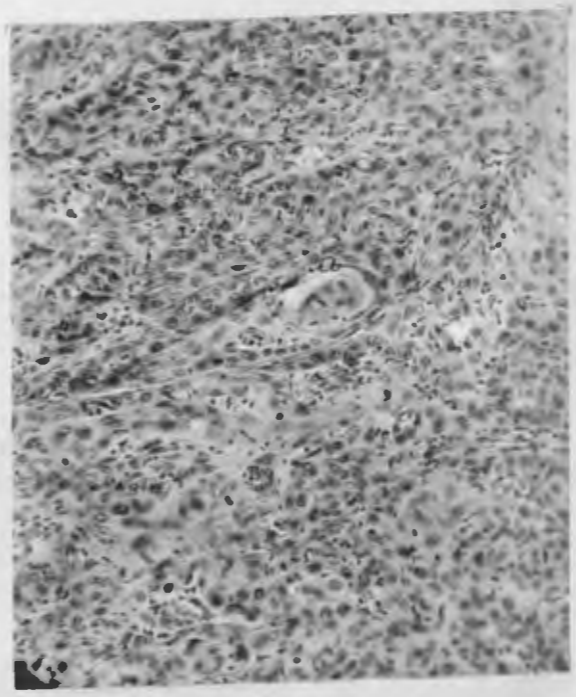
Grade 2, epithelioma (a), normal epithelium (b), pearly body, undifferentiated epithelial cells.



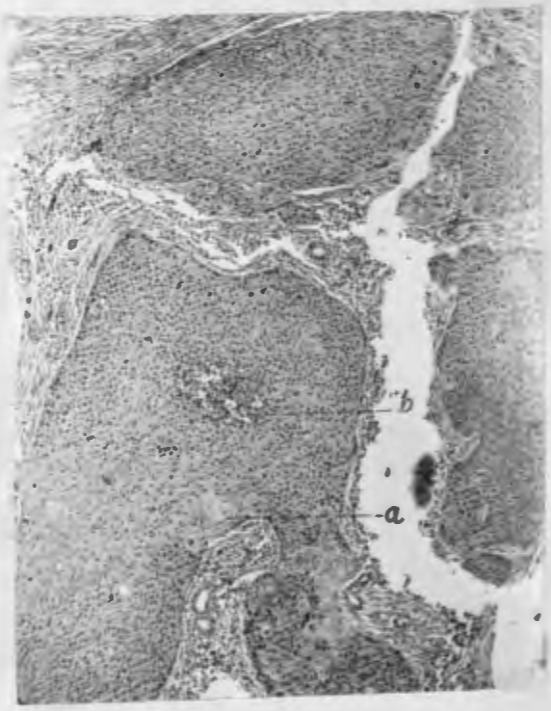
Grade 2, epithelioma (a), pearly body (b), undifferentiated cells



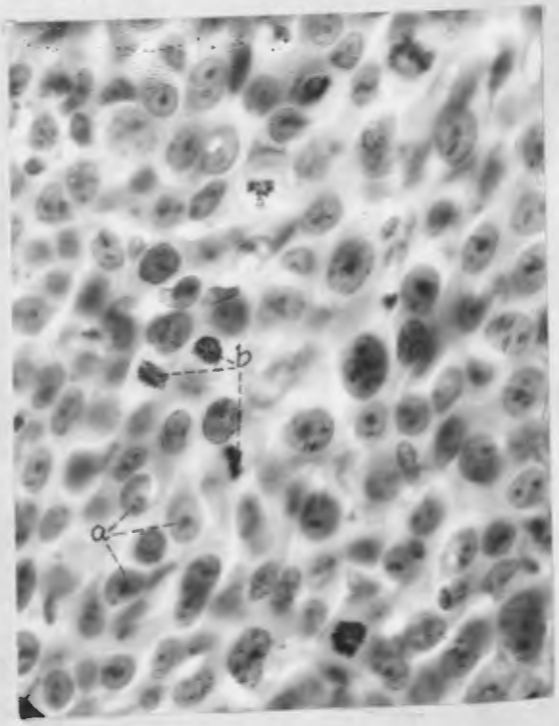
Grade 2, epithelioma,(a) normal epithelium,(b) epithelioma.



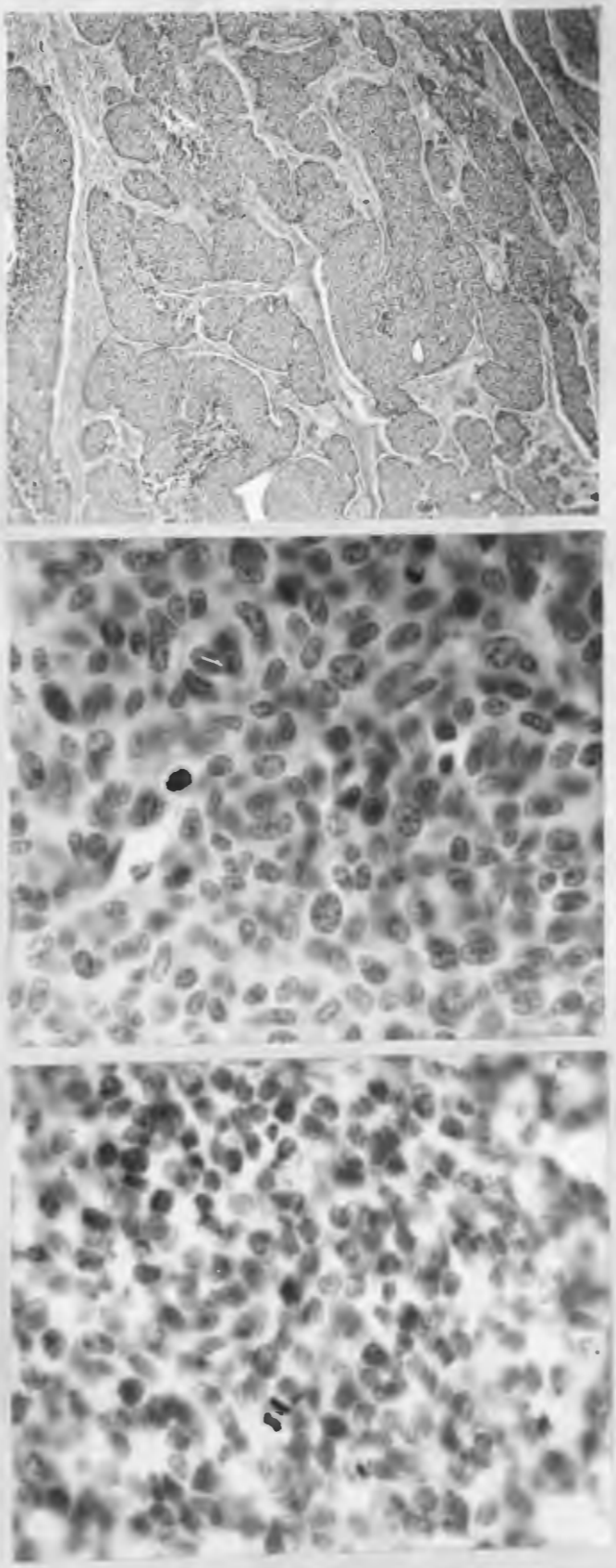
Grade 3 epithelioma, (a) epithelial cells showing practically complete differentiation.



Grade 3. Epithelioma (a), practically completely differentiated cells,(b) undifferentiated cells.



Very malignant area of a Grade 3 epithelioma,(a) "one-eyed cells" (b), mitotic figures.



Grade 4, epitheliomas showing irregular pale staining cells; very few "one-eyed cells" are to be seen.

BASAL-CELL EPITHELIOMA*

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In the second of a series of articles on epithelioma published in 1918, MacCarty and I[1] classified such tumors into six types or apparent types and described each. The tumor commonly known as the rodent ulcer has been termed basal-cell epithelioma because its cells tend to differentiate to a form similar to the cells of the basal or germinative layer of the epidermis. This type, which, like other epitheliomas, may be found on any surface covered with protective epithelium, develops practically always above the clavicle. The majority of its lesions attack the cheek, the eyelids, the nose, the forehead, the ear, the canthi and the temporal regions.

Basal-cell epithelioma often appears in the skin as an elevated, whitish nodule which resembles an adenoma or cyst of a sebaceous gland, as an ulcer with indurated borders, or as a scaly lesion. The latter type, which exfoliates its superficial layers to a shiny surface but which shows little tendency to heal completely (Figs. 4, 5, 6, 7, 8 and 9), is usually found in persons who are exposed to intense sunlight. The cells of the basal-cell epithelioma vary greatly in morphology and in arrangement. They may be long and slender, short and thick, round, oval, or spindle shaped. In arrangement they may be alveolar or glandlike and resemble the structure of the thyroid; they may present a cactus-like appearance, a diffuse or circumscribed solid mass of cells, or a combination of these different types (Figs. 10, 11, 12, 13, 14, 15, 16 and 17).

Since, as a matter of fact, all tumors arising in protective epithelium are basal-cell epitheliomas, their cellular differentiation is their only distinguishing fea-

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* Read before the Southern Minnesota Medical Association, Mankato, Jan. 20, 1919.

1. Broders, A. C., and MacCarty, W. C.: Epithelioma, Surg., Gynec. & Obst. 27: 141 (Aug.) 1918.

ture. Because of some common characteristics many basal-cell epitheliomas are undoubtedly diagnosed endotheliomas, alveolar sarcomas, round-cell sarcomas, spindle-cell sarcomas, and adenocarcinomas. Moreover, the cells of a pure basal-cell epithelioma are not supposed to contain prickles or spines; but because these do sometimes appear, it is often difficult to determine whether an epithelioma should be called a basal-cell or squamous-cell epithelioma, especially since

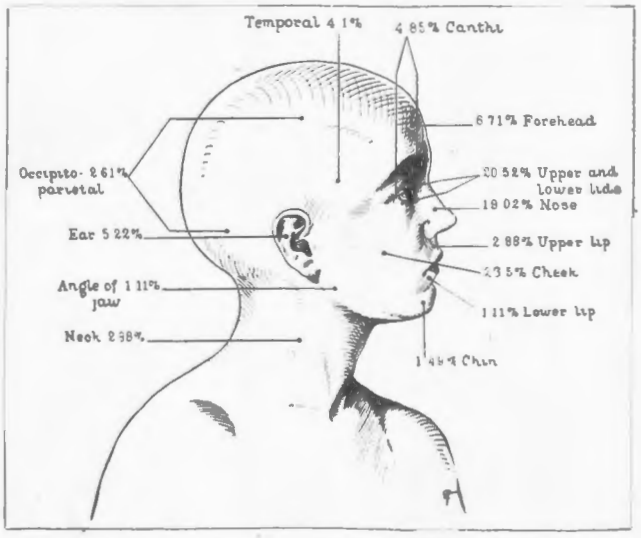

Fig. 1.—Location and percentage of basal-cell epitheliomas above the clavicle.

prickle cells are found in so-called basal-cell epitheliomas, and basal cells can always be seen in squamous-cell epitheliomas. It now seems to be a well established fact that a basal-cell epithelioma can change into a squamous-cell epithelioma, or at least into an epithelioma in which the squamous cells predominate. We know, beyond a doubt, that basal cells and squamous cells may be shown intimately connected in a neoplasm (Fig. 18), and this may account for the contention of some pathologists that basal-cell epitheliomas do occasionally metastasize.

In the series of cases here reported, none have been included without a thorough microscopic examination.

In distinguishing between cases that should be classified as basal-cell epithelioma and those that should be classified as squamous-cell epithelioma, the following rule has been adhered to: If the majority of the cells of the epithelioma are of the squamous-cell type, it is classified as a squamous-cell epithelioma; but if the majority are of the basal-cell type, it is classified as a basal-cell epithelioma.

TABLE 1.—BASAL-CELL EPITHELIOMA

	No.	Per Cent.
Patients	268	
Percentage of 2,000 cases of general epithelioma	...	13.4
Males	165	61.6
Females	103	38.4
Average age, years	56.7	
Oldest, years	87	
Youngest, years	23	
FAMILY HISTORY OF MALIGNANCY		
Males	17	10.3
Females	12	11.65
Total	29	10.82
PERSONAL HISTORY		
History of previous mole, wart, pimple, eczema, scab, ulcer, etc.	...	37.1
History of injury	...	9.3
Average duration of lesion, years	7½	
Longest duration of lesion, years	45	
Shortest duration of lesion, months	3	
Average greatest diameter of lesions, cm.	2	
Greatest diameter of lesion, cm.	12	
Smallest diameter of lesion, cm.	.5	
Males: OCCUPATION		
Farmer	82	56.16
Laborer	8	5.47
Carpenter	7	4.79
Merchant	6	4.10
Real estate dealer	6	4.10
Miscellaneous (26 occupations)	37	25.38
Females:		
Farm workers	39	43.33

There is, however, one tumor classified by some pathologists as a basal-cell epithelioma which is not included in these statistics: as we term it, a basal-cell-like epithelioma. This tumor occurs in the nose, in the pharynx, in the antrum of Highmore, in the parotid gland, in the cavity of the mouth, and in similar places. Although it is of long duration and has a microscopic structure similar to that of the basal-cell epithelioma, the trained eye will detect a difference; also, such tumors will metastasize, while the basal-cell epithelioma which occurs on the outer surface of the body is not supposed to do so.

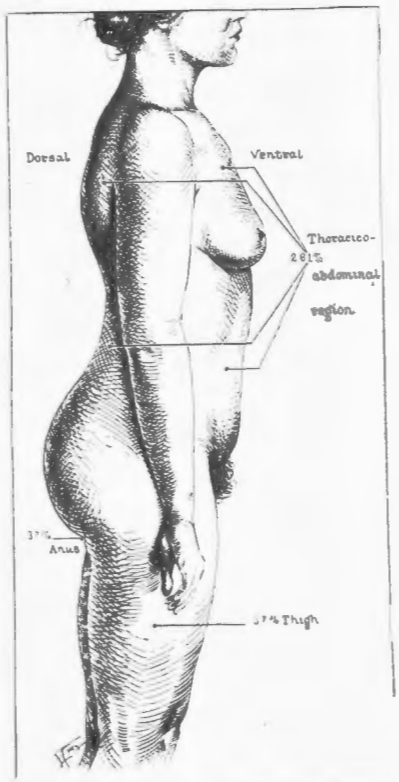

Fig. 2.—Location and percentage of basal-cell epitheliomas of trunk and thigh.

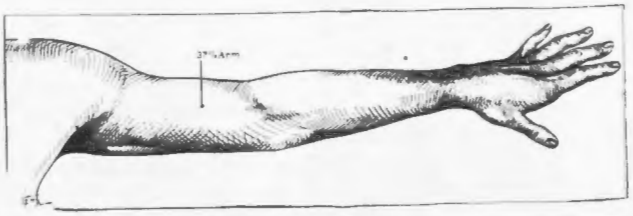

Fig. 3.—Location and percentage of basal-cell epitheliomas of upper extremity.

In presenting this series of cases of basal-cell epithelioma, I have endeavored to classify the findings as briefly as possible, and, at the same time, to bring out the most important points. Its chief object is to pre-

TABLE 2.—LOCATION OF THE LESION

	No.	Per Cent.
Single lesion	252	
Multiple lesions	16	
Cheek	...	23.5
Eyelids	...	20.52
Nose	...	19.02
Forehead	...	6.71
Ear	...	5.22
Canthi	...	4.85
Temporal region	...	4.10
Neck	...	2.98
Upper lip	...	2.98
Occipitoparietal region	...	2.61
Thoraco-abdominal region, ventral and dorsal	...	2.61
Chin	...	1.49
Angle of jaw	...	1.11
Lower lip	...	.37
Arm	...	.37
Anus	...	.37
Thigh	...	.37

TABLE 3.—TREATMENT

PREVIOUS TREATMENT OF LESION ELSEWHERE	Per Cent.
One or more treatments; acids (nitric and hydrochloric), carbon dioxid, copper sulphate, electricity, paste, radium, silver nitrate and roentgen ray	27.23
One or more operations	20.14
Operation without being treated with acids, carbon dioxid, etc., before, at, or after operation	14.55
Treatment with acids, carbon dioxid, etc., without operation	21.64
Operation and treatment with acids, carbon dioxid, etc.	36.19
TREATMENT AT MAYO CLINIC	
Excision with knife (one)	48.13
Excision with knife immediately followed by cautery (one)	26.86
Excision with cautery (one)	4.47
Miscellaneous (knife, cautery, roentgen ray, radium)	3.73
Excisions with knife immediately followed by cautery (two or more)	2.98
Excision with knife immediately followed by cautery and later by cautery (one)	2.98
Excision with knife (two or more)	2.23
Cautery (once)	2.23
Excision with knife followed later by cautery (one)	1.86
Excisions with cautery (two or more)	1.48
Cauteries (two or more)	1.11
Inoperable	1.86

sent in tabulated form a collective history of the cases, so as to furnish data of the initial appearance, clinical manifestations, treatment, and ultimate fate of the basal-cell epithelioma. As the patients whose cases are tabulated here came to the Mayo Clinic between Nov. 1, 1904, and July 22, 1915, which period ante-

dates the active use of radium in the treatment of this type of neoplasm, practically no account is given in this article of our experience with the curative properties of radium.

Fig. 4 (A 50531).—Basal-cell epithelioma of scalp.

SUMMARY

1. Our present series of cases represents 13.4 per cent. of 2,000 cases of general epithelioma.

2. Basal and squamous cells can be shown intimately connected in a neoplasm.

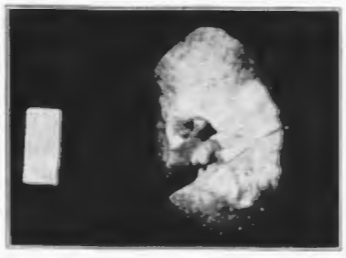

Fig. 5 (A 55948).—Basal-cell epithelioma of nose.

3. It seems to be a well-established fact that a basal-cell epithelioma can change into a squamous-cell epithelioma, or at least into an epithelioma in which the squamous cells predominate.

4. Basal-cell epithelioma occurs more often in males than in females, the proportion being about 3:2 in favor of the former.

Fig. 6 (A 33173).—Basal-cell epithelioma of eyelid.

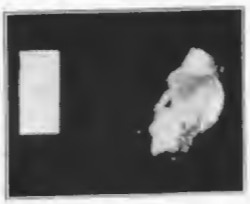

Fig. 7 (A 96196).—Basal-cell epithelioma of eyelid.

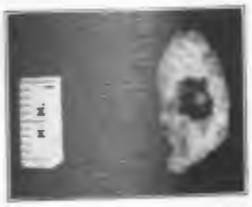

Fig. 8 (A 98228).—Basal-cell epithelioma of forehead.

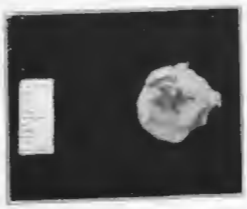

Fig. 9 (A 59758).—Basal-cell epithelioma of cheek.

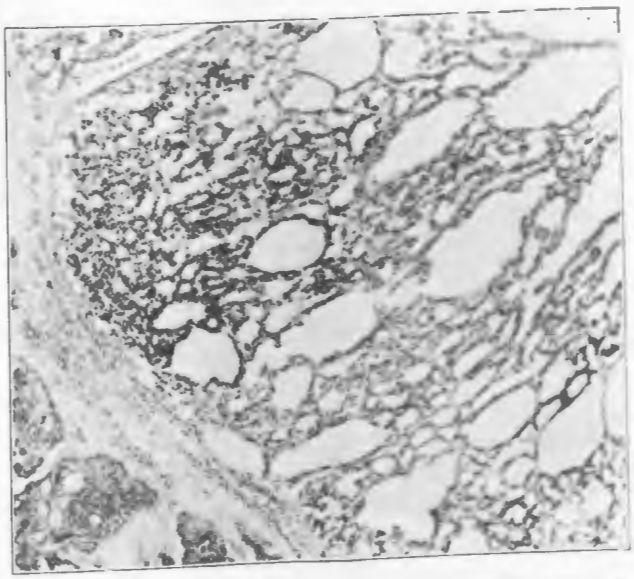

Fig. 10 (A 38151).—Basal-cell epithelioma of the outside of the n
Note the close resemblance to thyroid.

5. The disease occurs in patients past middle life; their average age is 56.7 years.

6. It occurs more often in farmers than in any other class of people.

TABLE 4.—ULTIMATE RESULT

	No.	Per Cent.
Patients heard from	145	54.10
Patients living	110	75.86
Patients dead	35	24.13
CONDITION OF LIVING PATIENTS		
No recurrence	83	75.45
Slight recurrence	22	20
No improvement	5	4.54
TREATMENT IN CASES IN WHICH THERE WAS NO RECURRENCE		
One excision with knife	38	45.77
One excision with knife followed immediately by cautery	24	28.91
One excision with cautery	8	9.62
Miscellaneous (various combinations of excisions and cauteries)	7	8.43
Two excisions with knife	3	3.61
One excision followed immediately by cautery and later by another cautery	3	3.61
Total	83	
Average greatest diameter of tumor, cm.	1.75	

Of the 83 living patients with a good result, 25 (30.12 per cent.) were either operated on or treated with acid, carbon dioxid, etc., elsewhere.

Length of time since last operation or only operation:

1 year and more	2 cases	7 years and more	5 cases
2 years and more	2 cases	8 years and more	3 cases
3 years and more	17 cases	9 years and more	3 cases
4 years and more	15 cases	10 years and more	8 cases
5 years and more	13 cases	11 years and more	1 case
6 years and more	9 cases	12 years and more	4 cases
		13 years and more	1 case

Average: 6 years, 1.6 months. Total 83 cases

TREATMENT IN CASES IN WHICH THERE WAS SLIGHT RECURRENCE		
One excision with knife	9	40.90
One excision with knife followed immediately by cautery	6	27.27
Miscellaneous (various combinations of excisions and cauteries)	5	22.73
Two or more excisions with cautery	2	9.09
Total	22	
Average greatest diameter of tumor, cm.	2	

Of the 22 living patients with a fair result there were 13 (59.09 per cent.) either operated on or treated with acid, carbon dioxid, etc., elsewhere.

TREATMENT IN CASES IN WHICH THERE WAS NO IMPROVEMENT	
Miscellaneous (various combinations of excisions and cauteries; one patient refused operation and was treated with roentgen ray)	5
Average greatest diameter of tumor, cm.	3.75

Of the 5 living patients with a bad result there were 4 (80 per cent.) either operated on or treated with acid, carbon dioxid, etc., elsewhere.

7. A family history of malignancy and a personal history of injury play a negligible part.

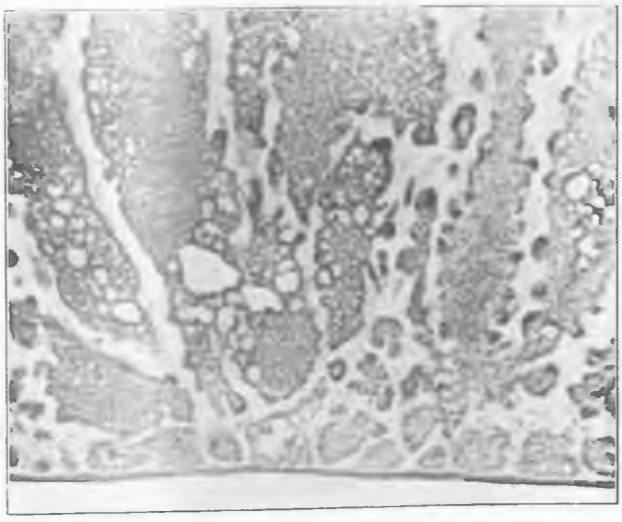

Fig. 11 (A 33009).—Basal-cell epithelioma of forehead, showing glandlike and solid areas.

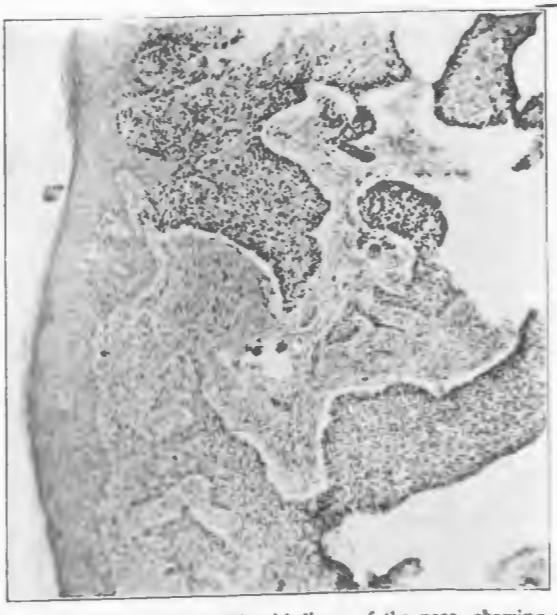

Fig. 12 (A 38366).—Basal-cell epithelioma of the nose, showing solid plugs of cells.

8. Previous mole, wart, pimple, eczema, scab, ulcer, etc., are associated in 37.1 per cent. of the cases.

9. The duration of the lesion shows a marked variation; it extends from three months to forty-five years, with an average of seven years and one month.

TABLE 5.—MORTALITY

Average age at time of death, years	69
Oldest, years	91
Youngest, years	48
Average length of life after the last or only operation, 4 years, 3.6 months.	

CAUSE OF DEATH ACCORDING TO RELATIVE OR HOME PHYSICIAN

	No.	Per Cent.
Basal-cell epithelioma	11	31.42
Heart disease	5	14.28
Carcinoma of stomach	3	8.57
Apoplexy	3	8.57
Carcinoma of colon	1	2.85
Carcinoma of liver	1	21.85
Carcinoma of uterus	1	2.85
Carbuncle	1	2.85
Cold and bronchial obstruction	1	2.85
Diabetes	1	2.85
Gangrene of foot	1	2.85
Hemorrhage of throat	1	2.85
Unknown	5	14.28
Total	35	
Average age of patients who died of basal-cell epithelioma, years	59.7	
Oldest, years	79	
Youngest, years	48	
Length of life after the last or only operation, years	4.12	
Average greatest diameter of lesions of patients known to be dead, cm.	2.67	
Average greatest diameter of lesions of those who died of basal-cell epithelioma, cm.	4.32	

TREATMENT OF PATIENTS WHO DIED

One excision with knife	18	51.42
One excision with knife immediately followed by cautery	11	31.42
Miscellaneous (various combinations of excisions and cauteries, one case inoperable)	6	17.14

TREATMENT OF PATIENTS WHO DIED DUE TO BASAL-CELL EPITHELIOMA

One excision with knife	4	36.36
One excision with knife immediately followed by cautery	4	36.36
Miscellaneous (one inoperable)	3	27.27
Fifteen (42.85 per cent.) of the 35 patients known to be dead were either operated on or treated with acids, carbon dioxid, etc., before entering the Mayo Clinic.		

COMPLICATIONS IN THREE FATAL CASES

Carcinoma of the breast	1
Carcinoma of the colon	1
Carcinoma of the body of the uterus	1

10. Ninety-six and twenty-eight hundredths per cent. of all the lesions occur above the clavicle.

11. Thirty-six and nineteen hundredths per cent. of all the patients had been either operated on or treated with acids, carbon dioxid, etc., before entering the Mayo Clinic.

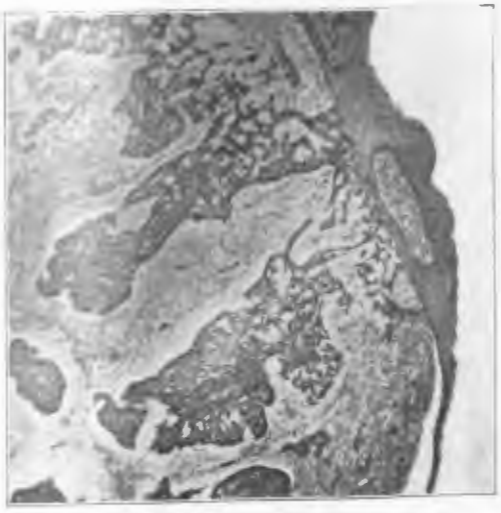

Fig. 13 (A 71769).—Basal-cell epithelioma of the cheek similar t Figure 11.

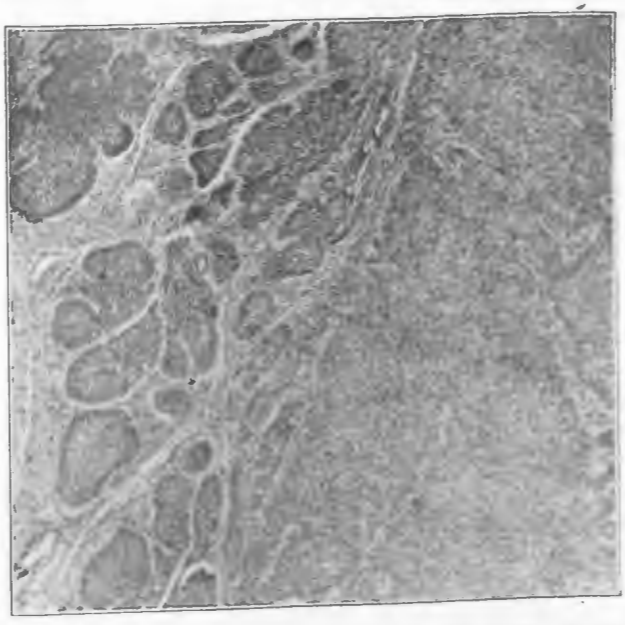

Fig. 14 (A 61661).—Basal-cell epithelioma of eyelid showing circumscribed and diffuse masses of cells.

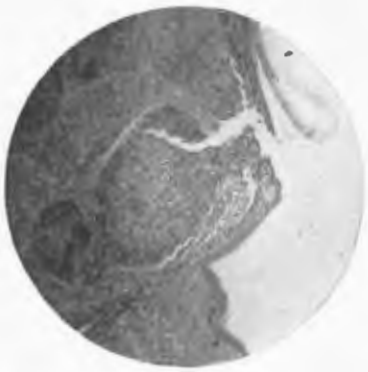

Fig. 15 (A 98228).—Basal-cell epithelioma of forehead; same as Figure 8.

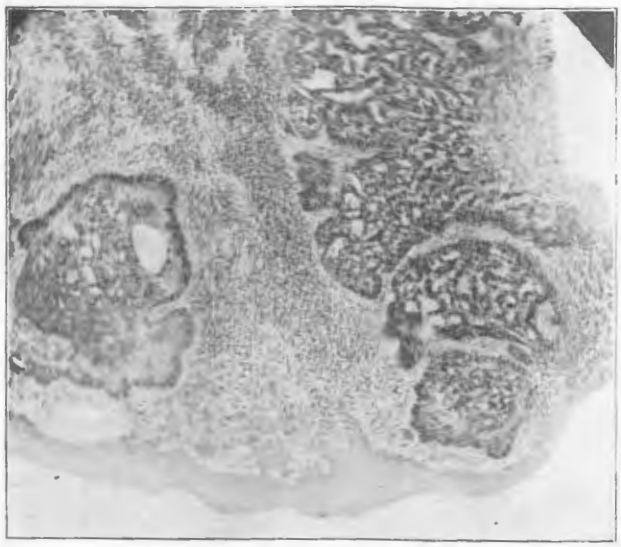

Fig. 16 (A 38151).—Basal-cell epithelioma of the outside of the nose, showing connection with epidermis; same as Figure 10.

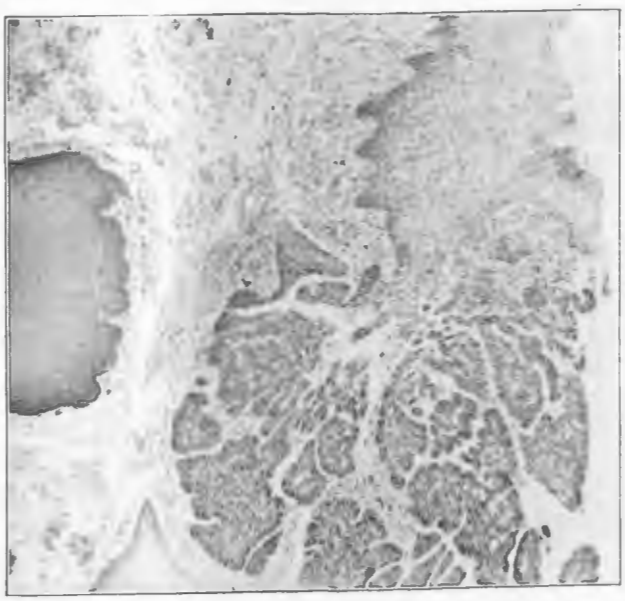

Fig. 17 (A 20310).—Gland type of basal-cell epithelioma of the outside of the nose, showing connection with epidermis.

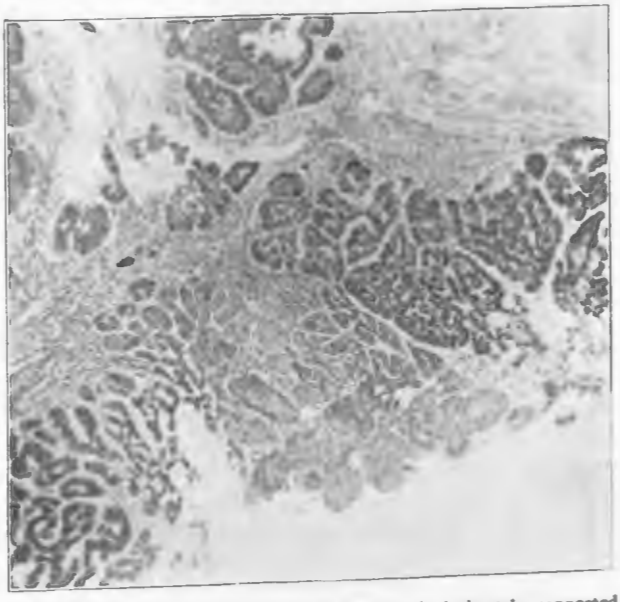

Fig. 18 (A 20310).—Gland type of basal cells intimately connected with squamous cells (typical metaplasia), adjacent to microscopic field of Figure 17.

12. In approximately 75 per cent. of all the cases treated at the clinic there was either one excision with the knife alone or one excision with the knife immediately followed by cautery.

13. Of the 54.1 per cent. of patients heard from, 75.86 per cent. are living, of whom 75.45 per cent. report a good result.

14. In the cases in which a good result was reported, 74.68 per cent. of the patients had either one excision with the knife alone or one excision with the knife immediately followed by cautery.

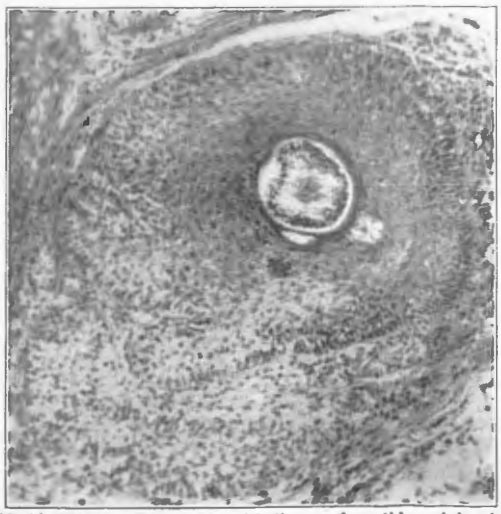

Fig. 19 (A 96196).—Basel-cell epithelioma of eyelid—originating from a hair follicle; same as Figure 7.

15. The patients who had been treated with acids, carbon dioxid, etc., before entering the clinic did not get so good a result as those who had had no previous treatment.

16. The low grade of malignancy of the neoplasm is evidenced by its long duration, lack of metastasis in a single case in this series, response to proper surgical treatment, and by the fact that 75.45 per cent. of the patients reported living have been free from the disease on an average of six years, one and six-tenths months.

17. Of the patients reported dead, fewer than one third died from this disease.

18. Excessive exposure to sunlight as a cause of the neoplasm has not been borne out by the facts in our series of cases. It was noted that the hand, which is exposed to sunlight at least as much as any part of the body above the clavicles, did not show lesions.

19. Practically all of the neoplasms in our series had their origin in the germinal layer of the epidermis of the skin. Only one was demonstrated to have originated from a hair follicle (Fig. 19).

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Squamous-Cell Epithelioma of the Lip

A STUDY OF FIVE HUNDRED AND THIRTY-SEVEN CASES

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ROCHESTER, MINN.

SQUAMOUS-CELL EPITHELIOMA OF THE LIP

A STUDY OF FIVE HUNDRED AND THIRTY-SEVEN CASES *

A. C. BRODERS, M.D.
ROCHESTER, MINN.

Of all the malignant neoplasms with which man is afflicted, few cause more concern and inconvenience than that of epithelioma of the lip. In the past, pathologists have been content to classify cancer of the lip as cancer, without any distinction as to the degree of malignancy. It is a well established fact that some cancers of the lip are fatal to patients and others are not. There must be a reason for this. One theory is that some persons are resistant to cancer, and this seems to be borne out in a certain percentage of cases.

Undoubtedly a large proportion of cancer cells are destroyed by the defense cells of the body; of these, the fibrous connective tissue cell is the most important, since it cuts off nourishment from the cancer cells.

The endothelial leukocyte and lymphocyte evidently also play an important rôle in the destruction of cancer cells, for practically always they may be seen in the neighborhood of a cancerous growth. Foreign body giant cells that are most probably formed from the endothelial leukocytes are not infrequently found lying adjacent to cancer cells.

The most important factor in squamous-cell epithelioma of the lip seems to be the degree of cellular activity. The cells of some epitheliomas of the lip show a marked tendency to differentiate, that is, to produce a growth similar to the normal; the pearly body is an example. The pearly body corresponds to the horny layer of the epidermis. In other squamous-

* From the Section on Surgical Pathology, Mayo Clinic.
* Presented before the Richmond Academy of Medicine and Surgery, Richmond ,Va., Nov. 25, 1919, and before the Roanoke Academy of Medicine, Roanoke, Va., Dec. 1, 1919.

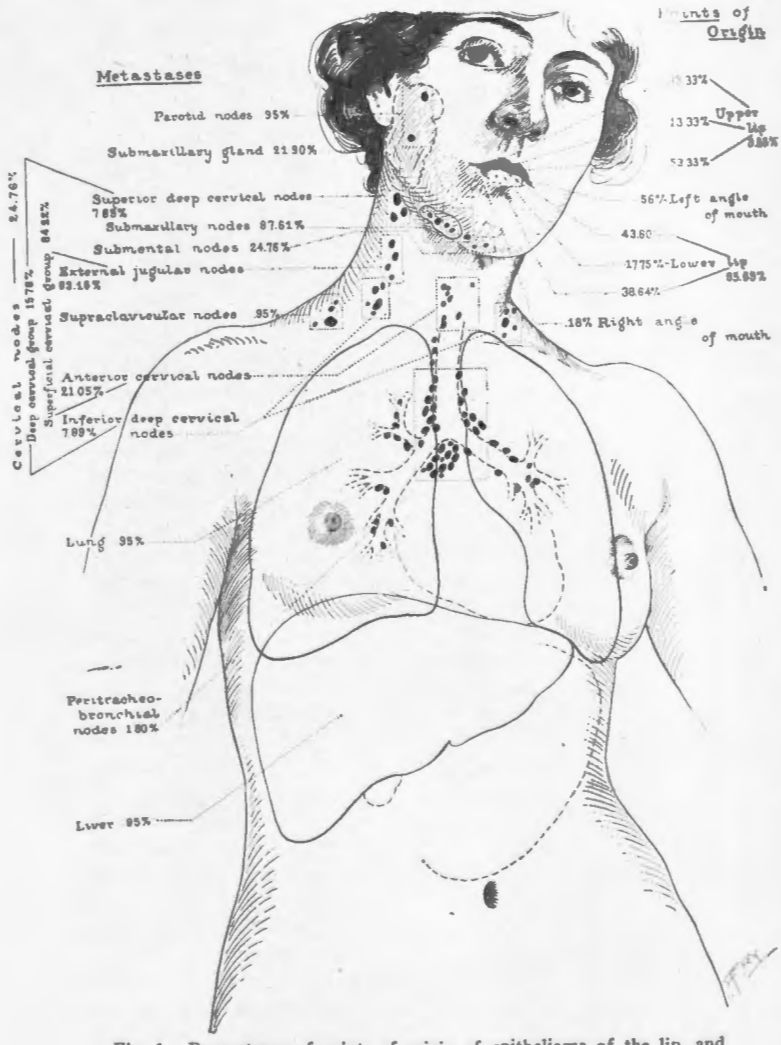

Fig. 1.—Percentages of points of origin of epithelioma of the lip, and percentages of location of metastasis.

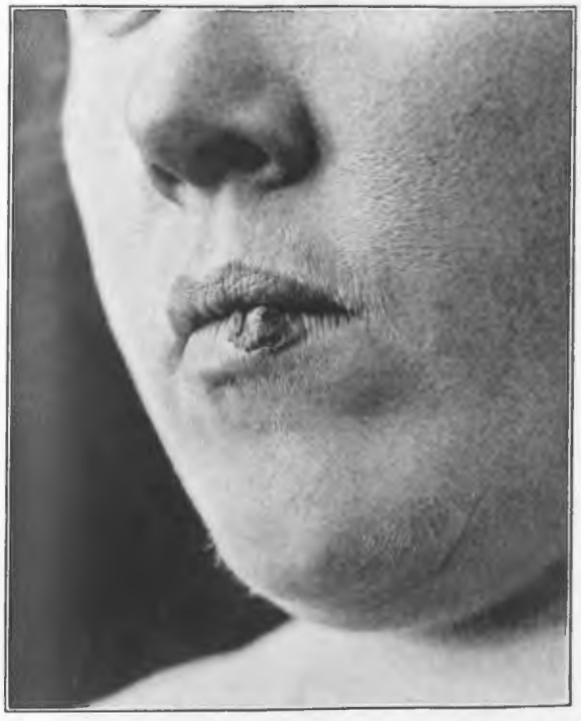

Fig. 2 (a 188878).—Typical elevated or wartlike epithelioma of the lip.

Fig. 3 (a 265421).—Typical depressed or ulcer-like epithelioma of the lip.

Chronic ulcers of the lip, like chronic ulcers of the stomach, should be examined very closely for cancer, provided syphilis has been eliminated. MacCarty[1] has demonstrated early cancer in the epithelium at or near the edge of gastric ulcers; practically the same process

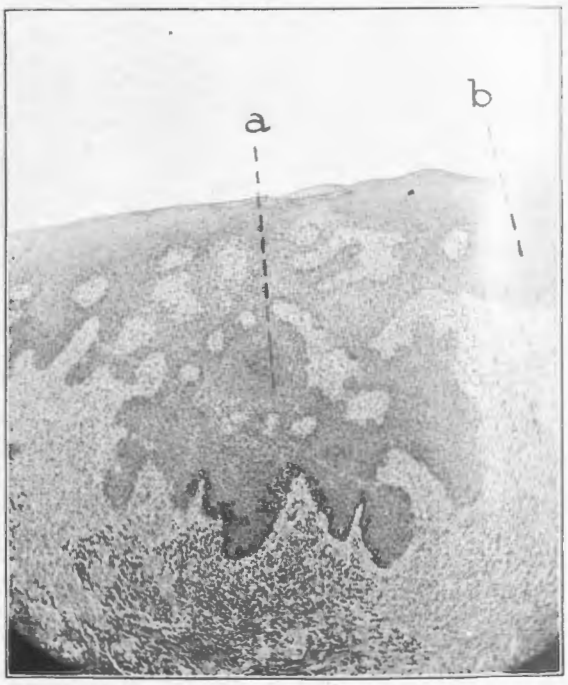

Fig. 6 (a 98158).—Grade 1 epithelioma of the lip with marked differentiation; low degree of malignancy; patient well five years after operation: *a*, epithelioma; *b*, normal epithelium.

is found in early cancer on ulcer of the lip. In the lip the cancer starts in the stratum germinativum of the epithelium at or near the border of the ulcer. Not all cancers of the lip are preceded by ulcers, but the majority are.

I shall present the facts in statistical form and make the deductions, not from one, but from various stand-

1. MacCarty, W. C.: Pathology and Clinical Significance of Gastric Ulcer: From a Study of Material from Two Hundred and Sixteen Partial Gastrectomies for Ulcer, Ulcer and Carcinoma, and Carcinoma. Surg., Gynec. & Obst. **10**: 449-462, 1910.

points: (1) the duration and size of the lesion; (2) the use or nonuse of tobacco; (3) the use or nonuse of caustics, pastes or plasters, etc., before treatment at the clinic; (4) metastasis or no metastasis; (5) cellular activity, and (6) other points of general interest.

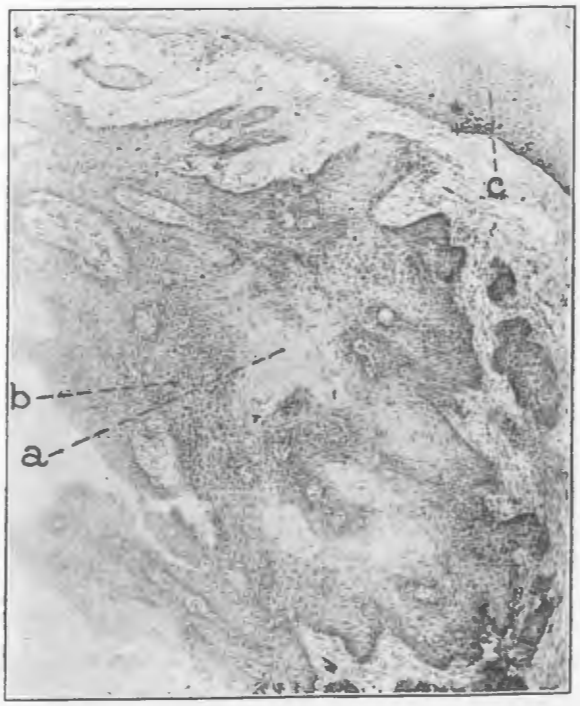

Fig. 7 (a 64692).—Grade 1 epithelioma of the lip showing marked differentiation, although it is of a slightly higher degree of malignancy than the epithelioma shown in Figure 6; patient well seven years after operation; *a*, completely differentiated area; *b*, partially differentiated cells; *c*, normal epithelium.

CONCLUSIONS

1. The 537 cases of squamous-cell epithelioma of the lip in this series represent 26.85 per cent. of 2,000 cases of general epithelioma.

2. Squamous-cell epithelioma of the lip occurs more often in males than in females; the proportion is 49: 1. It occurs in patients past middle life; their average age is 57.3 years.

3. The disease occurs most often in farmers; they represent 56.7 per cent. of the cases.

4. A family history of malignancy plays a negligible part.

5. The site of the cancer was preceded by a sore or an ulcer in 63. 3 per cent. of the cases.

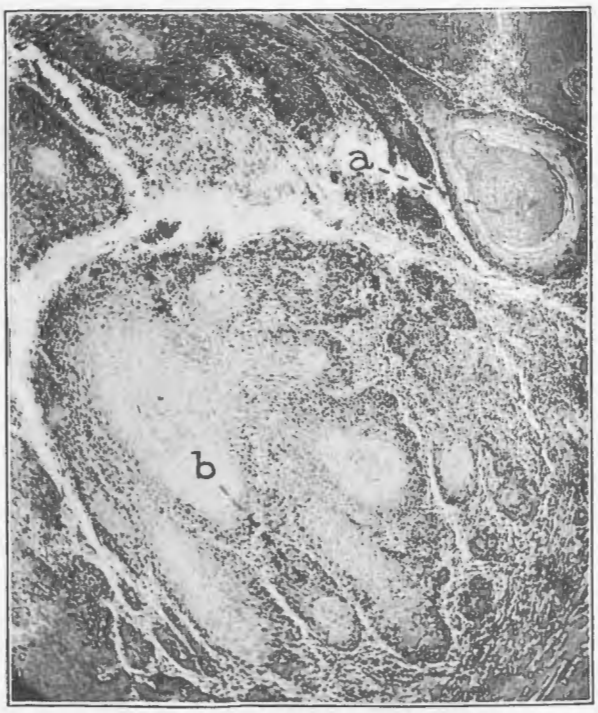

Fig. 8 (a 99884).—Grade 2 epithelioma of the lip; not so much differentiation as in epithelioma shown in Figure 7; patient died from epithelioma of the lip four and one-half years after operation: *a*, completely differentiated area or pearly body; *b*, undifferentiated cells.

6. About one fifth of all the patients do not use tobacco, while one half of the female patients do not use it.

7. Of the patients using tobacco, 93.33 per cent. smoke; 78.48 per cent. of these use a pipe.

8. A comparison of 500 men without epithelioma of the lip with the 537 patients with epithelioma of the lip

shows that the percentage of tobacco users and non-tobacco users is practically the same; 78.6 per cent. users and 21.4 per cent. nonusers in the former group, and 80.49 per cent. users and 19.51 per cent. nonusers in the latter group, but that the average age of the men without epithelioma of the lip is about nineteen years

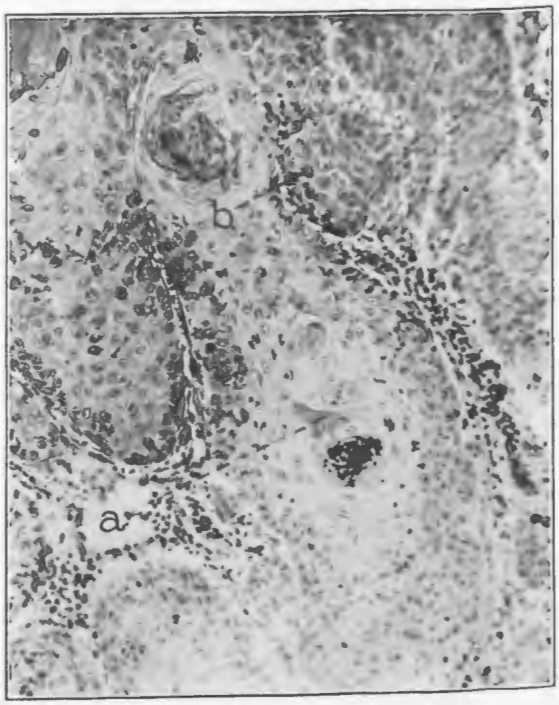

Fig. 9 (a 59017).—Grade 2 epithelioma of the lip; about the same degree of malignany as in epithelioma shown in Figure 8; patient well more than seven years after operation: *a*, partially differentiated cells; *b*, undifferentiated cells.

less than the average age of the patients with epithelioma of the lip at the time of onset.

9. The most remarkable difference in a comparison of the patients with epithelioma of the lip and the men without epithelioma of the lip is in the method of smoking. The total number of pipe smokers in the former is 78.48 per cent. and the total number of cigaret smokers is only 1.16 per cent., while in the latter the

TABLE 1.—SQUAMOUS-CELL EPITHELIOMA OF THE LIP: FIVE HUNDRED AND THIRTY-SEVEN CASES (26.85 PER CENT. OF TWO THOUSAND CASES OF GENERAL EPITHELIOMA)

Patients	537	
		Per Cent.
Males	526	(97.95)
Females	11	(2.05)
Age:		
Youngest patient		21
Oldest patient		97
Average age of patients		57.3
Occupation:		Per Cent.
Farmer		56.7
Laborer		9.0
Merchant		3.83
Traveling salesman		2.87
Railroad employee		2.87
Carpenter		2.68
Lawyer		1.34
Blacksmith		1.15
Clerk		1.15
Other occupations 59, each below 1 per cent		18.4
Family history of malignancy		14.9
Previous lesion at site of cancer:		
Sore or ulcer (coldsore, 10.6 per cent.)		63.3
Crack		4.1
Leukoplakia		3.7
Tobacco:		
Patients using tobacco		80.49
Patients not using tobacco		19.51
Females using tobacco (smoke)		45.45
Females not using tobacco		45.45
Methods of using tobacco:		
Patients who smoke only		69.82
Patients who chew only		6.31
Patients who smoke and chew		23.5
Patients who use snuff		0.35
Total number of smokers		93.33
Total number of chewers		29.82
Total number of snuffers		0.35
Methods of smoking:		
Pipe only		40.69
Cigars only		19.18
Pipe and other methods and with chewing		37.79
Cigars with other methods and with chewing		31.97
Total number of pipe smokers		78.48
Total number of cigar smokers		51.16
Total number of cigaret smokers		1.16
History of injury		8.38
		Years
Average duration of lesion		2.58
Longest duration of lesion		28.00
Shortest duration of lesion		0.08
		Cm.
Greatest diameter		12.5
Average greatest diameter		2.4
Origin of lesion:		Per Cent.
Lower lip		95.69
Upper lip		3.55
Left angle of mouth		0.56
Right angle of mouth		0.18
Lower lip:		
Left lower lip		43.60
Right lower lip		38.64
Middle lower lip		17.75
Upper lip:		
Left upper lip		53.33
Right upper lip		33.33
Middle upper lip		13.33

11. The duration of the lesion shows a marked variation, from 0.08 years to 28 years, with an average of 2.58 years.

12. The greatest diameter of any lesion is 12.5 cm.; the average, 2.4 cm.

13. The lesion originated on the lower lip in 95.69 per cent. of the cases, on the upper lip in 3.55 per cent.,

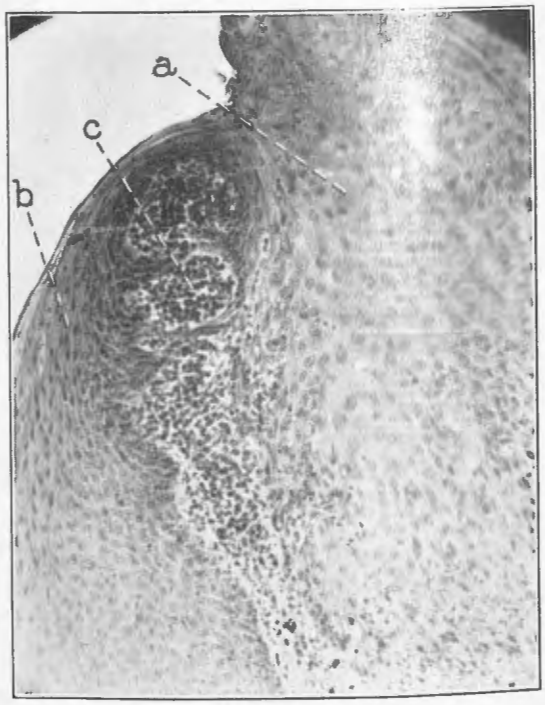

Fig. 10 (a 72479).—Grade 2 epithelioma of the lip: *a*, epithelioma; *b*, normal epithelium; *c*, lymphocytes

at the left angle of the mouth in 0.56 per cent., and at the right angle of the mouth in 0.18 per cent.

14. Twenty-nine and five hundredths per cent. of the patients were treated with acid, paste or plaster, etc., before they entered the clinic.

15. Seventeen and eighty-seven hundredths per cent. of the patients were operated on before they entered the

16. Ninety-six and eight hundredths per cent. of the patients were operated on at the clinic.

17. In 87.01 per cent., the regional lymph nodes were removed.

18. Of the 449 cases in which the lymph nodes or salivary glands were removed, metastasis was demonstrated in 23.38 per cent.; the submaxillary lymph nodes

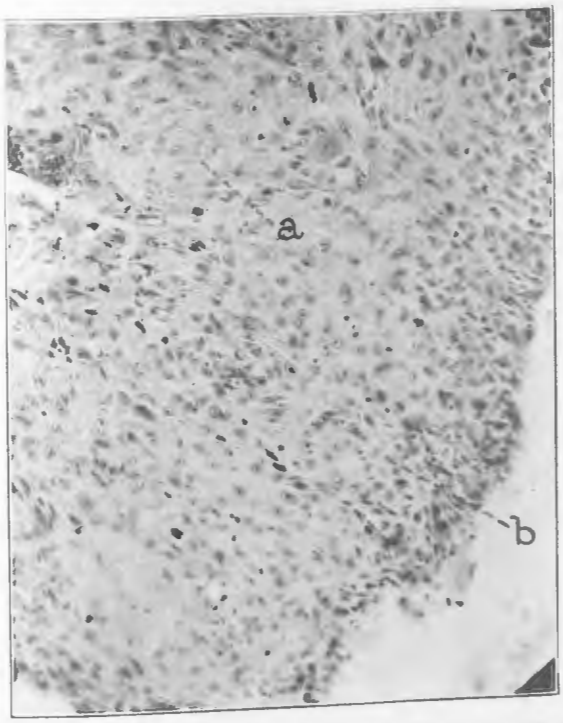

Fig. 11 (a 38260).—Grade 3 epithelioma of one of the left submaxillary lymph nodes, secondary to epithelioma of the lip; slight differentiation; the patient died from epithelioma five months after the last operation, and twenty months after the onset of the disease: *a*, partially differentiated cells; *b*, undifferentiated cells.

were involved in 87.61 per cent.; the submaxillary salivary glands in 21.90 per cent.; the submental lymph nodes in 24.76 per cent., and the cervical lymph nodes in 24.76 per cent.

19. In a division of the epitheliomas according to cellular activity, on a basis of 1 to 4, Grade 1 represents

TABLE 1.—SQUAMOUS-CELL EPITHELIOMA OF THE LIP: FIVE HUNDRED AND THIRTY-SEVEN CASES (26.85 PER CENT. OF TWO THOUSAND CASES OF GENERAL EPITHELIOMA)

Patients	537	
		Per Cent.
Males	526	(98.05)
Females	11	(2.05)
Age:		
Youngest patient		21
Oldest patient		82
Average age of patients		63.3
Occupation:		Per Cent.
Farmer		30.7
Laborer		7.0
Merchant		2.53
Traveling salesman		.87
Railroad employee		.87
Carpenter		.68
Lawyer		1.34
Blacksmith		1.15
Clerk		1.15
Other occupations 59, each below 1 per cent.		18.4
Family history of malignancy		14.9
Previous lesion at site of cancer:		
Sore or ulcer (coldsore, 10.6 per cent.)		63.3
Crack		4.1
Leukoplakia		3.7
Tobacco:		
Patients using tobacco		80.49
Patients not using tobacco		19.51
Females using tobacco (smoke)		45.45
Females not using tobacco		45.45
Methods of using tobacco:		
Patients who smoke only		69.82
Patients who chew only		6.31
Patients who smoke and chew		23.5
Patients who use snuff		0.35
Total number of smokers		93.33
Total number of chewers		29.82
Total number of snuffers		0.35
Methods of smoking:		
Pipe only		40.69
Cigars only		19.18
Pipe and other methods and with chewing		37.79
Cigars with other methods and with chewing		31.97
Total number of pipe smokers		78.48
Total number of cigar smokers		51.16
Total number of cigaret smokers		1.16
History of injury		8.38
		Years
Average duration of lesion		2.58
Longest duration of lesion		28.00
Shortest duration of lesion		0.08
		Cm.
Greatest diameter		12.5
Average greatest diameter		2.4
Origin of lesion:		Per Cent.
Lower lip		95.69
Upper lip		3.55
Left angle of mouth		0.56
Right angle of mouth		0.18
Lower lip:		
Left lower lip		43.60
Right lower lip		38.64
Middle lower lip		17.75
Upper lip:		
Left upper lip		53.33
Right upper lip		33.33
Middle upper lip		13.33

TABLE 2.—FIVE HUNDRED MEN WITHOUT EPITHELIOMA OF THE LIP

Average age, years	36.07
	Per Cent.
Users of tobacco	78.6
Nonusers of tobacco	21.4
Methods of using tobacco:	Per Cent.
Smoke only	82.95
Chew only	4.32
Smoke and chew	12.72
Snuff	0.20
Total number of smokers	95.67
Total number of chewers	17.04
Total number of snuffers	0.20
Methods of smoking:	
Pipe only	6.11
Cigars only	16.48
Cigarets only	26.32
Pipe and other methods, and chewing	31.91
Cigars and other methods, and chewing	42.02
Cigarets and other methods, and chewing	30.05
Total number of pipe smokers	38.03
Total number of cigar smokers	58.51
Total number of cigaret smokers	59.04

TABLE 3.—TREATMENT ELSEWHERE IN SQUAMOUS-CELL EPITHELIOMA OF THE LIP

	Per Cent.
Nonsurgical:	
1. One or more treatments alone or in various combinations of acids, carbon dioxid, copper sulphate, electricity, mercury, paste or plaster, potassium iodid, radium, roentgen ray, scarlet red, shoemakers' wax, and silver nitrate	29.05
2. Paste or plaster alone or in combination with other nonsurgical treatments	51.28
3. Caustics (acids or silver nitrate) alone or in combination with other nonsurgical treatments	35.89
4. Roentgen ray alone or in combination with other nonsurgical treatments	18.58
5. Paste or plaster alone or in combination with other nonsurgical treatments (proportion of all epitheliomas of lip)	14.89
6. Caustics (acids or silver nitrate) alone or in combination with other nonsurgical treatments (proportion of all epitheliomas of lip)	10.42
7. Roentgen ray alone or in combination with other nonsurgical treatments (proportion of all epitheliomas of lip)	5.4
Surgical:	
1. One or more operations	17.87
2. Excision of growth from lip without removing lymph nodes	53.12
3. Excision of V from lip without removing lymph nodes	5.2
4. Excision of growth and one or more groups of lymph nodes	16.66
5. Excision of V from lip and one or more groups of lymph nodes	6.25
6. Miscellaneous	18.75
Surgical and nonsurgical:	
1. One or more operations and one or more treatments with acids, carbon dioxid, etc., alone or in various combinations	4.65
2. Operations without treatment with acids, carbon dioxid, etc., before or after operation	13.22
3. Treatment with acids, carbon dioxid, etc., without operation	24.39
4. Operation and treatmeut with acids, carbon dioxid, etc.	37.61

total number of pipe smokers has dropped to 38.03 per cent., and the total number of cigaret smokers has risen to 59.04 per cent.

10. A history of injury plays a negligible part.

TABLE 4.—PATIENTS OPERATED ON AT THE MAYO CLINIC

	No.
Cases (96.08 per cent. of 537)	516
1. Excision of submental lymph nodes, submaxillary lymph nodes and salivary glands of both sides, and V-shaped excision of epithelioma of the lip (one operation) (39.34 per cent. of 516).	203
2. V-shaped or quadrilateral shaped excision of epithelioma of the lip (10.85 per cent. of 516)	56
3. Excision of submental lymph nodes, submaxillary lymph nodes, and salivary glands of both sides and quadrilateral shaped excision of epithelioma of the lip (one operation) (4.84 per cent. of 516)	25
4. Excision of submental lymph nodes and submaxillary lymph nodes and salivary glands on one side, and V-shaped excision of epithelioma of the lip (one operation) (3.29 per cent. of 516).	17
5 Unilateral block dissection (one operation) (2.9 per cent. of 516)	15
6 Miscellaneous (various combinations of operations, cauteries, excisions of specimens for diagnosis, at one time or at different times) (38.76 per cent. of 516)	200
REMOVAL OF LYMPH NODES AND SALIVARY GLANDS	
Cases	449
1. Submental lymph nodes (97.1 per cent. of 449)	436
2. Submaxillary lymph nodes and salivary glands (unilateral) (12.91 per cent. of 449)	58
3. Submaxillary lymph nodes and salivary glands (bilateral) (84.18 per cent. of 449)	378
4. Cervical lymph nodes (16.7 per cent. of 449)	75
5. Block dissections (alone or combined with other operations) (10.02 per cent. of 449)	45
6. Cases in which the lymph nodes were removed months or years after the removal of the epithelioma of the lip (2.44 per cent. of 449)	11
7. Lymph nodes removed (one or more groups) (87.01 per cent. of 516)	449
8. Cases in which no lymph nodes were removed (12.98 per cent. of 516)	67
PATIENTS WITH INOPERABLE EPITHELIOMA	
Cases (3.9 per cent. of 537)	21

TABLE 5.—PATHOLOGIC FINDINGS IN CASES IN WHICH LYMPH NODES AND SUBMAXILLARY SALIVARY GLANDS WERE REMOVED

	No.	Per Cent.
Cases	449	
No metastasis found	344	76.62
Metastasis found	105	23.38
Submaxillary lymph nodes alone (one side)	44	41.90
Submaxillary lymph nodes and salivary glands (one side)	13	12.38
Submaxillary lymph nodes (one side) and submental lymph nodes	7	6.66

TABLE 5—*Continued*

	No.	Per Cent.
Submaxillary lymph nodes, salivary glands, and superior superficial cervical lymph nodes (one side)	6	5.71
Submental lymph nodes alone	5	4.76
Submaxillary lymph and superficial cervical lymph nodes (one side)	6	5.71
Submaxillary lymph nodes (both sides) and submental lymph nodes	5	4.76
Submaxillary lymph nodes (both sides), submental and anterior jugular lymph nodes (one side)	3	2.85
Miscellaneous (submaxillary lymph nodes and salivary glands, submental, cervical, parotid, supraclavicular and peribronchial lymph nodes; lung and liver, alone or in various combinations	16	15.23
Submaxillary lymph nodes, total involvement	92	87.61
Submaxillary salivary glands, total involvement	23	21.90
Submental lymph nodes, total involvement	26	24.76
Cervical lymph nodes (one or more groups)	26	24.76
Superior deep cervical nodes	3	7.89
Inferior deep cervical nodes	3	7.89
Exterior jugular nodes	24	63.15
Anterior cervical nodes	8	21.05
Supraclavicular nodes, total involvement	1	0.95
Parotid lymph nodes, total involvement	1	0.95
Peribronchial nodes, total involvement	2	1.90
Lung, total involvement	1	0.95
Liver, total involvement	1	0.95
Submaxillary lymph nodes, total involvement on both sides	13	12.38
Cervical nodes, total involvement on both sides	2	1.90

TABLE 6.—GRADE OF FIVE HUNDRED AND THIRTY-SEVEN CASES ON A BASIS OF 1 TO 4, ACCORDING TO CELLULAR ACTIVITY

	No.	Per Cent.
Grade 1	85	15.82
Grade 2	333	62.01
Grade 3	113	21.04
Grade 4	6	1.11

DURATION AND SIZE OF EPITHELIOMA ACCORDING TO GRADE

	Grade 1	Grade 2	Grade 3	Grade 4
	Years	Years	Years	Years
Longest duration	10.00	25.00	28.00	2.00
Shortest duration	0.10	0.08	0.08	0.91
Average duration	1.43	2.77	3.33	1.29
	Cm.	Cm.	Cm.	Cm.
Largest size	5.00	10.00	7.50	2.00
Smallest size	0.20	0.30	0.20	1.80
Average size	1.23	2.28	3.25	1.9

EPITHELIOMA PRECEDED BY ULCER

	No.	Per Cent.
Grade 1	52	15.29
Grade 2	225	66.17
Grade 3	60	17.64
Grade 4	3	0.88

PROPORTION OF EACH GRADE PRECEDED BY ULCER

Grade 1	61.17	per cent. of 85
Grade 2	67.56	per cent. of 333
Grade 3	53.09	per cent. of 113
Grade 4	50.00	per cent. of 6

INOPERABLE EPITHELIOMA ACCORDING TO GRADE

Grade 1	Grade 2	Grade 3	Grade 4
0	12	7	2

15.82 per cent.; Grade 2, 62.01 per cent.; Grade 3, 21.04 per cent., and Grade 4, 1.11 per cent.

20. The average duration of the lesion according to grade is longest in Grade 3, 3.33 years, and shortest in Grade 4, 1.29 years.

TABLE 7.—RESULTS

GENERAL ULTIMATE RESULTS

Patients traced (operable, 306; inoperable, 8) (58.47 per cent. of total)	314
Patients operated on	306
Patients dead (40.52 per cent.)	124
Patients alive (59.47 per cent.)	182
Good result (no recurrence (92.85 per cent. of 182)	169
Fair result (slight recurrence) (6.04 per cent. of 182)	11
Bad result (no improvement) (1.09 per cent. of 182)	2

DURATION OF LIFE SINCE LAST OR ONLY OPERATION, ACCORDING TO RESULT

	Good Result	Fair Result	Bad Result
	Years	Years	Years
Longest	14.39	13.68	2.80
Shortest	1.25	0.96	0.49
Average	7.76	6.8	1.65

MORTALITY

Deaths (42.05 per cent. of 314)	132
Deaths of patients with operable epithelioma (93.93 per cent. of 132)	124
Deaths of patients with inoperable epithelioma (6.06 per cent. of 132)	8

CAUSE OF DEATH OF PATIENTS OPERATED ON: DATA FROM RELATIVE, HOME PHYSICIAN, OR PATHOLOGIC RECORDS OF THE CLINIC

	No.	Per Cent.
Known cause	99	
Cancer of the lip	63	63.63
Heart disease	5	5.05
Nephritis	5	5.05
Pneumonia	4	4.04
Stomach trouble	3	3.03
Paralysis	3	3.03
"Following operation elsewhere"	3	3.03
Fall	2	2.02
Carcinoma of the stomach	1	1.01
Tumor of the stomach	1	1.01
Abdominal tumor	1	1.01
Diabetes	1	1.01
Carcinoma of the sigmoid	1	1.01
Sepsis	1	1.01
Tuberculosis	1	1.01
Hepatic disease	1	1.01
Cardiac and hepatic disease	1	1.01
Sarcoma of the liver	1	1.01
Lung trouble	1	1.01
Unknown	25	

CAUSE OF DEATH OF PATIENTS WHO DIED IN THE MAYO CLINIC (ALL OPERABLE)

Chronic nephritis and arteriosclerosis (more than 2 years after operation)	1
Epithelioma and abscess of the neck (52 days after operation)	1
Epithelioma (25 days and 4 months, respectively, after operation)	2
Pneumonia (few days after operation)	3
Sepsis (12 days after operation)	1
Total (1.55 per cent. of 516)	8
Actual operative mortality (0.77 per cent. of 516)	4

TABLE 8.—TOBACCO USERS OPERATED ON

	Grade 1	Grade 2	Grade 3	Grade 4
Number of patients	37	118	37	3
Patients living	34 (91.81% of 37)	92 (77.96% of 118)	10 (27.02% of 37)	
Patients living, good result	33 (97.05% of 34)	85 (92.39% of 92)	10 (100% of 10)	
Patients living, fair result	1 (2.94% of 34)	6 (6.52% of 92)		
Patients living, poor result		1 (1.08% of 92)		
Patients dead	3 (8.10% of 37)	26 (22.63% of 118)	27 (72.97% of 37)	3 (100% of 3)
Cause unknown		6	5	1
Good result	2 (66.66% of 3)	6 (30.00% of 20)	7 (31.81% of 22)	
Fair result	1 (33.33% of 3)			
Poor result		14 (80.00% of 20)	15 (68.18% of 22)	2 (100% of 2)

	Per Cent.
Total good result (patient recovered from epithelioma and is living, or recovered from epithelioma and died from other cause)	78.14
Total fair result (patient living with slight recurrence or died from other cause)	4.37
Total poor result (patient lived with no improvement or died from epithelioma)	17.48

TABLE 9.—NONUSERS OF TOBACCO OPERATED ON

	Group 2	Group 3	Group 4
Number of patients	7	37	7
Patients living	6 (85.71% of 7)	29 (78.37% of 37)	4 (57.14% of 7)
Patients living, good result	6 (100% of 6)	29 (100% of 29)	2 (50.00% of 4)
Patients living, fair result			2 (50.00% of 4)
Patients dead	1 (14.28% of 7)	8 (21.62% of 37)	3 (42.85% of 7)
Cause unknown		1	
Good result	1 (100% of 1)	5 (71.42% of 7)	
Poor result		2 (28.57% of 7)	3 (100% of 3)

TOTAL RESULTS

	Per Cent.
Total good result (patient recovered from epithelioma and is living, or recovered from epithelioma and died from other cause)	86.00
Total fair result (patient living with slight recurrence)	4.00
Total poor result (patient died from epithelioma)	10.00

TABLE 10.—PATIENTS OPERATED ON TREATED WITH PASTES, PLASTERS, ACIDS, ETC., BEFORE ENTERING THE CLINIC

Patients concerning whom information has been received				94
Patients living (53.19 per cent. of 94)				50
	Grade 1	Grade 2	Grade 3	Grade 4
Patients living, good result	5 (11.11% of 45)	34 (75.55% of 45)	6 (13.33% of 45)	
Patients living, fair result		1 (33.33% of 3)	2 (66.66% of 3)	
Patients living, poor result		1 (50.00% of 2)	1 (50.00% of 2)	
Patients dead				44 (46.80% of 94)
Cause unknown		4	3	
Good result		5 (55.55% of 9)	4 (44.44% of 9)	
Poor result		9 (32.14% of 28)	16 (57.14% of 28)	3 (10.71% of 28)

TOTAL RESULTS

Total good result (patient recovered from epithelioma and is living, or recovered from epithelioma and died from other cause)	62.06% of 87
Total fair result (patient living with slight recurrence)	3.44% of 87
Total poor result (patient living with no improvement or died from epithelioma)	34.48% of 87

TABLE 11.—PATIENTS OPERATED ON NOT TREATED WITH PASTES, PLASTERS, ACIDS, ETC., BEFORE ENTERING THE CLINIC

Patients concerning whom information has been received				212
Patients living (61.79 per cent. of 212)				131
	Grade 1	Grade 2	Grade 3	Grade 4
Patients living, good result	34 (27.64% of 123)	83 (67.47% of 123)	6 (4.87% of 123)	
Patients living, fair result	1 (12.50% of 8)	7 (87.50% of 8)		
Patients dead				81 (38.20% of 212)
Cause unknown		10	9	1
Good result	4 (16.00% of 25)	17 (68.00% of 25)	4 (16.00% of 25)	
Fair result	1 (100.00% of 1)			
Poor result		18 (51.30% of 35)	17 (48.45% of 35)	

TOTAL RESULTS

Total good result (patient recovered from epithelioma and is living, or recovered from epithelioma and died from other cause)	77.08% of 192
Total fair result (patient living with slight recurrence or died from other cause)	4.68% of 192
Total poor result (patient died from epithelioma)	18.22% of 192

TABLE 12.—PATIENTS WITH METASTASIS OPERATED ON

Patients concerning whom no information was received	36 (34.29% of 105)
Patients from whom information was received	69 (65.71% of 105)
Patients living	12 (17.39% of 69)

	Grade 1	Grade 2	Grade 3	Total Number of Good Results
Patients living, good results*	.....	5 (50% of 10)	5 (50% of 10)	10 (83.33% of 12)
Patients living, fair result*	.....	.....	1 (100% of 1)	
Patients living, poor result*	.....	.....	1 (100% of 1)	

DURATION OF LIFE OF PATIENTS WITH GOOD RESULT FROM LAST OR ONLY OPERATION

Longest	11.73 years
Shortest	3.29 years
Average	6.18 years

Patients dead	57 (82.6% of 69)

Grade 1	Grade 2	Grade 3	Grade 4
.....	15 (34.09% of 44)	26 (59.09% of 44)	3 (6.81% of 44)

	Years
Longest duration of life from last or only operation of patients who died from epithelioma	2.5
Shortest duration of life from last or only operation of patients who died from epithelioma	0.066
Average duration of life from last or only operation of patients who died from epithelioma	0.79
Longest duration of life from last or only operation of patients who died from epithelioma or other cause	4.88
Shortest duration of life from last or only operation of patients who died from epithelioma or other cause	0.016
Average duration of life from last or only operation of patients who died from epithelioma or other cause	0.86

CAUSE OF DEATH

Epithelioma	44 (91.66% of 48)
Lung trouble	1 (2.08% of 48)
Sepsis	1 (2.08% of 48)
Heart disease	1 (2.08% of 48)
Pneumonia	1 (2.08% of 48)
Not stated	9

* In the ten patients with metastasis who reported a good result, and in the one who reported a fair result, the submaxillary lymph nodes on only one side were involved. In the one patient who reported a poor result, the submaxillary lymph nodes and the salivary gland on only one side were involved.

TABLE 13.—PATIENTS WITH METASTASIS IN SUBMAXILLARY LYMPH NODES ON ONE SIDE ONLY

Patients concerning whom no information was received	14 (30.81% of 44)	Patients living, fair result	1 (9.09% of 11)
Patients concerning whom information was received	30 (69.18% of 44)	Patients dead	19
Patients living	11	Patients dead from epithelioma	14 (82.35% of 17)
Patients living, good result	10 (90.9% of 11)	Patients dead from other cause	3 (17.64% of 17)
		Patients dead from cause not stated	2

TABLE 14.—PATIENTS WITHOUT METASTASIS OPERATED ON

Patients concerning whom no information was received	146
Patients concerning whom information was received	198
Patients living (76.26% of 198)	151

	Grade 1	Grade 2	Grade 3	Total Number of Good Results
Patients living, good result	35 25.00% of 140)	99 (70.71% of 140)	6 (4.28% of 140)	140 (92.71% of 151)
Patients living, fair result	1 (10.00% of 10)	8 (80.00% of 10)	1 (10.00% of 10)	
Patients living, poor result	.....	1 (100% of 1)		
Patients dead	.....	.....	.....	47 (23.73% of 198)
Cause unknown	.....	10		
Good result	3 (12.50% of 24)	18 (75.00% of 24)	3 (12.50% of 24)	
Fair result	1 (100% of 1)			
Poor result	.....	9 (75.00% of 12)	3 (25.00% of 12)	
Total good result (patient recovered from epithelioma and is living or recovered from epithelioma and died from other cause)				164 (87.23% of 188)
Total fair result (patient living with slight recurrence, or died from other cause)				11 (5.85% of 188)
Total poor result (patient living with no improvement, or died from epithelioma)				13 (6.91% of 188)

TABLE 15.—PATIENTS WITH AND WITHOUT METASTASIS OPERATED ON

	Grade 1	Grade 2	Grade 3	Grade 4
Patients with metastasis		39 (37.14% of 105)	63 (60.00% of 105)	3 (2.85% of 105)
Patients without metastasis	67 (19.47% of 344)	248 (72.09% of 344)	29 (8.43% of 344)	

DURATION OF LESION BEFORE EXAMINATION AT CLINIC

	Years		Years
Longest duration (patient with metastasis)	28.00	Patient without metastasis	25.00
Shortest duration (patient with metastasis)	0.16	Patient without metastasis	0.08
Average duration (patient with metastasis)	3.27	Patient without metastasis	2.40

SIZE OF LESION AT THE TIME OF EXAMINATION AT THE CLINIC

	Cm.		Cm.
Largest size (patient with metastasis)	12.5	Patient without metastasis	10.00
Smallest size (patient with metastasis)	1.0	Patient without metastasis	0.2
Average size (patient with metastasis)	3.74	Patient without metastasis	2.01

ASSOCIATION OF EPITHELIOMA OF THE LIP WITH OTHER MALIGNANT NEOPLASMS

	Cases
Nonmelanotic melano-epithelioma on shoulder	1
Squamous-cell epithelioma of cheek	1
Squamous-cell epithelioma of bladder	1
Basal-cell epithelioma of eyelid	1
Adenocarcinoma of sigmoid	1
	5 (0.93% of 537)

TABLE 16.—DURATION OF LIFE AFTER OPERATION OF PATIENTS WITHOUT METASTASIS

ACCORDING TO GRADE

Good result:	Grade 1	Grade 2	Grade 3
Number of patients	35	98	6
	Years	Years	Years
Longest duration	14.39	14.31	12.22
Shortest duration	1.73	1.25	4.3
Average duration	7.59	7.54	7.17
Fair result:			
Number of patients	1	8	1
	Years	Years	Years
Longest duration	4.39	13.68	7.32
Shortest duration	.....	0.96	
Average duration	.....	7.54	

DURATION OF LIFE AFTER OPERATION OF PATIENTS OF ALL GRADES

	Good Result	Fair Result	Poor Result
	Years	Years	Years
Longest duration	10.19	.....	4.51
Shortest duration	0.36	.....	0.51
Average duration	4.47	6.73	1.85

DURATION OF LIFE AFTER OPERATION OF ALL PATIENTS WITHOUT METASTASIS

	Years
Longest duration	10.19
Shortest duration	0.36
Average duration	3.68

DURATION OF LIFE OF PATIENTS OF ALL GRADES

	Good Result	Fair Result
	Years	Years
Longest duration	14.39	13.68
Shortest duration	1.25	0.96
Average duration	7.53	7.2

DURATION OF LIFE AFTER OPERATION OF PATIENTS WITHOUT METASTASIS WHO ARE DEAD

Good result—Patients did not die from epithelioma:

	Grade 1	Grade 2	Grade 3
Number of patients	3	18	3
	Years	Years	Years
Longest duration	5.8	10.19	9.3
Shortest duration	3.5	0.36	2.02
Average duration	4.28	4.24	6.07

Fair result—Patients did not die from epithelioma but had slight recurrence:

Number of patients	1
	Years
Longest duration	6.93

Poor result—Patient died from epithelioma:

	Grade 2	Grade 3
Number of patients	3	3
	Years	Years
Longest duration	4.51	1.52
Shortest duration	1.00	0.51
Average duration	2.15	0.95

TABLE 17.—RESULTS FOLLOWING OPERATION ACCORDING TO GRADE

	Grade 1	Grade 2	Grade 3	Grade 4
Information received from patients operated on	45 (52.94% of 85)	192 (59.81% of 333)	65 (62.26% of 113)	4 (100% of 4)
Patients living	40 (88.88% of 45)	128 (66.66% of 192)	16 (24.6% of 65)	
Patients living, good result	39 (97.5% of 40)	119 (92.96% of 128)	13 (81.25% of 16)	
Patients living, fair result	1 (2.5% of 40)	8 (6.25% of 128)	2 (12.50% of 16)	
Patients living, poor result	.....	1 (0.78% of 128)	1 (6.25% of 16)	
Patients dead	5 (11.12% of 45)	64 (33.33% of 192)	49 (75.38% of 113)	4 (100% of 4)
Good result	4 (80.00% of 5)	23 (45.09% of 51)	6 (15.78% of 38)	
Fair result	1 (20.00% of 5)			
Poor result	.....	28 (54.90% of 51)	32 (84.21% of 38)	4 (100% of 4)
Not stated	.....	13	11	
Total good result (patient recovered from epithelioma and is living or recovered from epithelioma and died from other cause)	43 (95.55% of 45)	142 (79.32% of 179)	19 (35.18% of 54)	
Total fair result (patient living with slight recurrence or died from other cause)	2 (4.45% of 45)	8 (4.46% of 179)	2 (3.70% of 54)	
Total poor result (patient living with no improvement or died from epithelioma)	.....	29 (16.20% of 179)	33 (61.11% of 54)	4 (100% of 4)
Total result not stated	.....	13	11	

21. The average size of the lesion according to grade is largest in Grade 3, and smallest in Grade 1.

22. Of the patients operated on and traced, 40.52 per cent. are dead and 59.47 per cent. are alive.

Fig. 12 (a 74162).—Grade 4 epithelioma of the liver secondary to epithelioma of the right side of the upper lip; no differentiation; numerous mitotic figures; high degree of malignancy; the patient died four and one-half months after the last operation, and eleven months after the onset of the disease, with metastatic epithelioma of the lymph nodes of the right side of the neck, right peritracheobronchial nodes, right lung, and liver: *a*, mitotic figures.

23. Of the living patients, 92.85 per cent. report a good result, having been free from the disease on an average of 7.76 years.

24. Of the patients operated on who have died, concerning whom information has been received, 63.63 per cent. died from epithelioma.

25. Eight, or 1.55 per cent., of the patients who were operated on died in the clinic, while the actual operative mortality was only 0.77 per cent.

26. The users of tobacco who were operated on did not obtain quite so good total good results as the nontobacco users; 78.14 per cent. in the former, and 86 per cent. in the latter.

27. In the inoperable cases, the nontobacco users reached as high as 30.76 per cent.

28. The patients who were treated with pastes, plasters, etc., before entering the clinic did not get such good total good results as those who were not so treated; 62.06 per cent. in the former and 77.08 per cent. in the latter; moreover, 31.91 per cent. of the former who were operated on had metastasis, while only 19.48 per cent. of the latter operated on had metastasis.

29. Of the patients with metastasis, 17.39 per cent. are living and 82.6 per cent. are dead.

30. Of the living who had metastasis, 83.33 per cent. report a good result. In these patients the submaxillary lymph nodes on only one side were involved.

31. No patient with the cervical nodes or more than one group of any lymph nodes involved has been reported living.

32. Of the patients reported dead who had metastasis, 91.66 per cent. died from epithelioma.

33. If a patient has the submaxillary lymph nodes on one side only involved, he has a 1 to 3 chance of getting a good result, and will be living and well on an average of 6.18 years after operation.

34. Of the patients operated on in whom no metastasis was demonstrated, 76.26 per cent. are living, and 23.73 per cent. are dead; of the living, 92.71 per cent. report a good result.

35. The average duration of the lesion in the patients with metastasis is 3.27 years, as compared with 2.40 years in those without metastasis; the average size of the lesion is 3.74 cm. in the patients with metastasis, as compared with 2.01 cm. in those without metastasis.

36. Among the known causes of death, deaths from epithelioma were as follows: none of Grade 1; 54.90 per cent. of Grade 2; 84.21 per cent. of Grade 3, and 100 per cent. of Grade 4.

37. Some malignant neoplasm was associated with the epithelioma of the lip in 0.93 per cent. of the patients.

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STUDIES IN CLINICO–PATHOLOGIC STANDARDIZATION AND EFFICIENCY[1]

I. LEGITIMATE ACTUAL ERROR IN DIAGNOSIS OF MAMMARY CONDITIONS

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A COMPARATIVE examination of the clinical and pathological diagnoses in the following series of 1800 mammary pathological conditions operated upon in this clinic reveals certain items in medical efficiency of value from several standpoints.

NUMBER OF PATHOLOGICAL DIAGNOSIS

Clinical Diagnosis	Carcinoma	Fibro-adenoma	Intracanalicular Fibro-adenoma	Chronic Mastitis	Cyst	Total
Carcinoma	722	7	0	27	7	763
Epithelioma	2	0	0	0	0	2
Carcinoma?	90	12	0	38	17	157
Sarcoma?	3	0	0	1	0	4
Sarcoma	1	1	0	0	1	3
Adenoma	10	34	10	25	9	88
Fibro-adenoma	5	58	9	3	4	79
Intracanalicular fibroma	0	0	3	0	0	3
Fibroma	0	10	10	4	0	24
Cyst adenoma	0	3	1	1	0	5
Tumor	44	83	31	88	49	295
Benign	6	15	0	5	4	30
Benign?	2	0	0	2	2	6
Nodules	1	3	1	3	0	8
Cyst	6	9	0	10	12	37
Cyst?	0	0	0	0	3	3
Chronic mastitis	9	24	10	139	8	190
Chronic mastitis?	1	0	0	3	0	4
Papilloma	0	0	0	1	0	1
Ulcer	1	0	0	0	0	1
Tuberculosis	2	0	0	0	0	2
Abscess	2	0	0	0	0	2
Myxoma	0	0	0	0	1	1
No diagnosis	26	35	1	26	4	92
Total	933	294	76	376	121	1800

This table presents the following detailed facts.

PERCENTAGE OF ACTUAL ERROR

	Total Number	Percentage
Mammary carcinomata diagnosed in the surgical laboratory	933	
Mammary carcinomata diagnosed benign by the clinician	41	4
Mammary carcinomata not positively diagnosed by clinicians	170	18
Clinical diagnoses of carcinoma in series	763	
Clinical diagnoses of carcinoma which were incorrect	41	5
Chronic mastitides diagnosed in the surgical laboratory	376	
Chronic mastitides diagnosed a malignant condition by the clinician	28	7
Clinical diagnoses of chronic mastitis which were incorrect	51	26
Clinical diagnoses of chronic mastitis which were carcinoma	9	4
Fibro-epithelial neoplasms diagnosed in surgical laboratory	370	
Fibro-epithelial neoplasms diagnosed a malignant condition	8	2
Clinical diagnoses of fibro-epithelial neoplasms	200	
Clinical diagnoses of fibro-epithelial neoplasms which were a malignant condition	15	7
Cysts diagnosed in the surgical laboratory	121	
Cysts diagnosed carcinoma or sarcoma by clinician	8	6
Clinical diagnoses of cyst	37	
Clinical diagnoses of cyst which were carcinoma	6	16
Clinical diagnoses of adenoma	88	
Clinical diagnoses of adenoma which were carcinoma	10	11
Clinical diagnoses of fibro-adenoma	79	
Clinical diagnoses of fibro-adenoma which were carcinoma	5	6
Clinical diagnoses of benign	30	
Clinical diagnoses of benign which were carcinoma	6	20

The actual error consists of a clinical diagnosis of a malignant condition when a benign condition really exists or vice versa. In these errors the indicated operation would be either too radical or not radical enough; the patient would be a victim of too little or too much surgery. Such actual error from a clinical diagnostic standpoint is certainly inevitable and unavoidable from the nature of the pathologic conditions involved, especially since it is a physical impossibility always to differentiate benign from malignant conditions by any known clinical methods. The nature of certain advanced pathologic conditions in the breast are very evident to the experienced clinician, but that there are conditions the diagnoses of which are certainly not evident is clearly revealed in the table presented above. These uncertain conditions are apparently more numerous than the ordinary professional impression seems to convey.

Legitimate as the error is from the standpoint of the insufficiency of signs, symptoms, and clinical history, it is absolutely illegitimate when viewed from the standpoint of surgical pathologists who unfortunately are painfully inadequate in quality and quantity in the hospitals of this and other countries.

In the past this inadequacy was unavoidable on account of a lack of operative surgery in early pathologic conditions, the small number of pathologists to study early malignant conditions in association with inflammatory lesions and the scarcity of pathologists as a result of the rush of laboratory men into

[1] A series of four papers read before the Academy of Medicine, Scranton, Pennsylvania, October 19, 1916; Montour County Medical Society, Danville, Pennsylvania, October 20, 1916; and the Southern Minnesota Medical Society, December 5, 1916.

the fields of immunology, serology, and bacteriology, and lastly, the inadequacy of monetary and moral compensation sufficiently great to allow constructive, energetic men of vision to spend their lives in this branch of medicine.

Recent years have somewhat altered these circumstances. Surgeons by their own initiative and perfection of surgical technique have opened a new field for the pathologist who happens to be especially interested in the immediate clinical aspect of efficiency in therapeutics and fresh tissue research. This field presents methods which give to the surgeon during operations the same type of service which range-finders give artillerymen in battle. During operative procedure accurate gross and microscopic diagnoses may be given to the operator in from fifteen seconds to three minutes during which time no operation can be completed and no extra material risk is added to the duration of the anæsthesia.

In one organ alone, i.e., the breast, one may see efficiency in one item which in itself is positive proof of the valuable service rendered by the modern fresh tissue surgical pathologist. This item consists of the fact that out of 933 mammary carcinomata the surgical pathologist discovered during operation 211 (22 per cent) carcinomata which the clinician and surgeon had diagnosed benign or doubtful conditions. Only positively recorded clinical diagnoses are included in this number.

The practical surgeon today, however, is beginning to learn that clinical diagnoses in the breast are frequently not positive. When the surgical pathologist picks up 22 per cent of the total mammary carcinomata by means of his special training and methods he renders a service of supreme value not only to the surgeon but to the patient.

The question which arises from these facts is: Can surgical work be done on this organ efficiently and justly without such assistance? The answer is evident in the figures presented in this paper and one strongly suspects that what has been termed the legitimate error becomes an illegitimate error without such assistance. This statement may appear to be too radical in view of the fact that enough men, especially trained in surgical pathologic diagnosis, are not available to supply all of the hospitals. This does not alter, however, the truth relative to surgical and clinical efficiency.

An extensive and wordy dissertation upon this question could not emphasize this truth to any greater advantage than the figures themselves.

II. THE APPARENT ERROR IN THE DIAGNOSIS OF MAMMARY CONDITIONS

In the first article of this series a comparative analysis of the clinical and pathological diagnoses of 1800 operative pathologic mammary conditions was made from the standpoint of the legitimate actual error in clinical diagnoses. It was pointed out that while there is a definite clinical error dependent upon inadequacy of clinical methods this legitimate error becomes illegitimate from the standpoint of justice to the patient simply because such error might be avoided by the utilization of properly trained surgical pathologists in immediate conjunction with operative procedure.

While the apparent error is not of such serious moment to the patient, it occurs in a much higher percentage of clinical diagnoses than does the actual error. It consists of calling a benign condition by the name of another benign condition or a malignant condition by the name of some other malignant condition. In neither case would the error in nomenclature change the operative procedure and, therefore, would not cause the patient to undergo any unnecessary radical or insufficient treatment. It is of interest and importance only from the standpoint of efficiency of nomenclature in the transference of thought from one scientific individual to another.

Any business or military code with an error of from 8 to 50 per cent would not be tolerated and still the medical profession, which is

striving for scientific efficiency, utilizes such a code. The following figures represent the facts for one organ; i.e., the mammary gland:

	Total Number	Percentage
Chronic mastitides diagnosed in the surgical laboratory	376	
Chronic mastitides diagnosed fibro-epithelial neoplasm	33	8
Clinical diagnoses of chronic mastitis	190	
Clinical diagnoses of chronic mastitis which were fibro-epithelial neoplasms	34	17
Fibro-epithelial neoplasms diagnosed in the surgical laboratory	370	
Fibro-epithelial neoplasms diagnosed chronic mastitis	34	9
Fibro-epithelial neoplasms diagnosed some other benign condition	32	8
Cysts diagnosed in the surgical laboratory	121	
Cysts diagnosed in fibro-epithelial neoplasms	14	11
Clinical diagnoses of cyst	37	
Clinical diagnoses of cyst which were fibro-epithelial neoplasms	9	24
Clinical diagnoses of cyst which were chronic mastitis	10	27
Clinical diagnoses of adenoma	88	
Clinical diagnoses of adenoma which were chronic mastitis	25	28
Clinical diagnosis of adenoma which were fibro-epithelial neoplasms	44	50

In this series the following nomenclature was utilized by the clinicians.

[1] Adenoma
[1] Adenofibroma
Lipoma
Benign
Cyst
[1] Carcinoma
Chronic mastitis
[1] Cystic fibro-adenoma
[1] Cyst adenoma
Cystic degeneration
[1] Fibroma
[1] Fibro-adenoma
Sarcoma
[1] Fibro-myxoma
Growth
Lipoma
Lump
Myxoma
Mass
Malignant
Nodule
[1] Neuroma
No diagnosis
Papilloma
Placque
Retention cyst
Sebaceous cyst

[1] Purely pathologic terms utilized by the clinician.

These names were applied to the following pathologic conditions:

Adenofibroma
Adenoma
[1] Adenomyxofibroma
[1] Angioma
[1] Andenofibromyxoma
[1] Adenomyxoma
Benign
Cyst
[1] Cystic fibroma
Cystadenoma
[1] Chondrolipofibroma
Cystic fibro adenoma
Cystic adenofibroma
[1] Calcareous tumor
Chronic mastitis
[1] Cystic intracanalicular papillary adenofibroma
[1] Calcareous adenoma
[1] Cystic calcareous fibroma
[1] Calcareous intracanalicular adenofibroma
Carcinoma
[1] Dermoid
[1] Embryoma
Fibro-adenoma
Fibroma
Fibromyxoma
[1] Fibrolipoma
[1] Fibromyoma
[1] Fibrocystadenoma
[1] Fibromyxo-adenoma
[1] Intracanalicular myxoma
[1] Intracanalicular fibroma
[1] Intracanalicular fibro-adenoma
[1] Intracanalicular adenofibroma
[1] Intracanalicular papilloma
[1] Intracanalicular fibromyxoma
[1] Intracystic papilloma
[1] Intracanalicular myxofibroma
[1] Intraductal papilloma
[1] Intracanalicular adenomyxoma
[1] Intracanalicular fibro-adenomyxoma
[1] Intracanalicular papilloma (malignant)
Lipoma
[1] Myxofibroma
[1] Myxofibro-adenoma
Myxoma
[1] Myxo-adenofibroma
[1] Papillary cyst
[1] Papillary fibro adenoma
[1] Papillary fibrocystadenoma
[1] Pericanalicular fibroma
Sebaceous cyst.

[1] Pathologic terms not utilized by the clinician

In utilizing this nomenclature the following errors were made.

Pathologic Diagnosis	Clinical Diagnosis
Diffuse lipoma	called chronic mastitis
Cyst	called fibro-adenoma
Fibro-adenoma	called adenoma
Fibro-myxoma	called carcinoma
Adenofibroma	called fibro-adenoma
Fibro-adenoma	called retention cyst
Fibro-adenoma	called adenofibroma
Adenofibroma	called carcinoma
Fibroadenoma	called fibroma
Cystic fibro-adenoma	called myxoma
Andenofibroma	called chronic mastitis
Cystic fibro-adenoma	called chronic mastitis
Cysts	called carcinoma
Cysts	called chronic mastitis
Fibro-adenoma	called chronic mastitis
Intracanalicular fibroma	called carcinoma
Lipoma	called cyst
Papillary fibrocystadenoma	called cystadenoma
Cyst	called adenoma (early carcinoma)
Fibro-adenoma	called cystadenoma
Cystadenoma	called adenoma
Adenofibroma	called fibroma
Intracanalicular papilloma	called chronic mastitis
Intracanalicular fibro-adenoma	called fibroma
Fibrolipoma	called chronic mastitis
Intracanalicular fibro-adenoma	called adenoma
Adenofibroma	called cystadenoma
Fibrocystadenoma	called adenoma
Intracanalicular fibro-adenoma	called fibro-adenoma
Intracanalicular fibro-adenoma	called chronic mastitis
Myxoma	called neuroma
Intracanalicular adenofibroma	called fibroma
Cyst	called adenoma
Adenomyxoma	called adenoma
Lipoma	called fibroma

These facts, vivid as they are, mean something to an analytical mind which is dealing with scientific efficiency and from them the following generalization may be logically made: The medical profession is trying to adapt detailed pathologic nomenclature and terminology to conditions which do not always reveal their detailed characteristics through signs and symptoms. This usage on the part of clinicians has been the logical outcome of the natural evolution of our knowledge of medicine, but the evolution should not stop at this stage. Efficiency demands, at least, an attempt at correction.

Experience with this series of cases has taught that the clinicians and surgeons really desire certain fundamental facts in so far as the patient is concerned; they want to know whether the condition is benign or malignant and whether it is operable or inoperable. These are the essential factors which the practical surgical pathologist must face with the clinicians and surgeons. Detailed names play a very small rôle in the rendition of his assistance in such conditions.

It has been urged by some surgeons who have had some training in pathology, that

they should be able to make their own gross diagnoses. This is ideal and possible if surgeons would spend time enough in learning pathology. Six months, a year or five years of training in gross pathology will not keep a surgeon from making a high percentage of error in gross diagnoses.[1] It must be fully realized by the medical profession that in many conditions a microscopic diagnosis is absolutely necessary. This requires special training and experience far beyond that which can be obtained in the regular medical course or during internship in a laboratory or perhaps a course abroad.

Nomenclature and classifications which have been made by excellent surgeons, who were poor pathologists, have been largely responsible for much of the chaos in clinical pathology. Synonyms and classifications are almost as numerous as textbooks. There are apparently no signs, symptoms, and clinical histories which will positively differentiate any of the following conditions: adenoma, adenofibroma, cystic-fibro-adenoma, cystadenoma, fibroma, fibro-adenoma, myxoma, lipochondrofibroma and fibromyxoma. And still the clinicians and surgeons continue to utilize such terms in spite of their cognizance that the clinical differential diagnosis is impossible by any known methods.

The clinicians in this series of cases have automatically shown evidence of the inefficiency of such usage and have substituted in their practice, during recent years, the terms benign, tumor, growth, lump, nodule, and mass. To them these terms are practically synonymous and do not describe a detailed microscopic condition which they cannot see. This is a hopeful sign for scientific efficiency in medicine.

In this series of cases the clinicians refrained from using such terms as

Intracanalicular—
Myxoma,
Fibroma,
Fibro-adenoma,
Adenofibroma,
Papilloma,
Fibromyxoma,
Adenomyxoma.

These neoplasms, however, form a group which constitutes a much higher percentage of benign solid tumors of the breast than do the fibromata, adenomata, adenofibromata, fibro-adenomata, cystadenomata, myxomata and fibromyxomata, terms with which the clinician is perhaps much more familiar.

The percentage of error in terminology is greatest in the benign group of conditions. From a standpoint of clinical efficiency these mistakes represent only an apparent error and certainly do not reflect upon the clinician's ability to render scientific service to his patients.

The names sound well, but what is needed and demanded today is clear, concise, accurate and simple scientific medical practice which can be expressed in a clear, concise, accurate and simple scientific clinico-pathologic terminology and nomenclature.

[1] In a series of consecutive examinations of 1582, surgical specimens by the writers, it was absolutely necessary to make microscopic diagnoses in 29.3 per cent.

III. THE AVOIDED ERROR IN THE DIAGNOSIS OF MAMMARY CONDITIONS

In the first two papers of this series the legitimate and apparent errors in clinical diagnosis of 1800 mammary pathologic specimens were considered. It was pointed out that the legitimate error becomes an illegitimate error when surgery of the breast is not accompanied by the immediate assistance of microscopic diagnosis and that the apparent error, while of no great importance from the patient's standpoint, is a result of a clinically inefficient pathologic nomenclature.

The third type of error in this series has been called the "avoided error" by which term is meant that error which did not occur simply because the clinician utilized some doubtful or non-specific nomenclature such as carcinoma? benign? malignant? chronic mastitis? cyst? sarcoma? tumor, nodule, growth, mass and no diagnosis and left the

actual diagnosis for the surgical pathologist to make.

The frequency of such a clinical habit may be seen in the following percentages:

	Total Number	Percentage
Mammary carcinoma diagnosed in the surgical laboratory	933	
Mammary carcinoma diagnosed a possible malignant condition	96	10
Clinical diagnoses of carcinoma?	157	
Clinical diagnoses of carcinoma? which were benign	67	42
Clinical diagnoses of carcinoma? which were malignant	90	57
Chronic mastitides diagnosed in the surgical laboratory	376	
Chronic mastitides diagnosed a possible malignant condition	44	11
Chronic mastitides diagnosed "no diagnosis"	26	6
Chronic mastitides diagnosed "tumor"	88	23
Chronic mastitides diagnosed a possible malignant condition, tumor, nodule or no diagnosis	161	42
Fibro-epithelial neoplasms diagnosed in the surgical laboratory	370	
Fibro-epithelial neoplasms diagnosed a possible malignant condition	12	3
Fibro-epithelial neoplasms diagnosed "no diagnosis"	36	9
Fibro-epithelial neoplasms diagnosed "tumor"	114	30
Cysts diagnosed in the surgical laboratory	121	
Cysts diagnosed "tumor"	49	40
Cysts diagnosed carcinoma?	17	14
Cysts diagnosed benign?	2	1
Cysts diagnosed no diagnosis	4	3
Clinical diagnoses of "tumor"	295	
Clinical diagnoses of "tumor" which were a malignant condition	44	14
Clinical diagnoses of "tumor" which were a benign condition	251	86

Perhaps the most interesting feature in this group of errors is the fact that 42 per cent of the clinical diagnoses of "carcinoma?" were actually benign.

Another interesting and important feature is the apparent realization on the part of the clinician that absolute diagnoses in the breast are not possible in a great many cases.

This realization may be seen in the frequency of avoided errors which consist of "carcinomata?" 157, "sarcoma?" 4, "tumor" 295, "benign?" 6, "nodule" 8, "cyst?" 3, "chronic mastitis?" 4, and "no diagnosis" 92, a total of 569 or 31 per cent of all diagnoses. Those figures certainly show a simple truth, i.e., that the present pathologic nomenclature is quite inefficient from a clinical standpoint and suggests the necessity of a more adequate nomenclature.

IV. CLINICO-PATHOLOGIC NOMENCLATURE OF MAMMARY CONDITIONS

In the first three papers of this series it has been clearly shown that an analysis of 1800 mammary pathologic conditions from the comparative standpoint of clinical and pathologic diagnoses reveals certain diagnostic errors which prove at least three definite things:

1. A legitimate actual error (1) of from 2 to 26 per cent.

2. An apparent error (2) of from 8 to 50 per cent.

3. An avoided error (3) of from 1 to 57 percent.

Coincidently with the determination of these percentages it was shown that 31 per cent of the clinical diagnoses of mammary conditions were made with a full recognition on the part of the clinician that a positive diagnosis could not be made. It was also shown that the actual or so-called legitimate error becomes an illegitimate error if not checked during operations by the immediate services of a well-trained surgical pathologist.

The apparent and avoided errors signified one essential fact, i.e., that the present pathologic nomenclature was inadequate, inefficient and unscientific when utilized for clinical diagnoses.

In view of these facts and the necessity for greater efficiency a simple clinico-pathologic nomenclature has been utilized successfully by the writer.

For the sake of convenience all pathologic conditions in the breast may be divided into encapsulated and non-encapsulated (diffuse) conditions, the history of which is dependent upon the reaction of the component tissues of the breast regardless of the irritative or destructive agencies.

It has been shown in the breast and other organs that the aggregations of specialized and differentiated cells which we call tissues react to irritation in certain ways. Under certain conditions the tissue cells are rapidly or gradually destroyed and there is a successful or unsuccessful attempt on the part of nature at their replacement or regeneration. The success of this attempt means healing, and the unsuccessful gradual attempt is associated with the following histological pictures dependent upon the quality, quantity, and duration of action of the destructive agent:

1. Primary cytoplasia when the differentiated tissue cells are present plus an hypertrophy of the regenerative cells of the tissues.

2. Secondary cytoplasia when the differentiated cells have partially or completely disappeared plus an hyperplasia of the regenerative cells.

3. Tertiary cytoplasia when the hyperplastic regenerative cells have migrated into the surrounding stroma (4).

An unsuccessful attempt at replacement and regeneration in the presence of any acute, virulent destruction such as pyogenic infections results in abscess or necrosis and destruction of the whole organism. An unsuccessful attempt at replacement and regeneration in the presence of chronic non-virulent tissue destruction results in a neoplastic hyperplasia of the regenerative cells of one or more of the tissues without their complete differentiation into tissues, or the eventual destruction of the whole organism. It is this neoplastic hyperplasia with or without subsequent differentiation into tissues which is of importance in chronic mastitis, and benign and malignant new-growths.

It is self-evident that a new-growth of cells benign or malignant must grow from something and that the cells of any tissue which is capable of growth are the regenerative cells. In the epithelial tissue of the breast these lie between the columnar or cuboidal secretory cells and the stroma. In the connective tissue the regenerative cells are the fibroblasts. In the presence of a chronic destruction of either or both of these special tissues there is an hypertrophy of the regenerative cells. This hypertrophy is often associated with or followed by hyperplasia and sometimes by migration.

In the condition of hypertrophy there is no evidence which warrants a suggestion of clinical malignancy because practically all chronic mastitides present this picture and every clinician and pathologist knows that all chronic mastitides are not associated with either benign or malignant neoplasms.

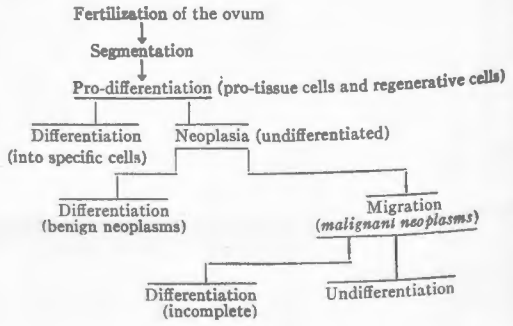
In the condition of hyperplasia of the regenerative cells the problem of malignancy or benignancy becomes more difficult because the hyperplastic regenerative cells are frequently morphologically identical with malignant cells but are still within the normal bounds of their specific tissues (5).

Who is there who has the power to say whether these growing cells will be brought back to their normal power of differentiation by means of normal tissue control or continue to grow and migrate into neighboring and distant tissues and become malignant?

In so far as the clinician, pathologist, and patient are concerned this is an indeterminate condition which definitely forms a histological line of demarcation between that which is definitely benign and that which is malignant.

The biological history of the evolution of these regenerative cells may be shown in the accompanying diagram, in which there is represented segmentation of the fertilized ovum and the production of cells which either produce, immediately, the tissues or the regenerative cells which later become differentiated into tissues. When the cells which are produced in this stage of pro-differentiation become differentiated in the normal course of embryologic development, normal tissues and a normal organism result.

It has been shown that in adult life the regenerative cells which occur in the stage of pro-differentiation in the postnatal organism do sometimes become hyperplastic (secondary cytoplasia); that they produce new-growths in which the tissues are differentiated and that they sometimes produce new-growths which consist of undifferentiated migratory cells. The new-growths with differentiation constitute the benign neoplasms. The new-growths with migration and incomplete differentiation constitute the malignant neoplasms.



These facts are true not only of epithelial tissue but also of connective or fibrous tissue and perhaps all tissues. In benign fibro-epithelial neoplasms the condition of secondary and tertiary cytoplasia also sometimes occurs, hence the presence of malignant conditions arising in the so-called fibro-epithelial neoplasms which are usually benign. In so far as the reaction of the tissues of the breast is concerned, it matters not whether they are encapsulated or non-encapsulated they react in these three degrees to chronic destruction. Upon the degree of reaction will depend the life history of the breast and consequently the whole body of which the breast is a part. Biologically in these three stages, we have cellular destruction, cellular hypertrophy, cellular hyperplasia, and cellular migration.

The regenerative cells possess certain possibilities. They reproduce specialized differentiated tissue cells, they reproduce themselves as undifferentiated cells and they migrate as undifferentiated cells. From a clinical standpoint in the condition of hypertrophy they are carrying out a normal communistic existence, i.e., producing a special tissue which is to work in conjunction with other special tissues of the multicellular organism. In the second condition they produce an indeterminate condition the end result of which cannot be prophesied by any known methods. In the third condition experience has taught us that the cells, when they are in the stroma, continue their migration even to distant organs, grow and eventually destroy the life of the organism.

Regardless of whether we call a chronic inflammatory mammary condition, chronic mastitis and benign tumors, e.g., adenomata, fibromata, adenofibromata, fibro-adenomata, fibromyxomata, myxofibromata, myxomata or intracanalicular fibro-adenomata, adenofibromata, myxomata, adenomyxomata or any other names which have been given to the various conditions or whether we call a condition Schimmelbusch's disease, Reclue's disease, abnormal involution, senile parenchymatous hypertrophy or any other of the 10 or 12 synonyms, or whether we call carcinoma scirrhus, adenocarcinoma, comedocarcinoma or carcinoma simplex or any other name, the fact relative to the conditions which are present remains simply one of reaction on the part of the cells involved and so far as the clinical, surgical, and pathological experience of the writers has been concerned the patient's welfare depends absolutely upon a decision as to whether the cytologic activity is benign, indeterminate, or malignant. The names of tumors play no great rôle. The nomenclature as it exists in textbooks does not produce a clear conception of what actually exists from the clinical standpoint. It is true that neoplasmata are grouped in textbooks into benign and malignant and under each group there is a long list of names of conditions which have been described in detail from the pathologists' standpoint but that this detailed description with its nomenclature has been of great efficiency to the clinician may be answered in the negative from the experience in this clinic. A glance at the percentages of error which has been made during the utilization of and on account of the present textbook nomenclature is sufficient to support the statements made above.

In summarizing the writer's solution of this problem it may be stated that the main object is the proper treatment of the patient which may be best accomplished by a simple realization of the fundamental facts that the history of the breast is the history of its tissues in their battle against irritants and destructive agencies of any kind and that all tissue cells react in certain ways to these agencies depending upon the quality, quantity, and duration of action. The histologic pictures of this reaction represent tissue destruction, tissue replacement, cellular regeneration, cellular neoplasia and cellular migration.

Clinical experience has taught that destruction of tissue cells may be complete and fatal to the organism or it may be incomplete and the destroyed tissues be replaced or regenerated. It may be incomplete and still great enough to prevent complete replacement or regeneration during which a new-growth (neoplasia) occurs, the cells of which may become differentiated and are benign, or remain undifferentiated migrate and are malignant. These

are the clinical effects of reaction, and it is these simple effects which should be borne in mind by the clinician, surgeon, and pathologist regardless of the name of the tumor.

The conditions of the tissues are really what the clinician desires. From this by correlation with clinical experience he may decide upon the benignancy or malignancy, the degree of treatment, and the future of the patient.

It may be definitely stated by a pathologist familiar with the stages of tissue reaction that there exists primary, secondary, or tertiary cytoplasia which have three definite clinical meanings regardless of names of tumors which do not always have definite clinical value. If the clinician or surgeon desires still to group his conditions into encapsulated and non-encapsulated then he is dealing with

Encapsulated or Non-encapsulated { Primary Secondary or Tertiary } Cytoplasia

His error then becomes dependent simply upon his ability to determine by signs, symptoms and clinical history whether he thinks a conditions is benign, malignant or doubtful. The tissue involved and the degree of involvement can only be decided by the surgical pathologist and this decision can be made during operations without added injury to the patient provided the lesion is excised instead of incised.

At this juncture clinicians will doubtless say that there are so many cases which are quite evident. True, as this is, there still remains a 5 per cent error in the diagnoses of carcinoma and a failure to discover 22 per cent of carcinomata. These percentages demand the immediate service of the laboratory. If the plan set forth in this series of papers be adhered to, the 5 per cent and 22 per cent will be done away with; the apparent error of 8 to 50 per cent will completely disappear and such non-descriptive and unscientific terms as mass, tumor, nodule, and growth and names of tumors with question marks will not be necessary in clinical diagnoses.

The medical code for pathologic conditions in the breast will be transformed from one of inefficiency to one of scientific efficiency and the patient will reap the benefit.

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2. Idem. The apparent error in the diagnosis of mammary conditions. Surg., Gynec. & Obst., 1917, xxv, 667.
3. Idem. The avoided error in the diagnosis of mammary conditions. Surg., Gynec. & Obst., 1917, xxv, 669.
4. MacCarty, Wm. Carpenter. Carcinoma of the Breast. Old Dominion M. J. and Tr. South. S. Ass., 1910, Dec.
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Tuberculosis Associated with Malignant Neoplasia

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July, 1916, pages 28-32

TUBERCULOSIS ASSOCIATED WITH MALIGNANT NEOPLASIA

REPORT OF TWENTY CASES *

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To Rokitansky[1] has been given the credit for teaching that tuberculosis and cancer are incompatible diseases; but since McCaskey,[2] in 1902, made the statement that he was strongly inclined to doubt that Rokitansky had ever held to this extreme view, it may be well to quote direct from Rokitansky's article on cyst formation:

> Cyst formation, as a new growth, is rarely found concurrent with tubercle, either in the same organ or in the same organism generally.

With regard to tuberculosis and cancer, he said:

> A similar antagonism, as shown from still more numerous observations, prevails between tubercle and carcinoma. Whenever their general correlation is susceptible of proof, cancer has seemed to succeed to tuberculosis, tubercle rarely to become developed after the extinction of cancer and its crasis.

Also:

> A corresponding result of much interest is afforded by a comparison of the scale of frequency of cancer and tubercle, as well as of several special local relations of both. They are diametrically opposed to one another, as thus:

FREQUENT	RARE
Lung tubercle	Lung cancer
Ovarium cancer	Ovarium tubercle
Salivary gland cancer	Salivary gland tubercle
Stomach cancer	Stomach tubercle
Esophagus cancer	Esophagus tubercle
Rectum cancer	Rectum tubercle
Ileum tubercle, etc.	Ileum cancer, etc.

* From the Department of Surgical Pathology, Mayo Clinic.

1. Rokitansky, C.: A Manual of Pathological Anatomy, London, Sydenham 1: 313-314, 1855.
2. McCaskey, G. W.: The Clinical Association of Cancer and Tuberculosis, with Report of a Case, Am. J. M. Sc. 124: 97-105, 1902.

From the foregoing, it is obvious that Rokitansky did not teach that the two diseases are incompatible but that an antagonism prevails. While a few writers have held to the view that an antagonism exists between active tuberculosis and cancer, by far the greater number are of the opinion that no antagonism exists. McCaskey is apparently inclined to the former

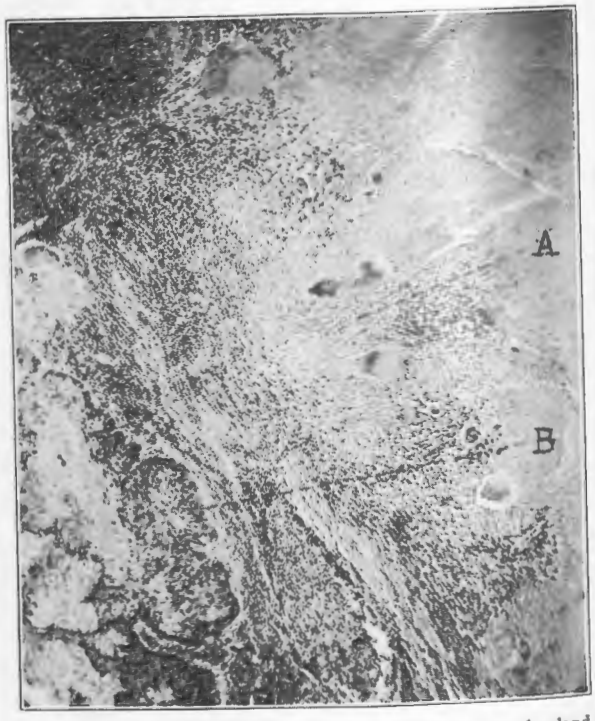

Fig. 1 (A 59139).—Tuberculosis and epithelioma in lymph gland of neck (low power): *A*, tuberculosis showing giant cells; *B*, epithelioma. The patient died.

view, and he has suggested the systematic local injection of tuberculin in the cancerous tissue in properly selected inoperable cases of cancer. Dabney,[3] writing in 1916, fourteen years later, practically agrees with McCaskey. He has injected the tuberculin in seven

3. Dabney, W. M.: Tuberculosis and Cancer: A Possible Explanation of the Long-Discussed Question of Their Mutual Antagonism with the Suggestion of the Use of Tuberculin for the Prevention of Recurrence of Cancer, M. Rec. **90**: 804-805, 1916.

cases of cancer, and in one, improvement of the patient's general condition immediately became very marked, and this improvement continued after three months or more of tuberculin therapy. Dabney used, as a basis for his argument in favor of the injection of tuberculin in cancer cases, that it would bring about a lymphocytosis in practically all cases; and as Murphy and Morton, and others have shown that lymphoid

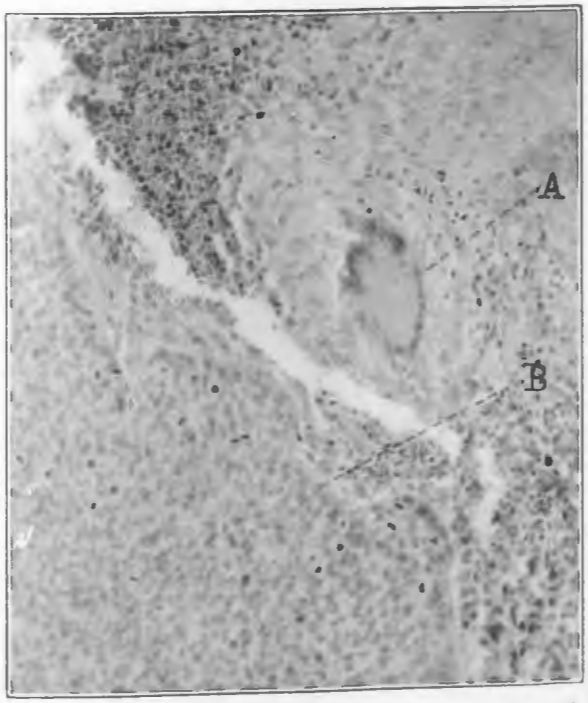

Fig. 2 (A 59139).—Same as Figure 1 (high power): *A*, giant cell of tuberculosis surrounded by epithelioid cells; *B*, epithelioma showing numerous mitotic figures.

activity is an essential factor in the immunity process of artificially engrafted cancer, it would seem that the tuberculosis that brought about a condition of lymphoid activity would exert an inhibitory influence in cancer.

From time to time the negative side of this question has been most ably defended, not only by observations made at necropsy but also from a surgical pathologic standpoint. The first and one of the most noted

defenders of the theory was Lebert.[4] Williams[5] found a history of phthisis in 151 (47.7 per cent.) of 316 cancerous families. Lubarsch,[6] in 1888, found carcinoma in 2,668 tuberculous cadavers in 117 (4.4 per cent.) instances, and in 3,868 nontuberculous cadavers he found the condition in 452 (11.7 per cent.) instances. In 569 carcinomatous cadavers he found tuberculosis in 117 (20.6 per cent.) instances, and in

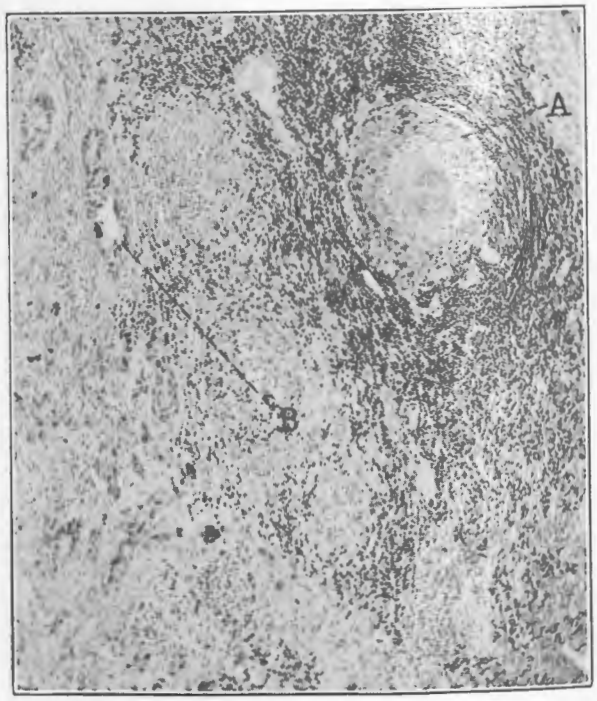

Fig. 3 (A 192320).—Tuberculosis and epithelioma in lymph gland of neck (low power): *A*, tubercle with giant cell; *B*, epithelioma. The patient's condition is unknown.

5,967 noncarcinomatous cadavers he found it in 2,551 (42.7 per cent.). His statistics indicate that carcinoma is found more often in nontuberculous than in tubercu-

4. Lebert, H.: Beiträge zur Kenntniss des Gallertkrebses, Virchows Arch. f. path. Anat. **4**: 214-215, 1852.
5. Williams, W. R.: Cancer and Phthisis as Correlated Diseases, Lancet **1**: 977, 1887.
6. Lubarsch, O.: Ueber den primären Krebs des Ileum nebst Bemerkungen über das gleichzeitige Vorkommen von Krebs und Tuberculose, Virchows Arch. f. path. Anat. **111**: 280-317, 1888.

lous persons, the proportion being about 3:1 in favor of the former. He has also shown that tuberculosis is found twice as often in noncarcinomatous as in carcinomatous persons. Moak,[7] quoting Lubarsch, mentions five possible combinations of cancer and tuberculosis:

1. Simple coincidence, the diseases having no apparent action the one on the other.
2. Metastatic carcinoma developing secondarily on a recent or old tuberculous focus.

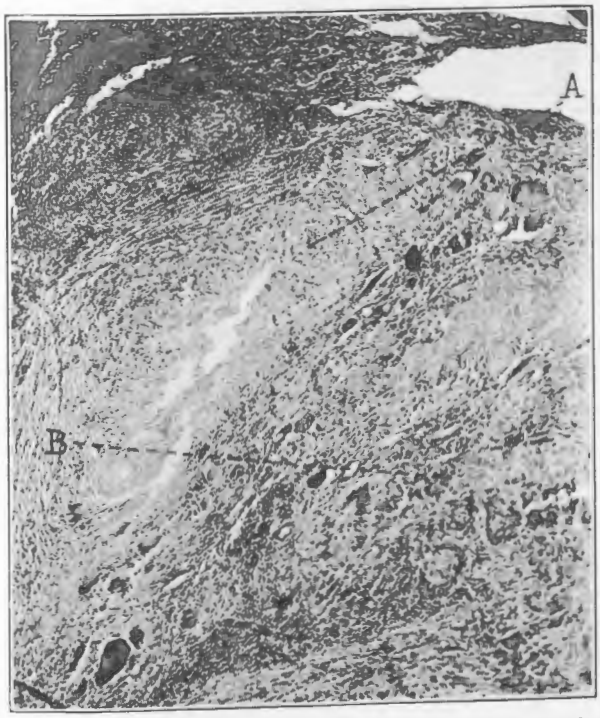

Fig. 4 (A 51290).—Tuberculosis and epithelioma in lymph gland of neck (low power): *A*, tuberculosis, showing necrotic area and giant cells; *B*, epithelioma. The patient is living and well, ninety-one months after operation.

3. A tuberculous infection becoming engrafted on a cancer in full evolution.
4. Chronic progressive tuberculosis on which develops a cancer.
5. The simultaneous development of both cancer and tuberculosis.

7. Moak, H.: On the Occurrence of Carcinoma and Tuberculosis in the Same Organ or Tissue, J. M. Res. 8: 128-147, 1902.

Naegeli,[8] in 420 necropsies on adults aged more than 18 years, showed that 93 per cent. had either active, latent or healed tuberculosis.

Hoffman's[9] statistics show that in the United States registration area for the year 1913, out of 93,293 deaths from tuberculosis, 73.39 per cent. occurred at ages under 45, and 26.61 per cent. at ages over 45, and that of 49,887 deaths from cancer at all ages, 15.46 per cent. occurred at ages under 45, and 84.54 per cent. at ages over 45.

TABLE 1.—CASES FROM THE LITERATURE OF THE RELATIONSHIP OF TUBERCULOSIS AND CARCINOMA AT NECROPSY

Author	Carcinoma	Associated Tuberculosis	Per Cent.
Cahen*	257	13	5.0
LeGoupils†.....?	632	53	8.4
Loeb‡	111	31	27.9
Lubarsch[6]	569	117	20.6
Rapok§	399	39	9.8
Sandu-Miclesco§	150	14	9.3
Schrader§	50	8	16.0
Williams[5]	166	27	16.2
	1,445	236	Average 16.3

* Cahen, cited by Lubarsch: Virchows Arch. f. path. Anat. 111:305-306, 1888.

† LeGoupils: Coincidence et rapports de la tuberculose et du cancer, Thèse de Paris, 1882, p. 38, cited by Lubarsch: Virchows Arch. f. path. Anat. 111:303, 1888.

‡ Loeb: Combination von Krebs und Tuberculose, Inaug.-Diss. München., 1889, cited by Naegeli: Virchows Arch. f. path. Anat. 148:437, 1897.

§ Cited by Naegeli: Virchows Arch. f. path. Anat. 148:436, 1897.

ANATOMIC LOCATION OF TUBERCULOSIS AND CANCER

Rokitansky and others have pointed out that these conditions are rarely found combined in certain organs, such as the esophagus, stomach, ileum, rectum, salivary glands, lungs, ovary, thyroid and pancreas. I was able to find but five positive and probable cases in which tuberculosis and cancer of the stomach were combined. The two diseases, in most instances, seem to select different anatomic points of origin, and by a metastatic process through the lymph or blood stream they meet at the starting point of one or the other, or at some point remote from their field of origin, such as the lymphatic glands.

8. Naegeli, O.: Ueber Häufigkeit, Localisation und Ausheilung der Tuberkulose, Voirchows Arch. f. path. Anat. **160**: 426-472, 1900.

9. Hoffman, F. L.: The Mortality from Cancer Throughout the World, Newark, Prudential, pp. 187-188, 1915.

Why one tissue or organ should be susceptible to malignant neoplasia or tuberculosis, and another should be, to a great extent, immune, is difficult to explain; nevertheless, such seems to be an established fact.

Tuberculosis associated with sarcoma has been reported by Ricker,[10] Trendweiler[10] and Iscovesco[10] (Moak). Tuberculosis associated with connective tissue malignant neoplasia is rare; the records of the

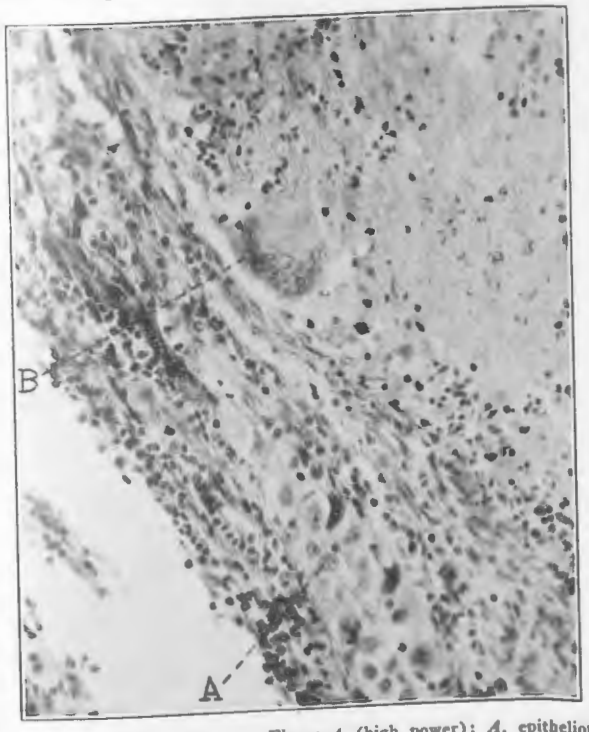

Fig. 5 (A 51290).—Same as Figure 4 (high power): *A*, epithelioma cells; *B*, giant cell of tuberculosis.

Mayo Clinic show that epithelial tissue malignant neoplasia is about nine times as frequent as connective tissue malignant neoplasia. As an indication of the frequency of the association of tuberculosis with malignant neoplasia, statistics are cited both from necropsy and surgical pathologic standpoints as in Table 1.

10. Cited by Moak: J. M. Res. **8**: 143, 1902.

CASES FROM THE LITERATURE FOUND BY THE SURGICAL PATHOLOGIST OR AT NECROPSY

Naegeli[11] reported three cases in which tuberculosis and carcinoma were associated. The first patient had carcinoma and tuberculosis of the rectum, the second carcinoma and tuberculosis of the ileum, and the third colloid carcinoma and tuberculosis of the cecum.

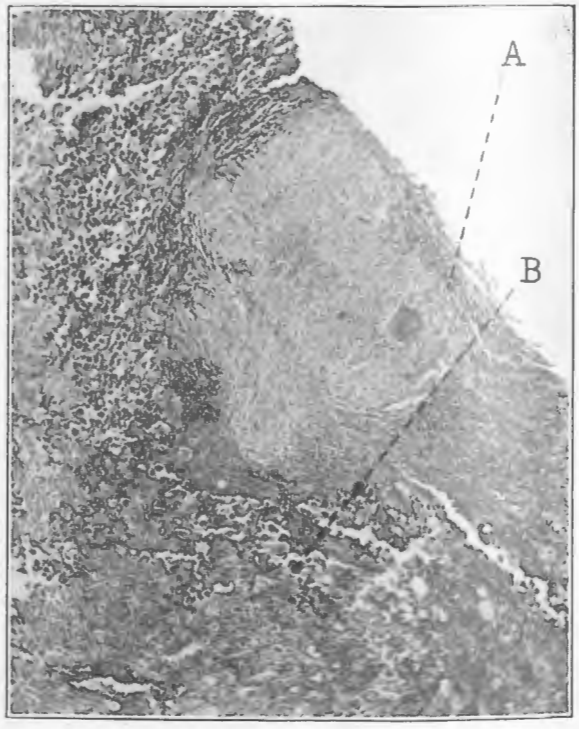

Fig. 6 (A 72500).—Tuberculosis and lymphosarcoma in lymph gland of neck (low power): *A*, tubercle with giant cell; *B*, lymphosarcoma cells. The condition of the patient is unknown.

TABLE 2.—CASES STUDIED IN THE SURGICAL PATHOLOGIC LABORATORY OF THE MAYO CLINIC

Cases	20
Males	14 (70%)
Females	6 (30%)
Average age	49 years
Oldest	77 years
Youngest	20 years
Family history of malignancy	2 (10%)
Family history of tuberculosis	3 (15%)
Personal history of tuberculosis	3 (15%)
Epithelioma of the lip	7
History of smoking	2 (28.5%)

11. Naegeli, O.: Die Combination von Tuberculose und Carcinom, Virchows Arch. f. path. Anat. **148**: 435-448, 1897.

TYPES OF MALIGNANT NEOPLASMS

Squamous cell epithelioma	13 (65%)
Melano-epithelioma	1 (5%)
Adenocarcinoma	5 (25%)
Lmyphosarcoma	1 (5%)
Average duration	21.5 months
Average greatest diameter	4.2 cm.
Greatest diameter	15 cm.
Smallest diameter	1 cm.

PRIMARY LOCATIONS OF MALIGNANT NEOPLASMS

Lip	7 (35%)
Cheek	3 (15%)
Breast	2 (10%)
Near angle of jaw	2 (10%)
Ear	1 (5%)
Nose	1 (5%)
Neck (lymph glands)	1 (5%)
Parotid gland	1 (5%)
Transverse colon	1 (5%)
Rectum	1 (5%)
Total with metastasis	11 (55%)
Total without metastasis	9 (45%)

LOCATIONS OF METASTATIC NEOPLASMS

Lymph glands of neck	9 (81.8%)
Lymph glands of axilla	2 (18.2%)

METASTASES TO NECK: PRIMARY LOCATIONS

Lip	4 (44.4%)
Cheek	2 (22.2%)
Ear	1 (11.1%)
Nose	1 (11.1%)
Neck	1 (11.1%)

METASTASES TO AXILLA: PRIMARY LOCATION

Breast	2 (100%)

LOCATIONS OF TUBERCULOUS PROCESSES

Lymph glands of neck	15 (75%)
Lymph glands of axilla	2 (10%)
Lymph glands of mesentery	1 (5%)
Omentum and peritoneum	1 (5%)
Lip	1 (5%)

THE RELATION OF THE ASSOCIATION OF TUBERCULOSIS AND MALIGNANT NEOPLASIA

In the same organ or tissue		8 (40%)
Lymph glands of neck (lymphosarcoma, primary 1)	7 (87.5%)	
Lymph glands of axilla	1 (12.5%)	
In the same microscopic field (low power) lymph glands of neck		7 (87.5%)
		5 (25%)
In the adjacent organs or tissues		3 (60%)
Lymph glands of the neck	1 (20%)	
Lymph glands of the neck and the parotid gland	1 (20%)	
Lymph glands of the axilla	1 (20%)	
Not intimately associated		7 (35%)
Malignant neoplasm—Tuberculosis:		
Lip—lymph glands of neck	3 (42.9%)	
Cheek—lymph glands of neck	1 (14.3%)	
Near angle of jaw—lymph glands of neck	1 (14.3%)	
Transverse colon—lymph glands of mesentery	1 (14.3%)	
Rectum—omentum and peritoneum	1 (14.3%)	

PRESENT CONDITION

Dead	4 (20%)
Living	10 (50%)
Condition unknown	6 (30%)

Three of the four patients who died had malignant metastases in the glands of the neck.

Two of the ten living patients have a recurrence of malignancy, three are in good health, and five have been operated on too recently to be considered. Of the three known to be in good health, 160 months, ninety-one months, and thirty-nine months, respectively, after their last operations, the latter two had epithelioma and tuberculosis in the glands of the neck.

Warthin[12] reported two cases of carcinoma and primary tuberculosis associated in the mammary gland; in the second case both diseases were in the axillary glands also.

Crowder[13] reported a case of tuberculosis and carcinoma of the cecum with tuberculosis of the lungs, peribronchial and retrocecal lymph glands.

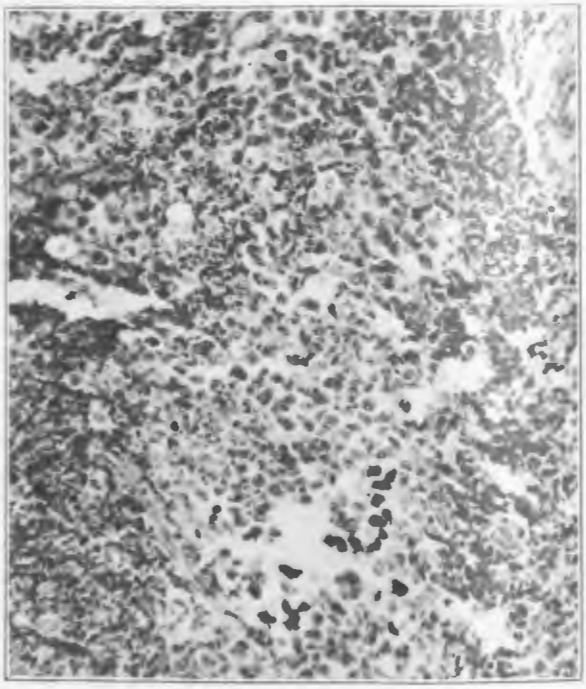

Fig. 7 (A 72500).—Same as Figure 6 (high power): lymphosarcoma cells.

Moak reported five cases of associated tuberculosis and carcinoma. The first case is practically the same as Warthin's second case; the primary tuberculosis and carcinoma in the mammary gland were associated with both diseases in the axillary glands. In the sec-

12. Warthin, A. S.: The Coexistence of Carcinoma and Tuberculosis of the Mammary Gland, Am. J. M. Sc. **118**: 25-35, 1899.

13. Crowder, T. R.: A Contribution to the Pathology of Chronic Hyperplastic Tuberculosis of the Caecum, Based on the Study of Two Cases, in One of Which Carcinoma of the Caecum Coexisted, Am. J. M. Sc. **111**: 668-693, 1900.

ond case, metastatic carcinoma was associated with tuberculosis in an axillary lymph gland. In the third, carcinoma of the mammary gland was associated with carcinoma and tuberculosis in a lymph gland, probably from the axilla. In the fourth, adenocarcinoma was associated with tuberculosis in the sigmoid flexure, and the same combination was in the liver and the

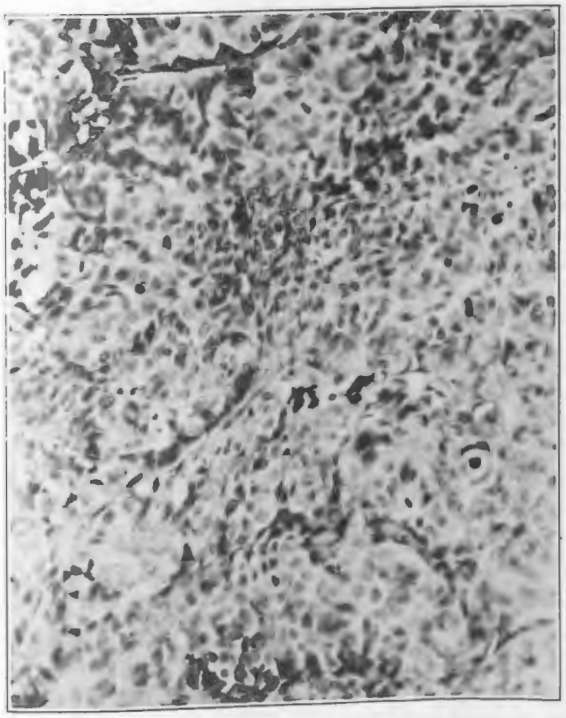

Fig. 8 (A 205751).—Melano-epithelioma of lymph gland of neck (high power).

left kidney. The fifth case showed an adenocarcinoma and tuberculosis of the lungs, bronchial glands, retroperitoneal hemolymph glands, suprarenal, liver and spleen, secondary to primary carcinoma of the prostate and primary tuberculosis of the lungs. Moak quotes Steinhauser[14] as having collected from the literature eighty-three instances of lupus and carcinoma of the

14. Steinhauser, cited by Moak: J. M. Res. 8: 142, 1902.

skin, and reported five new cases. Prior to the publication of the articles of Naegeli, Warthin, Crowder and Moak, in 1897, 1899, 1900 and 1902, respectively, a fairly large number of cases showing the association of the two conditions were reported, particularly in Europe, and since that time a fairly small number have appeared both here and abroad.[15]

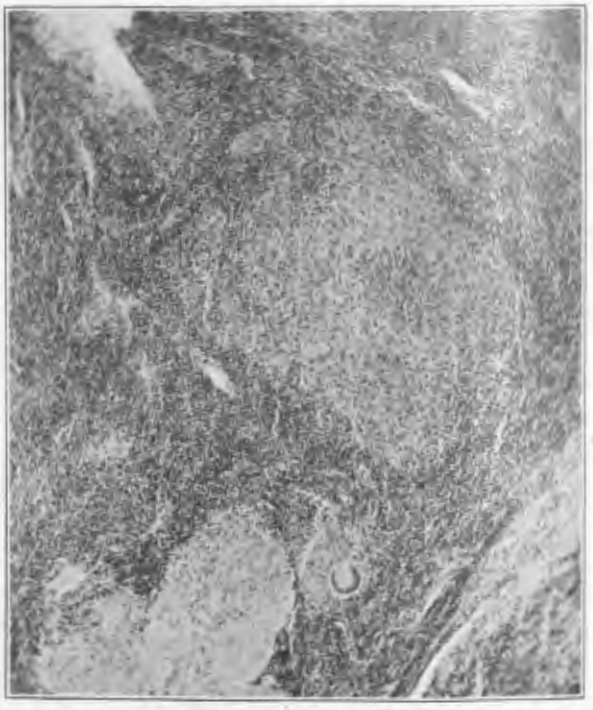

Fig. 9 (A 205751).—Tuberculosis in lymph gland, same as Figure 8, different field (low power). The condition of the patient is unknown.

CONCLUSIONS

1. The theory prevailing among the majority of physicians for a number of years and still prevailing among a few, that tuberculosis and malignant neoplasia are antagonistic, has not been borne out by the facts.

15. In addition to the references already given, the following will be found of interest:
Broders, A. C.: Tuberculosis of the Stomach, with Report of a Case of Multiple Tuberculous Ulcers, Surg., Gynec. & Obst. 25: 490-504, 1917.

2. The fact that some tissues or organs are, to a certain degree, immune from one or the other or both of these diseases does not prove that the two diseases are antagonistic.

3. If the observations of Naegeli are correct, in which he showed that in 93 per cent. of 420 necropsies on adults more than 18 years of age, either active, latent or healed tuberculosis had been present, then it is reasonable to believe that similar findings should prevail in an equal number of persons who have died with malignant neoplasia.

4. It would seem that the reason pathologists are not finding tuberculosis more frequently at necropsy in persons who have died with malignant neoplasia is that the pathologists are satisfied to find the malignant neoplastic condition, and therefore fail to make a thorough search for tuberculosis.

5. Since the surgical pathologist's examination is limited to the tissue removed by the surgeon, he is greatly handicapped in the search for the two conditions associated, while the pathologist doing a necropsy has access to a large part or the whole of the body.

6. The fact that active tuberculosis occurs most frequently in persons under 45, and malignant neoplasia, especially epithelial tissue malignant neoplasia, most frequently in persons over 45, does not prohibit the association of latent and healed tuberculosis with malignant neoplasia.

7. In our series of twenty cases the two conditions were associated in the same microscopic field seven times (35 per cent.).

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MELANO-EPITHELIOMA

A Report of Seventy Cases

By ALBERT COMPTON BRODERS, M.D., and WILLIAM CARPENTER MacCARTY, M.D.,
Rochester, Minnesota

From the Mayo Clinic

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MELANO–EPITHELIOMA[1]

A Report of Seventy Cases

By ALBERT COMPTON BRODERS, M.D., and WILLIAM CARPENTER MacCARTY, M.D.
Rochester, Minnesota
From the Mayo Clinic

THE variety of synonyms which have been applied to pigmented malignant neoplasmata indicates a lack of uniformity of opinion as to just what these tumors are histogenetically. They have been described as "melanosarcomata," "melanocarcinomata," "melanoblastomata," "melanomata," "melano-epitheliomata," "melanotic sarcomata," and "chromatophoromata." The majority of writers utilize the term "melanosarcoma." which has its basis of usage in the old classifications of neoplasmata. These classifications were founded upon a theoretical conception of the specific origin of tissues in the three embryonic layers. The principal cells of nævi or moles, having been thought to have their origin in connective tissue of the skin, were, therefore, mesoblastic and hence their neoplastic derivatives have been called sarcomata.

The conception that the spindle and oval cells which are characteristic of melanotic neoplasmata of the skin are of connective-tissue origin, is founded upon morphology, which we are rapidly learning is not an accurate criterion for the embryologic origin in any specific embryonic layer. Moreover, the direct continuity of the spindle and oval cells with the basal cells of the skin can be readily demonstrated not only in nævi (Fig. 1), but also in melanotic neoplasmata (Figs. 2, 3, 4, and 5).

The cells of the latter condition frequently assume an alveolar arrangement (Figs. 6, 7, and 8) which is very characteristic of epithelial tumors. Such alveolar growths have been called "alveolar sarcomata" and "endotheliomata," the latter term inferring their origin in the lining of vessels. In the authors' experience no evidence of vascular structure in connection with the alveolar arrangement has been demonstrable (Fig. 8).

We desire to utilize the term melano-epithelioma for the following reasons:

1. If the old three-layer hypothesis for the classification of tumors be adhered to, it may be well to remember that the pigment-bearing cells of the skin (Fig. 9) and perhaps the choroid (Fig. 10), both of which furnish the source of all of the tumors of this series, have

Fig. 1. (a91016.) A section of a mole showing the direct connection between the stratum germinativum and the subepithelial cells which are characteristic of moles.

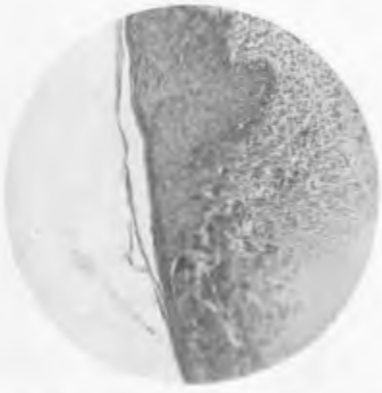

Fig. 2 (99046). Photomicrograph of an early migration of the malignant cells of the stratum germinativum in the skin of the right labium.

[1]Read before the Olmsted County (Minnesota) Medical Society, December 9 191

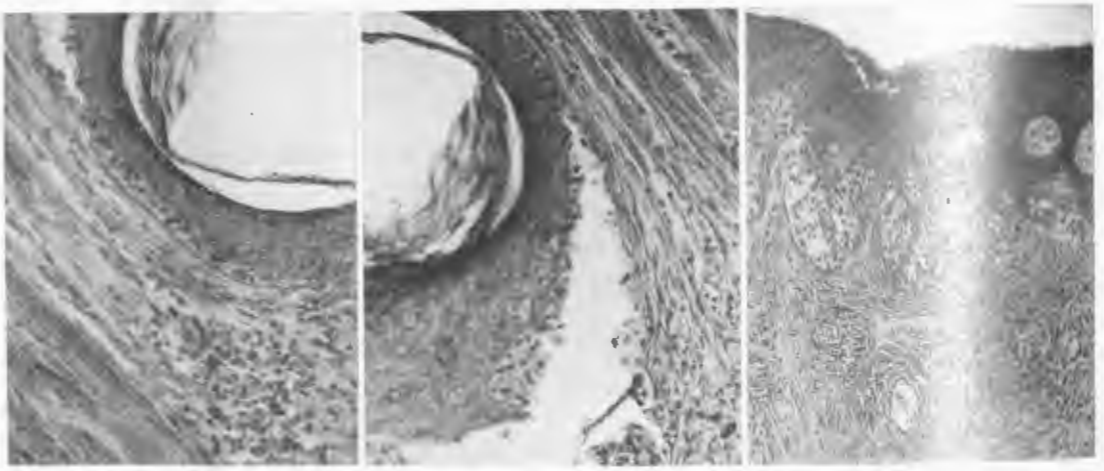

Fig. 3. Fig. 4. Fig. 5.

Fig. 3 (80193). Photomicrographs showing hypertrophic and hyperplastic cells of the stratum germinativum of the skin over the left groin.

Fig. 4 (80193). Photomicrographs of a portion of the same section (Fig. 3), showing a local hyperplasia with invasion by the cells of the stratum germinativum. The hypertrophic cells of the stratum germinativum are morphologically identical with the cells of the neoplasm.

Fig. 5 (80193). Photomicrograph of a typical melano-epithelioma arising in the germinal layer of the skin. The cells are in direct continuity with the stratum germinativum.

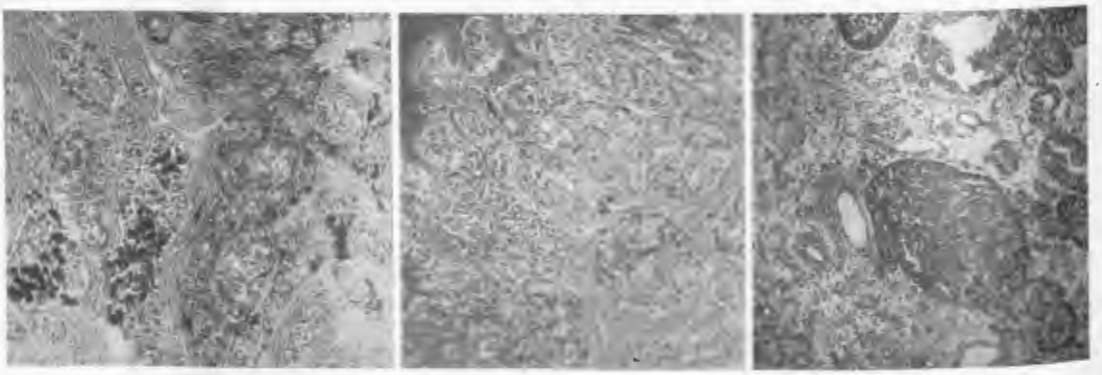

Fig. 6. Fig. 7. Fig. 8.

Sections (80193, 80193, and 123182 respectively) showing an alveolar arrangement of cells.

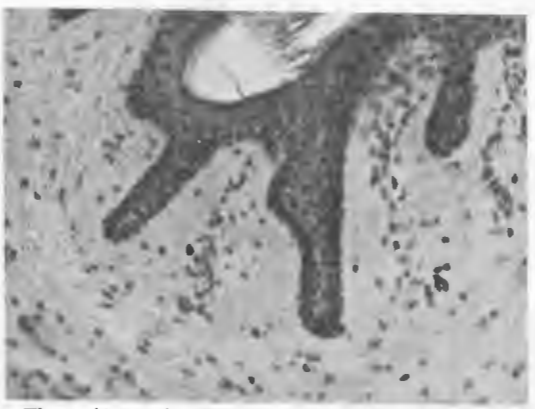

Fig. 9 (A67579). Section through skin showing the normal location of pigment cells.

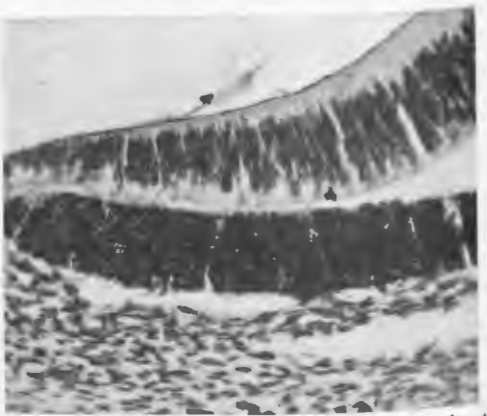

Fig. 10. Section through an embryonic eye showing the relation of the choroid to the retina.

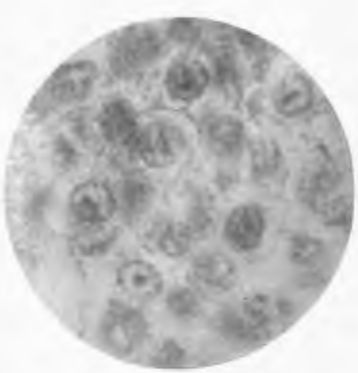

Fig. 11a.

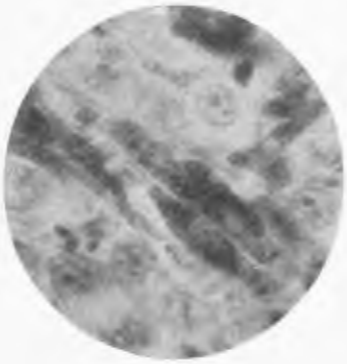

Fig. 11b.

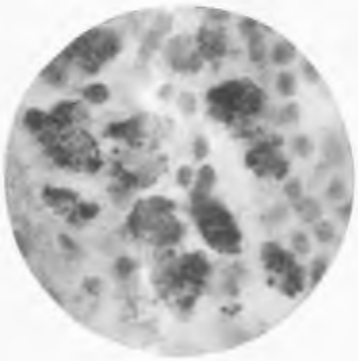

Fig. 11c.

Fig. 11 a, b, c (105603 and 36641). High power photomicrographs showing variety of cells which are found in melano-epitheliomata.

Fig. 12.

Fig. 13.

Fig. 14.

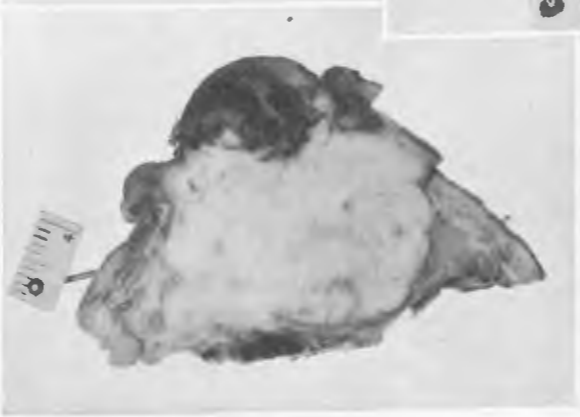

Fig. 15.

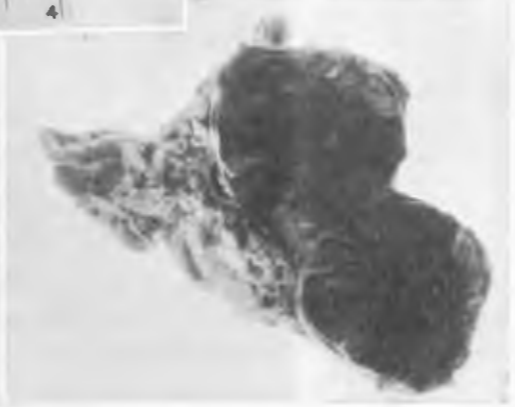

Fig. 16.

Fig. 12 (57193). A flat pigmented mole upon the inner side of right leg, metastasis in the right inguinal glands. Death within a year from operation.

Fig. 13 (123182). An elevated, almost pedunculated, pigmented malignant neoplasm upon the left internal malleolus.

Fig. 14 (70911). Gross section through a malignant pigmented hairy mole upon the right cheek. The neoplasm has not extended visibly into the subcutaneous tissues.

Fig. 15 (132905). Gross section showing the extension of a growth from a pigmented mole into the subcutaneous tissue. The growth in the subcutaneous tissue lacks pigment; location, right leg just below the knee.

Fig. 16 (143701). Metastatic growth of left axillary glands.

their origin in the ectoblastic layer rather than the mesoblastic layer. There still seems to be, however, some doubt as to the exact origin of the pigmented cells of the choroid, some authorities believing that they are a part of the embryonic optic bulb and others considering them a part of the mesoblastic tissue which lies adjacent to the retina (Fig. 10).

2. The downward growths of spindle and oval cells of moles or nævi and melanotic neoplasmata are in direct continuity with the stratum germinativum of the skin (Figs. 2, 3, 4, and 5).

3. The pigment-bearing cells of normal skin and of the downward growths of moles or nævi are in the basal layer (stratum germinativum) and not in the subjacent connective tissue (Figs. 2, 3, and 4).

4. In accord with more recent observations of the histogenesis of epithelial neoplasmata, they arise directly as a proliferation of the germinative or regenerative cells of the parenchyma of organs and not from either the differentiated cells or from "cell rests."

The cells of melano-epitheliomata may be oval (Fig. 11a) or spindle (Fig. 11b); all cells do not contain pigment (Fig. 11, a, b, c).

In our series of 70 cases the condition arose in both flat (Fig. 12) and pedunculated (Fig. 13) pigmented areas of the skin. The local growth may be discovered when there is no apparent invasion of the tissue subjacent to the pigmented nævus (Fig. 14). In the majority of cases, however, there is extension to the subjacent structures (Fig. 15). Pigment may occupy a large (Figs. 14 and 16) or small part of the tumors (Fig. 15).

The pathogenicity of this type of neoplasm may be seen to best advantage in the following tables:

1. Average age of patients, 49 years.
2. Number patients between the ages of 20 and 30 years 7
   Number patients between the ages of 30 and 40 years 13
   Number patients between the ages of 40 and 50 years 14
   Number patients between the ages of 50 and 60 years 20
   Number patients between the ages of 60 and 70 years 8
   Number patients between the ages of 70 and 80 years 7
   Number patients between the ages of 80 and 90 years 1
   Total 70
3. Oldest patient, 84 years; youngest, 21 years.
4. Average duration of lesion before examination, 11 years.[1]
5. Number of lesions which had their origin in birthmarks (nævi, warts or moles) 35 (50%)
   Number of lesions which had their origin in miscellaneous pigmented areas not typical moles 24
   Number of lesions which had their origin in the eye 4
   Number of lesions with origin unknown 7
6. Size of largest lesion was that of an orange.
   Size of smallest lesion was that of a pea.
7. The following anatomical locations of original growths were noted:

Scalp	1
Eye	4
Ear	2
Nose	1
Cheek	2
Jaw	5
Chin	1
Neck	1
Shoulder	3
Deltoid	1
Hand	2
Thumb	1
Breast	1
Chest	2
Back	3
Abdomen	1
Labium	2
Urethra	1
Groin	2
Hip	1
Thigh	2
Leg	8
Internal malleolus	1
Ankle	1
Heel	3
Foot	4
Toe	7
Not stated	7
Total	70

8. Anatomic location of metastases —
   Regional lymphatic glands ..... 36 cases
   General ..... 10 cases
   Liver ..... 2 cases
   Ovary ..... 1 case
9. Number of patients with a history of previous operation 39
10. Number of specimens excised for diagnosis 21
11. Number of correct clinical diagnoses, 41, 58.6% (out of 70 cases).
    Number of doubtful clinical diagnoses, 27, 38.6% (out of 70 cases).
    Number of incorrect clinical diagnoses, 2, 2.8% (out of 70 cases).
12. The number of patients operated on between April, 1904, and January, 1915, that have been heard from directly or indirectly by letter 38
    The mortality for patients operated on between April, 1904, and January, 1915, that have been heard from is ..... 33 or 86.8%
    The number of patients dying within one year from last operation 24 (63.2%)
    The number of patients dying within two years from last operation 4 (10.5%)

[1] This figure is only approximately correct, on account of the patients' inability to remember both the first appearance of moles and slight changes which took place in them.

The number of patients dying within four years from last operation..... 1 (2.6%)
The number of patients dying within eight years from last operation..... 1 (2.6%)
Dead, date unknown..... 3 (7.9%)

Total.....33

The number of patients operated on between April, 1904, and January 1, 1915, that have been heard from and are living:

1 year from last operation.....2 (5.3%)
2 years from last operation.....1 (2.6%)
3 years from last operation.....2 (5.3%)

Total.....5 (13.2%)
Dead with metastasis at end of 1 year after operation. 23
Dead with metastasis at end of 2 years after operation 4
Dead with metastasis at end of 4 years after operation 1
Dead with metastasis, date unknown..... 1
Dead without demonstrable metastasis at last operation at end of 1 year..... 1
Dead without demonstrable metastasis at last operation at end of 8 years[1]..... 1
Dead without demonstrable metastasis at last operation, date unknown..... 2
Dead with demonstrable metastasis at last operation 29 out of 33..... 87.9%
First year deaths with demonstrable metastasis 23 out of 24..... 95.8%
Living with demonstrable metastasis at last operation at end of 1 year..... 1
Living with demonstrable metastasis at last operation at end of 2 years..... 1
Living without demonstrable metastasis at last operation at end of 1 year..... 1
Living without demonstrable metastasis at last operation at end of 3 years..... 2
Average duration of life after last operation, 11 months, 3 days.[2]

The conclusions which may be drawn from the above-mentioned facts are:

1. The so-called "melanosarcoma" should be called properly a melano-epithelioma when such a condition arises in the skin.

2. The condition arises as a migratory hyperplasia of the basal (regenerative or germinative) layer of the skin and invades the subcutaneous tissues and distant organs as pigmented and non-pigmented oval, spherical, or spindle cells, all of which cells are frequently found in the same specimen or even in the same microscopic slide.

3. The evolution of such neoplasmata in regenerative cells corresponds to the evolution of cancer in the skin, mammary gland, prostatic gland, and stomach.

4. The alveolar arrangement of cells in this series shows no evidence of any relation to vascular endothelium.

5. The condition is one of middle life, although it may be found from childhood to old age.

6. An attempt at determination of the exact duration of the condition from its onset to a fatal termination has failed in this series.

7. There is no specific region of the skin which seems especially predisposed to the development of melano-epitheliomata unless it is on the lower extremities, which in this series form the greatest frequency of location.

8. Nævi certainly predispose to the development of the condition.

9. Metastasis is usually to the regional lymphatic glands.

10. From an economical or practical standpoint melano-epitheliomata which arise in the skin have a high mortality.

11. Melano-epitheliomata or melanosarcomata arising in the eye have a much better prognosis than melano-epitheliomata arising in the skin.

12. From a therapeutic standpoint the pathologic history of melano-epithelioma clearly points to the necessity of an early diagnosis and a radical removal of the primary lesion and regional lymphatic glands.

13. From a prophylactic standpoint pigmented areas of skin, such as warts and nævi, should be removed when these are in locations which are or have been subjected to injury.

[1] This case possessed a melano-epithelioma or melanosarcoma which had arisen in the choroid.

[2] This figure includes the eye case which lived eight years after operation.

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