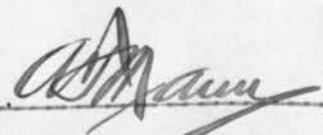
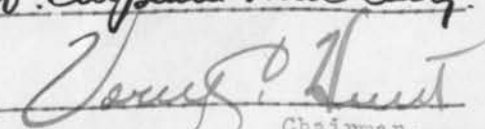


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REPORT
of
Committee on Thesis

The undersigned, acting as a Committee of the Graduate School, have read the accompanying thesis submitted by Lester Davis Powell for the degree of Master of Science in Surgery. 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 Surgery.



W. Carpenter MacCallister


Chairman.

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 Lester Davis Powell final oral examination for the degree of Master of Science in Surgery. We recommend that the degree of Master of Science in Surgery be conferred upon the candidate.

Joseph Hunt
Chairman

W. A. Dennis

B. J. Clawson

G. L. Cameron

Louis B. Wilson

Date *Dec. 1-1922*

THESIS

The Relationship of Cellular Differentiation, Fibrosis, Hyalinization and
Lymphocytic Infiltration to Postoperative Longevity in Patients
with Squamous-cell Epithelioma of the Skin and Lip.

Lester Davis Powell, B.A., M.D.

UNIVERSITY OF
MINNESOTA
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Submitted to the faculty of the Graduate School of the University of
Minnesota in partial fulfillment of the requirements for
the degree of Master of Science in Surgery.

October 1922.

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For years it has been recognized that in malignant conditions, some factors other than surgical skill have played a very important role in post-operative length of life. Wood states: There may be a spontaneous disappearance of a primary tumor following no therapeutic interference, following infection or following partial removal of the malignant tumor by surgery and that there may be disappearance of a primary tumor with coincident and subsequent growth of metastases. He also states that lymphocytosis has not been found to have any influence upon the growth of a tumor. Rous in his work, "Metastasis and Tumor Immunity", has made some very interesting observations: He used chickens and a transmissible avian tumor for his experimental work, and learned that some fowls were susceptible to the transplanted graft while others seemed to have a natural immunity. In the first few days after the inoculation of a transmissible tumor and while it was still growing and healthy, there occurred a rapid accumulation of lymphocytes about the nearby blood vessels. Later they extended around and into the tumor graft. At the end of a week the lymphocytes had infiltrated in such numbers as to make the region adjacent to the graft appear almost like a lymph node. However, he seemed undecided whether the lymphocytic infiltration forms a resistance to the transplanted tumor or whether the immunity against such a tumor is due to other factors. Da Fano, after a careful histological study of tumor grafts in mice and of the sparse cellular reaction about them has concluded that lymphocytes are in some way connected with tumor immunity. Taylor and Murphy, while working of "Effects of Cancer Immunity on Resistance to Tuberculosis", found that mice immunized against one of the transplantable mouse cancers developed a marked lymphoid reaction in the blood which lasted for weeks. The mice that were ineffectively immunized also showed a lymphoid reaction but decidedly less than in the mice effectively immunized. They felt that the lymphoid tissue of the body may be a determining factor in the phenomena of resistance in both cancer and tuberculosis. Rous and Murphy, who

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studied "The Histological Signs of Resistance to Transmissible Sarcoma of the Fowl", learned that the lymphocyte had an association with the process of resistance in the fowl similar to but less marked than in mammals.

MacCarty, in the belief that cellular differentiation, fibrosis, hyalinization and lymphocytic infiltration were all factors which probably had an influence on postoperative longevity in malignancy, studied "Involvement of Regional Lymphatic Glands in Gastric Carcinoma", and showed in this early work that the immediate hospital postoperative and post-hospital mortality were in direct proportion to the amount of lymphatic glandular involvement. Eight years later MacCarty and Mahle collected data on and studied microscopically ninety-nine of the two hundred cases previously studied and reported, to learn the relation of cellular differentiation and lymphocytic infiltration to postoperative longevity in cases which had died of recurrence or metastases. This work showed that no case with glandular involvement lived over eight years; cases without glandular involvement had a much greater average length of postoperative life; cases without glandular involvement and showing cellular differentiation lived 14 per cent longer than cases without glandular involvement and no cellular differentiation; cases with partial glandular involvement and showing cellular differentiation lived 20 per cent longer than the cases with partial glandular involvement and no cellular differentiation; in cases with complete glandular involvement, cellular differentiation was not associated with increased postoperative longevity; cases, with gastric carcinoma without glandular involvement but showing extensive lymphocytic infiltration, have greater average length of postoperative life; and that, regardless of glandular involvement the presence of lymphocytic infiltration is associated with a 23 per cent longer postoperative life. MacCarty and Sistrunk, in their clinical and pathological study of "Life Expectancy following Radical Amputation for Cancer of the Breast", learned that the three greatest single

factors which increased postoperative life are cellular differentiation, hyalinization and fibrosis. Their study shows that lymphocytic infiltration alone does not appear to be a main factor although it may be a contributing factor in prolonging postoperative life. Their work also shows that cellular differentiation and hyalinization in combination, the latter probably never occurring without a preliminary local lymphocytosis, are the two direct factors producing the greatest postoperative life. Broders, in his work, "Squamous Cell Epithelioma of the lip", has graded the tumors on the scale of 1 - 2 - 3 - 4, Grade 1 being the least malignant and Grade 4 the most malignant. Grade 1, or the least malignant, shows the tumor cells approaching and more closely resembling normal squamous cell epithelium or being in a higher state of differentiation. His grading is made on the malignant cell itself, although the presence or absence of mitotic figures, the presence of defense cells (fibrous tissue cells or abnormal presence of lymphocytes) plays a lesser role in governing the grade into which he places a tumor. In his paper "Squamous Cell Epithelioma of the Skin", he states: "As a rule the more marked the cellular differentiation in squamous cell epithelioma, the lower is the degree of malignancy".

The cases in this study are all from the series previously studied and graded by Dr. Broders. They represent all of the cases treated surgically at the Mayo Clinic for squamous cell epithelioma of the skin between November 1, 1904 and July 22, 1915, which have died from recurrence of the lesion or metastases.

The study of cellular differentiation, fibrosis, hyalinization and lymphocytic infiltration has been undertaken with an endeavor to determine what histological factors cause the great variations in postoperative longevity. Microscopic study of sections taken from many cases of epithelioma which were operable and some of which were inoperable has shown the presence of malignant

cells taking on forms which closely resemble normal squamous cell epithelium. They are well differentiated as shown by the presence of pearly bodies. This phenomenon is termed cellular differentiation (Fig. 1). In a great many of the cases we see the fibrous connective tissue cells working into and around the malignant tumor mass, and apparently forming a barrier to the tumor cells; this condition is known as fibrosis (Fig. 2). Another phenomenon, commonly seen, is the presence of lymphocytes scattered intimately about the tumor cells. In some cases they are in such abundance that it is difficult to find the malignant cells; we consider the abnormal presence of lymphocytes about a tumor as lymphocytic infiltration (Fig. 3). A condition less commonly present but nevertheless worthy of consideration is that of hyalinization, shown by a translucent or homogeneous condition of the connective tissue in and about the tumor growths (Fig. 4).

In the thirty-two cases of squamous cell eipthelioma of the skin treated surgically at the Clinic between November 1, 1904 and July 22, 1915, and known to have died from recurrence of the lesion or metastases, complete data has been obtained on twenty-nine cases. The tumors have been sectioned and studied microscopically without reference to clinical data, the comparison made and the following facts deducted:

Average length of postoperative life	444.6 days
Frequency of cellular differentiation	65.5 %
Frequency of lymphocytic infiltration	65.5 %
Frequency of fibrosis	41.3 %
Frequency of hyalinization	31. %
Frequency of cellular differentiation and lymphocytic differentiation combined	37.9 %
Frequency of cellular differentiation and fibrosis combined	27.5 %
Frequency of cellular differentiation and hyalinization combined	17.2 %
Frequency of lymphocytic infiltration and fibrosis combined	24.1 %
Frequency of lymphocytic infiltration and hyalinization combined	20.6 %
Frequency of fibrosis and hyalinization combined	27.5 %

Average length of postoperative life with cellular differentiation	534.1 days
Average length of postoperative life without cellular differentiation	274.7 "
Average length of postoperative life with lymphocytic infiltration	496.2 "
Average length of postoperative life without lymphocytic infiltration.	346.6 "
Average length of postoperative life with fibrosis	655.7 "
Average length of postoperative life without fibrosis	295.6 "
Average length of postoperative life with hyalinization	449.6 "
Average length of postoperative life without hyalinization	437.9 "
Average length of postoperative life with cellular differentiation and lymphocytic infiltration	644.5 "
Average length of postoperative life without cellular differentiation and lymphocytic infiltration	204. "
Average length of postoperative life with cellular differentiation and fibrosis	808.3 "
Average length of postoperative life without cellular differentiation and fibrosis	257.5 "
Average length of postoperative life with cellular differentiation and hyalinization	587 "
Average length of postoperative life without cellular differentiation and hyalinization	257.5 "
Average length of postoperative life with lymphocytic infiltration and fibrosis	739.8 "
Average length of postoperative life without lymphocytic infiltration and fibrosis	155.2 "
Average length of postoperative life with lymphocytic infiltration and hyalinization	404. "
Average length of postoperative life without lymphocytic infiltration and hyalinization	255.5 "
Average length of postoperative life with fibrosis and hyalinization	453.8 "
Average length of postoperative life without fibrosis and hyalinization	282.5 "
Average length of postoperative life with cellular differentiation, lymphocytic infiltration, fibrosis and hyalinization	444.6 "
Average length of postoperative life without cellular differentiation, lymphocytic infiltration, fibrosis and hyalinization	54. "

Total number of operated cases	29
Average age	60.7 yrs.
Oldest	77 "
Youngest	42 "
Males	25
Females	4
Average duration of preoperative lesion	6.1 yrs. or 2226.5 days

The locations of the lesions were:	22 cases
Head and neck	3 "
Buttock and sacral region	3 "
Extremities	1 case
Abdomen	

Postoperative longevity in cases of squamous cell epithelioma of the lip was studied along with squamous cell epithelioma of the skin for comparative purposes. The technical procedure was exactly the same as in the study of the squamous cell epithelioma of the skin. Of the cases operated upon at this Clinic for squamous cell epithelioma of the lip between November 1, 1904 and July 22, 1915, sixty-six are known to have died from recurrence of the malignancy or its metastasis. The required data was obtained in sixty-three of these and the resulting facts shown:

Average length of postoperative life	359.8 days
Frequency of cellular differentiation	71.4 %
Frequency of lymphocytic infiltration	92.1 %
Frequency of fibrosis	6.3 %
Frequency of hyalinization	6.3 %
Frequency of cellular differentiation and lymphocytic infiltration	66.6 %
Frequency of cellular differentiation and fibrosis	6.3 %
Frequency of cellular differentiation and hyalinization	4.7 %
Frequency of lymphocytic infiltration and fibrosis	4.7 %
Frequency of lymphocytic infiltration and hyalinization	4.7 %
Frequency of fibrosis and hyalinization	4.7 %
Average length of postoperative life with cellular differentiation	388. days
Average length of postoperative life without cellular differentiation	290.4 "
Average length of postoperative life with lymphocytic infiltration	365.9 "
Average length of postoperative life without lymphocytic infiltration	293. "
Average length of postoperative life with fibrosis	186.7 "
Average length of postoperative life without fibrosis	371.8 "
Average length of postoperative life with hyalinization	293.7 "
Average length of postoperative life without hyalinization	364.7 "
Average length of postoperative life with cellular differentiation and lymphocytic infiltration	386.8 "
Average length of postoperative life without cellular differentiation and lymphocytic infiltration	116. "
Average length of postoperative life with cellular differentiation and fibrosis	186.8 "
Average length of postoperative life without cellular differentiation and fibrosis	290.4 "
Average length of postoperative life with cellular differentiation and hyalinization	207.6 "
Average length of postoperative life without cellular differentiation and hyalinization	275. "
Average length of postoperative life with lymphocytic infiltration and fibrosis	174.6 "
Average length of postoperative life without lymphocytic infiltration and fibrosis	310.5 "
Average length of postoperative life with lymphocytic infiltration and hyalinization	317.3 "

Average length of postoperative life without lymphocytic infiltration and hyalinization	310.5 days
Average length of postoperative life with fibrosis and hyalinization	207.6 "
Average length of postoperative life without fibrosis and hyalinization	367.1 "
Average length of postoperative life with cellular differentiation, fibrosis, hyalinization and lymphocytic infiltration	200. "
Average length of postoperative life without cellular differentiation, fibrosis, hyalinization and lymphocytic infiltration	117. "
Total number of operated cases	63
Average age	59.2 yrs.
Oldest	97 "
Youngest	25 "
Males	61
Females	2 "
Average duration of preoperative lesion	3.57 " or 1303 days.

Conclusions

1. The average length of postoperative life in epithelioma of the skin is increased when the factors differentiation, lymphocytic infiltration, fibrosis and hyalinization are present.
2. Postoperative life is increased when any one factor or combination of factors is present in the skin. However this is not true with cases of epithelioma of the lip in the series studied.

In the lip, postoperative life was increased when the factors cellular differentiation or lymphocytic infiltration were present but with the factors fibrosis or hyalinization singly or in combination there was a decreased postoperative life. This discrepancy may be due to the fact that in the series of epithelioma of the lip only four cases of fibrosis and four cases of hyalinization were present. In three of the cases showing fibrosis, hyalinization was associated. One of these cases (18131) showing fibrosis and hyalinization was seventy-six years of age. The second case (38260) showing fibrosis and hyalinization was sixty-eight years of age. The third case (102029) with fibrosis and hyalinization was but forty-eight years of age but had had the lesion eleven years previous to operation. The one case (117833) with fibrosis alone

was seventy years of age. The one case (J1329) showing hyalinization alone was fifty-eight years of age and had had the lesion nine years previous to operation. Of the four cases showing fibrosis three had already lived an average life time and the fourth, although but forty-eight years of age had had the lesion for eleven years and could hardly be expected to have any defense power remaining. In other words, the presence of the factors fibrosis and hyalinization may account for his having had the lesion for such a long period. In the case of hyalinization, two of the cases had lived seventy-six and sixty-eight years respectively. The other two cases had their preoperative lesions eleven and nine years respectively and the defense offered by hyalinization must have been exhausted in that time.

3. The greatest percentage increase in postoperative life was noted when the presence of all the factors were checked against the absence of all the factors in epithelioma of the skin. Despite the fact that fibrosis and hyalinization showed a decreased postoperative life in the cases of epithelioma of the lip the presence of all the factors checked against the absence of all the factors showed an increase of postoperative life.

4. Before one can definitely state that cellular differentiation, lymphocytic infiltration, fibrosis and hyalinization prolong postoperative life as an entity, when in association with malignancy, a larger series of cases should be studied but from this series of ninety-two cases it seems that each of the factors, cellular differentiation, lymphocytic infiltration, fibrosis and hyalinization, should be considered as a defense factor in cases of malignancy.

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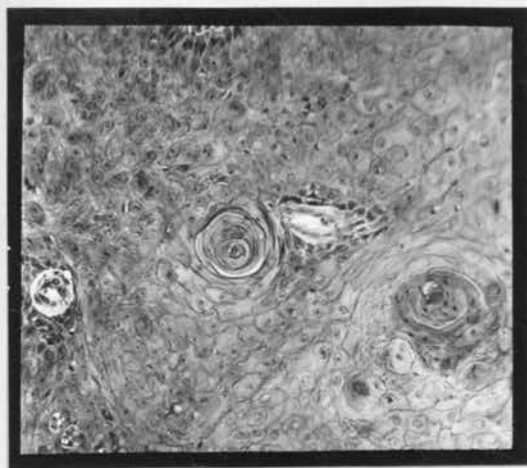


Fig. 1. Cellular differentiation in case of epithelioma of the skin. Two pearly bodies standing out prominently. X100.

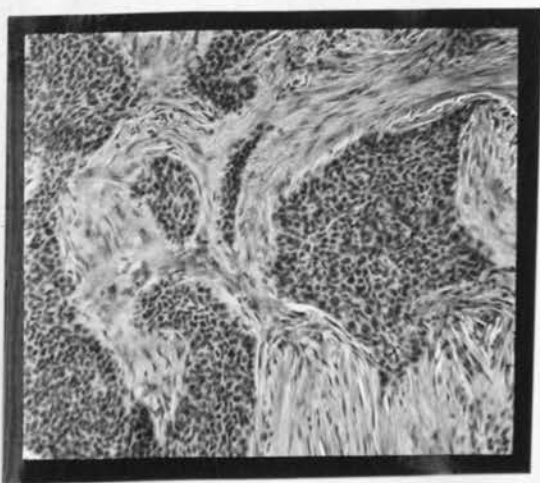


Fig. 2. Areas of malignant cells completely surrounded by dense fibrous connective tissue cells. X100.

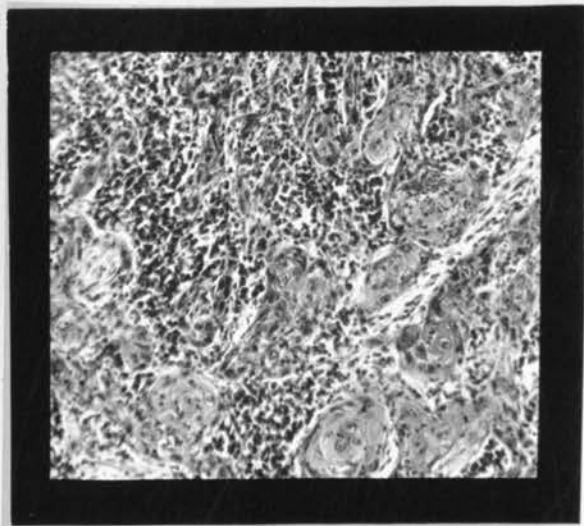


Fig. 3. Lymphocytic infiltration as shown by the lymphocytes in and about malignant cells. X100.

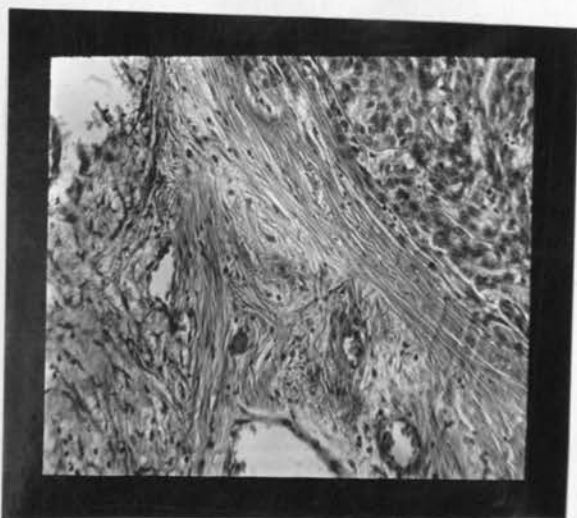


Fig. 4. Hyalinization in association with epithelioma cells. X100.

Legend - Charts: Solid line indicates duration of postoperative life with factors present. -----

Dotted line indicates duration of postoperative life without factors present. -----

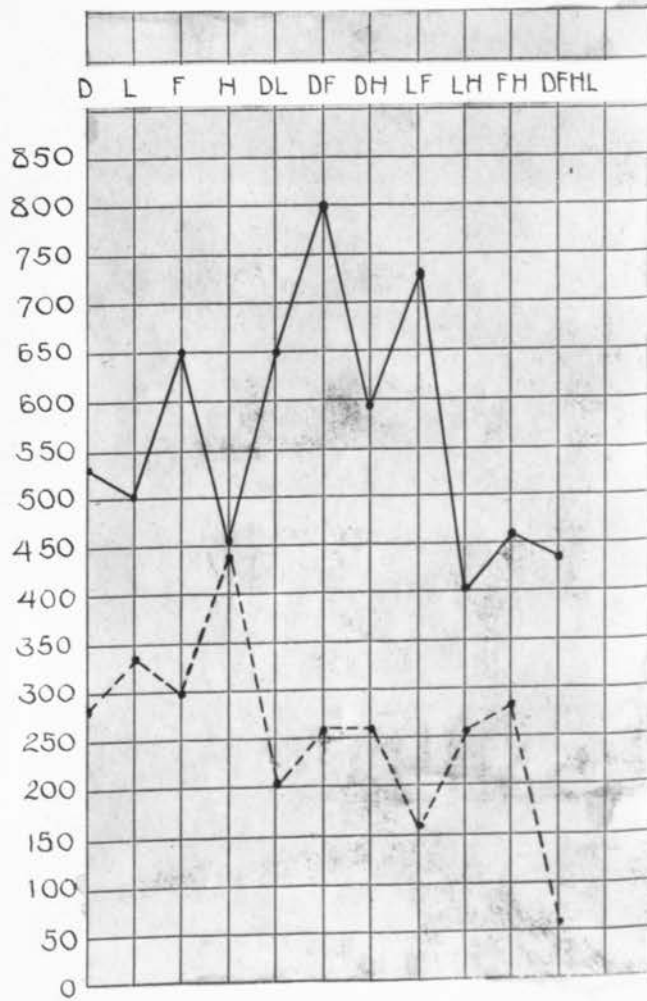


Chart 1. Average length of postoperative life with and without factors. (Skin)

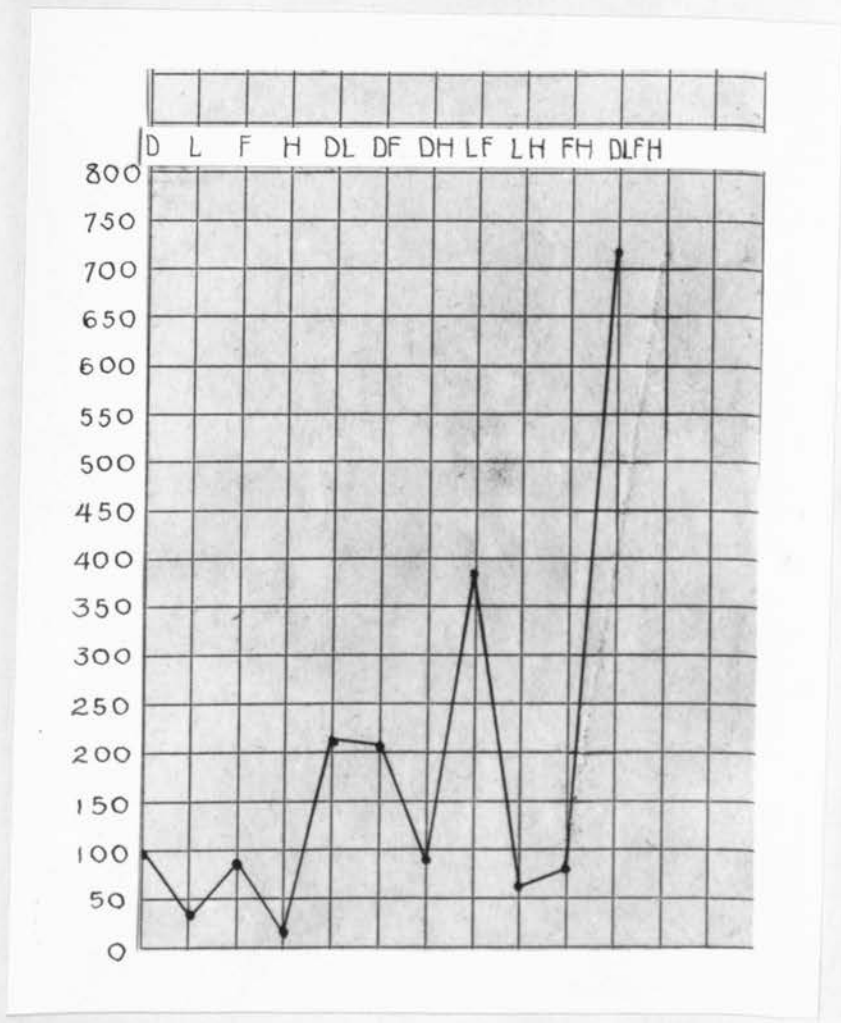


Chart 2. Percentage increase in postoperative life with factors checked against postoperative life without factors. (Skin)

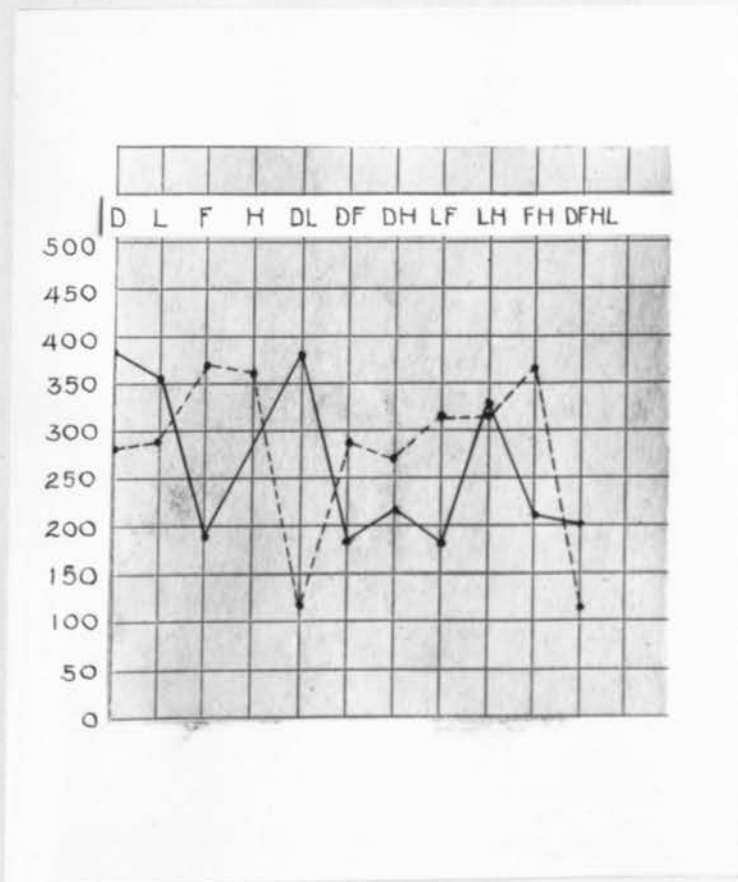


Chart 3. Average length of postoperative life with and without factors. (Lip)

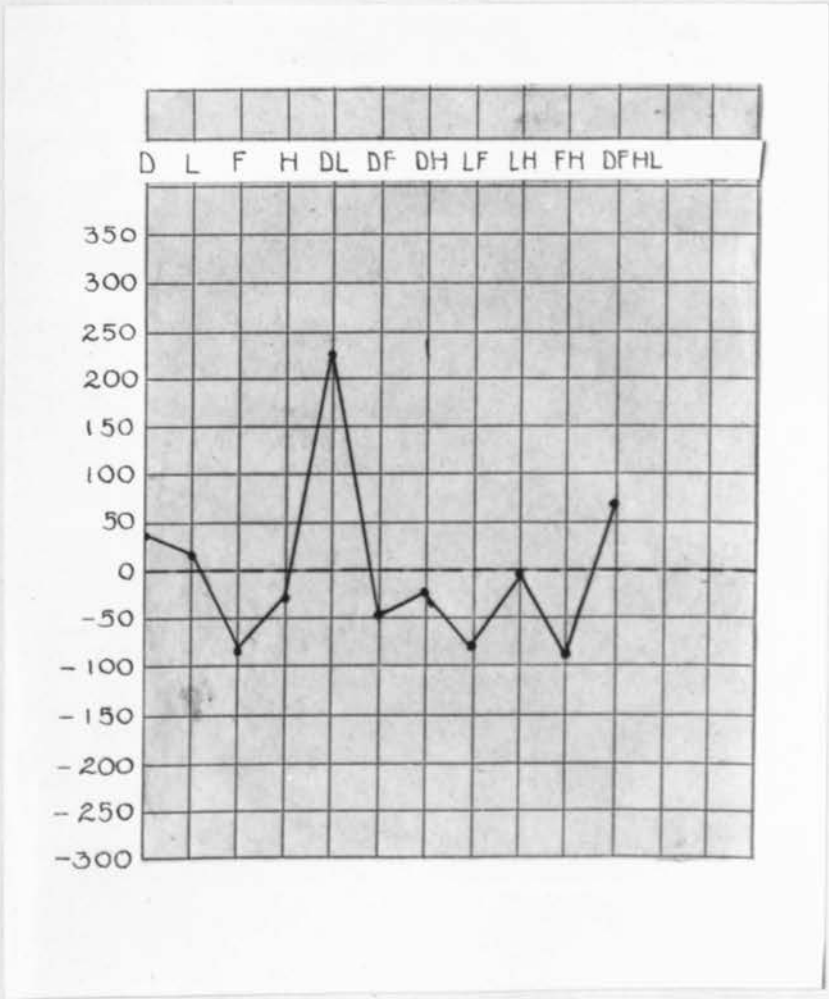


Chart 4. Percentage increase in postoperative life with factors checked against postoperative life without factors. (Lip)