THE BASES FOR THE HISTOLOGIC GRADING OF CARCINOMA OF THE BREAST

CUSHMAN D. HAAGENSEN, M.D.

(From the Institute of Cancer Research of Columbia University, F. C. Wood, Director, and St. Luke's Hospital, New York)

INTRODUCTION

It is just forty years since Hansemann, in his monograph "Studien über die Spezifizität, den Altruismus und die Anaplasie der Zellen," first presented the idea that a scale might be drawn up to represent the degree to which the morphology of a tumor departs from that of the mother cells from which it arises. Hansemann described and presented photomicrographs of three grades of anaplasia in squamous-cell carcinoma and in adenocarcinoma. At this time he suggested the possibility that the grade of anaplasia might be correlated with the degree of clinical malignancy of the tumor as evidenced by its tendency to metastasize, but lacking data bearing on this point he made no claim that such a relationship existed. He set to work, however, to discover the end-results for all the tumors which he graded histologically.

Nine years later, in the second edition of his book, "Die mikroskopische Diagnose der bösertigen Geschwülste," he concluded that a relationship did indeed exist between grade of anaplasia and grade of malignancy. Highly anaplastic tumors almost always recurred and metastasized. Those showing a lesser grade of anaplasia were sometimes cured.

Hansemann's interesting observation received comparatively little attention in his own country, and it is only in recent years, and particularly in the United States, that histologic grading has been studied extensively. Good evidence has accumulated that for a few special types of carcinoma, such as that in the cervix and in the rectum, the grade of anaplasia is a useful gauge of the grade of malignancy. For tumors in general, however, the majority of pathologists have shown a just reserve in making prognoses on the basis of grading. The relationship of grade of anaplasia to malignancy must be studied separately for each type of tumor, and the necessary follow-up data upon which to base such studies are, in general, not yet available in American clinics.

For it should be remembered that the test of the value of grade

1 Read before the American Association for Cancer Research, May 8, 1933, at Washington, D. C.
of anaplasia as an indicator of prognosis is necessarily a pragmatic one. Statistical rather than anecdotal evidence, as Dr. Frank Mathews puts it, is what is required. In undertaking an investigation of this relationship for a particular type of cancer the histologic sections should be studied and the grade of anaplasia estimated without knowledge of the clinical features. The findings should then be compared with the five-year results of treatment. To insure a fair comparison the same statistical requirements should be met which are followed in the computation of success of treatment; that is, a series of at least one hundred consecutive unselected cases of a particular type of cancer, treated in a uniform manner, should be studied. The five-year follow-up should be at least 95 per cent complete.

**Previous Attempts to Grade Carcinoma of the Breast**

Although it might be supposed that studies of the value of grading in breast cancer meeting the requirements mentioned above would readily be made, since the disease is frequent, and abundant pathological material is secured by radical mastectomy, the fact is that Greenough's 1925 study of a series of cases from the records of the Massachusetts General Hospital is the only one of its kind which approximates the ideal requirements which we have suggested. Greenough distinguished three grades of anaplasia, which he designated as low, medium, and high malignancy. When the cases were graded on this basis and the different grades compared with the percentages of five-year cures obtained, a striking relationship between the grade of anaplasia and curability was apparent.

Since Greenough's careful study a number of workers have made similar attempts to grade breast cancer. Agreement has by no means been reached, however. At one extreme are found pathologists who take the position that grading has little if any practical value, while at the other extreme are those enthusiasts who claim almost a mathematical accuracy for prognoses based on histological grading. Very likely the cause of this disagreement is the number of variable conditions in the problem which all are trying to solve. The lack of uniformity of the method of treatment in the series of cases under consideration, the incompleteness of the follow-up data, and the inadequacy of the histologic material are some of the variables which have handicapped investigators.

To this already formidable list of variable conditions affecting the problem must be added the factors of the situation of the tumor in the breast, accidental invasion of blood vessels by the tumor, and the amount of trauma to which the tumor has been
subjected (both by the patient herself and by examining physicians). It is to be hoped, however, that when the question of the relationship of histologic structure to prognosis is studied in a large enough series of cases, the disturbing effect of these latter factors will be statistically less important, since on the average their effect should be the same in all of the grades of malignancy.

The most confusing variable has undoubtedly been the choice of histologic characteristics used as a basis for grading. Hansemann himself, in estimating the grade of anaplasia of adenocarcinoma, used the loss of an adenoid arrangement and the number of normal and atypical mitoses as criteria. Greenough in his grading of breast cancer followed Hansemann fairly closely. His basis was the grade of differentiation as shown by the arrangement of cells around an open gland lumen, by the degree of secretory activity as indicated by the presence of vacuoles and droplets of mucoid material, by the uniformity of size of cells and nuclei as opposed to variations in size, by the absence or presence of hyperchromatic changes in the nucleus, and by the presence of few or many mitotic figures and whether or not they were irregular. He graded 73 cases in which complete data were available. He did not state the percentage of his total number of cases which had been lost track of. Sixty-eight per cent of Greenough's patients with Grade 1 tumors were alive five years after operation, and 33 per cent of those with Grade 2 tumors, while none of those with Grade 3 tumors survived that period.

Other pathologists have used as bases for grading breast carcinoma a wide variety of histological characteristics, for many of which no valid evidence exists proving a relationship to grade of malignancy. It is convenient to divide these attempts at grading into three groups: the Anglo-American school, which has in the main followed Greenough; the French school led by Delbet; the German school. In this review we shall discuss only those studies of breast carcinoma which have been based upon data ample enough to warrant serious consideration. Moreover, we shall not refer to studies treating of the grading of tumors in general, for it would seem that the validity of grading must be worked out separately for each different form of cancer.

White was the first to apply Greenough's method of grading. He selected at random from his records 100 cases for which the five-year end-results were known (his entire series consisted of 213 cases), and classified them into three grades of malignancy according to Greenough's criteria. Grade I was found to show 66 per cent cures, Grade II but 47 per cent, and Grade III no cures. White concluded that such a system of grading gave considerable information in some types of cases.
Patey and Scarff were the next to grade breast cancer along similar lines. They studied a series of 50 cases which had been followed for three years or more. They did not state the percentage of their total cases which had been lost track of. In their grading they attached chief importance to tubule formation, which they regarded as a favorable sign, and to variations in the size of the nuclei and to hyperchromatism of the nuclei, which they regarded as unfavorable signs. They concluded that there is a definite relationship between the histological character and the clinical course of carcinoma of the breast, and emphasized the point that in tumors of a low grade of malignancy the early or favorable stage is of longer duration and the patients are therefore more likely to present themselves for treatment before there has been much spread of the disease.

As part of their 1928 study of the malignancy of breast carcinoma, Lee and Stubenbord presented the results of histological grading of a series of 100 cases by Dr. Ewing. The cases were classified into three grades of malignancy. There were 52 per cent of five-year cures in the Grade I group, 33 per cent in the Grade II group, and 29 per cent in the Grade III group. In this paper Dr. Ewing does not state the criteria upon which he based his grading, but elsewhere he has given his support in a general way to Hansemann’s thesis that increase in malignancy is evidenced by an increasing degree of anaplasia, and he has listed the signs of anaplasia as “a cellular character, marked variations in size in either direction from the originating cells, increase of chromatic nuclear substance, abundance and abnormality of mitoses, and loss of polarity and diffuse infiltrative growth of cells.” Unfortunately, in this paper Lee and Stubenbord give no indication of how their 100 primary operable cases were selected, and what the percentage of lost cases was in the group from which they were chosen. The value of their statistics, including those dealing with grading, is therefore much less than if their records had been complete.

Smith and Bartlett applied Greenough’s criteria of grading to a series of 205 cases, and found that by this method an approximate prognosis could be made. Five-year end-results were available for 58 per cent of these cases. Of those with Grade 1 tumors 87 per cent survived, while only 42 per cent of those with Grade 2 tumors, and 13.6 per cent of those with Grade 3 tumors were still alive.

MacCarty has also attempted to correlate the morphology of breast carcinoma with prognosis. The histologic features which he has found to be significant differ, however, from those emphasized by Greenough. Without using formal grades, MacCarty
divided 91 fatal cases into those which showed his so-called "defensive factors" and those which did not. These factors were cellular differentiation, lymphocytic infiltration, fibrosis, and hyalinization. To judge from his illustrations, MacCarty means by cellular differentiation the tendency of cells to be arranged in a regular order around a central opening in the form of an acinus. He found that the patients whose tumors showed these "defensive factors" lived somewhat longer, and concluded that "the three greatest single factors in increased postoperative longevity...are cellular differentiation, hyalinization, and fibrosis." The value of MacCarty's study is somewhat vitiated by the fact that his series included only those cases which ended fatally. In a problem such as this, in which prognosis as to curability is being investigated, the tumors of the cured patients should also be studied.

Flothow has recently applied MacCarty's prognostic criteria to a larger series of 222 cases of breast carcinoma from the Mayo Clinic, including both living and dead patients. Averaging the number of "defensive factors" present in each case, he found that in the 88 cases in which the lymph nodes were involved but the patient living more than five years after operation, 70 per cent of the "defensive factors" were present. In the 33 cases in which the lymph nodes were free but the patient had died, only 26 per cent of the "defensive factors" were present. Unfortunately, Flothow was able to include in his study only 73 per cent of the total number of carcinomas of the breast which had been radically removed at the clinic, presumably because of incomplete follow-up data. This large percentage of lost cases introduces a factor of error which greatly detracts from the value of his study.

Heuper has devised the most elaborate of all the plans which have been advanced for grading breast cancer. He believes that no less than twenty different histologic factors are of prognostic significance. Included are the nucleocytoplasmic ratio, the number of pencil cells, the vascularity of the stroma, and the amount of round-cell infiltration. Each factor is assigned a numerical value corresponding to the degree to which it is present, the total forming a "histological malignogram." It must be said that the relationship to prognosis of many of these histologic factors is largely theoretical, and Heuper presents no valid evidence to substantiate their significance. His "histological malignogram" is expressed in a mathematical detail which is out of all proportion to the accuracy of the available knowledge concerning the significance of these different factors.

A number of American pathologists, including Plaut and Reimann, have reached the conclusion that the histologic character-
istics of breast carcinoma are of little or no prognostic significance. Reimann is perhaps the most incredulous of all. He attempted to grade as to malignancy a series of 105 consecutive cases of carcinoma of the breast. Ninety-five per cent of the patients had been traced, but the length of time for which they had been followed is not stated. In the grading, small cell size, much mitosis, and little degeneration were taken as unfavorable. Streaks of cells, small nests, large nests, sheets of cells, and mucoid and adenoid types were taken as of decreasing order of malignancy. Vascular thrombosis was considered unfavorable. When the cases were divided on this basis into three grades of malignancy, Reimann found no correlation whatever between his grading and the actual end-results.

Twenty-five years ago, in his important report of the end-results of his radical operations for breast cancer, Halsted made a contribution to the knowledge of the relationship of histologic type to prognosis which should not be overlooked in a survey of American contributions. The three-year end-results were known in 92 per cent of his 228 cases. The percentages of cures in the different histologic types of the disease were as follows:

<table>
<thead>
<tr>
<th>Histologic Type</th>
<th>Percentage of Cures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer cysts</td>
<td>33.3 per cent</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>75 per cent</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td>48 per cent</td>
</tr>
<tr>
<td>Circumscribed scirrhous</td>
<td>46.4 per cent</td>
</tr>
<tr>
<td>Small infiltrating scirrhous</td>
<td>35.5 per cent</td>
</tr>
<tr>
<td>Large infiltrating scirrhous</td>
<td>20.5 per cent</td>
</tr>
</tbody>
</table>

From this table the favorable significance of adenocarcinoma, in which the degree of anaplasia is comparatively slight, is apparent. Halsted himself did not discuss this relationship of histologic type to prognosis, but his recognition of the relationship is shown by the fact that he used the histologic type in deciding the extent of the operation required. He stated: "We find ourselves for the past two years again performing the neck operation for most cases. We omit it in hopeless cases, in most "duct cancers," and in some carcinomata of emphatically adenomatous type in which the axilla at operation is not macroscopically involved."

The interest of the French in relating the morphology of breast cancer to its prognosis was first aroused by the attempts of Delbet. As a result of the comparison of the histologic findings and the end-results of operation in his series of 153 cases, Delbet concluded that it is possible to make prognoses from the histology in some but not all cases. He found the "large-cell type" the most malignant of all. The "independent-cell type," in which the cells are arranged loosely without having any orderly architectural relationship to each other or to the stroma, was also highly malignant,
Delbet looked especially for invasion of blood vessels by the tumor cells and placed all cases with that characteristic in a separate group of "hemophilic carcinomas." The malignancy of this group was indicated by the fact that all of the 26 patients so classified were dead within four years. "Clear-celled" carcinomas, in which the transparent cytoplasm suggested a Grawitz tumor, had a favorable prognosis. A very similar type, "carcinoma with clear cytolysis," in which the cytoplasm appeared to be dissolving, probably also had a good prognosis. Delbet laid the greatest stress, however, on the prognostic significance of mucous secretion. According to him this is invisible in breast carcinoma with ordinary staining technic, but is brought out by the mucicarmine stain. The mucus then appears as droplets or smudges of carmine in the cytoplasm of the parenchymal cells, or as irregular masses excreted within the lumina of the acini, or it may infiltrate the stroma. When the so-called gelatinous type of breast cancer is stained by this method, the gelatinous material takes the carmine stain. Delbet recut from the old blocks and stained with mucicarmine sections from 54 of his cases for which he had follow-up records. Twenty-four, or 44 per cent, of these showed mucous secretion in all or in a portion of the tumor. Of these "secreting carcinomas," 21 were followed for at least five years, at the end of which time 10, or 48 per cent, remained well. When it is recalled, however, that Delbet had the five-year follow-up records for only 65 per cent of the total number of cases upon which he operated and which were histologically verified, and further that he did the mucicarmine stain in only one-half of these cases which he was able to follow, it becomes apparent that the opportunity for error in his data as to the curability of his "secreting" type is very great. From these data it is impossible to subscribe to his definite conclusion, that this type of carcinoma is comparatively benign.

Leroux and Perrot, on the basis of a study of the morphology of 27 cases in which the end-results were known (the percentage of their total cases which had not been traced is not stated) confirm the prognostic significance of the mucicarmine stain in breast carcinoma. They distinguish two broad histologic types of the disease. In Type 1 the epithelial cells contain droplets of secretion which stain with mucicarmine, the stroma is dense and shows an affinity for mucicarmine, and there is infiltration by lymphocytes. In Type 2 the epithelial cells do not contain droplets of secretion, the stroma is not prominent, there are no foci of lymphocytes, and areas of necrosis are seen. The tumors which approach Type 1 are favorable, while those which resemble Type 2 usually recur rapidly and metastasize widely.
Moureau and Lambert have followed Delbet closely in their grading of breast carcinoma. From the study of 136 cases in which the three-year results of treatment were known they have concluded that the microscopic morphology is of great value in estimating a prognosis. They did not state the percentage of their total number of cases which had been lost track of. In 20 cases they had only old frozen sections to study. They found that polymorphism was the most grave sign. When the parenchymal cells lost all semblance of an orderly arrangement and infiltrated diffusely, and when they showed a tendency to grow into blood vessels, the prognosis was also bad. An affinity for the mucicarmine stain these authors regarded as a distinctly favorable prognostic sign. In the group of 22 tumors which they classified on this basis as “secreting,” there were 95 per cent of three-year survivals, while of the 56 patients in the non-secreting group, only 55 per cent survived that long.

Bertrand and de Nagy are the only workers who have disagreed with Delbet's interpretation of the prognostic significance of the mucicarmine stain. They did the mucicarmine and other stains on a series of 68 breast carcinomas. Twenty-eight, or 41 per cent, of these were found to contain mucus. Of these “secreting” tumors 23, or 82 per cent, were found at operation to have axillary metastases. In only 62 per cent of their “non-secreting” group of tumors was axillary metastasis found. Bertrand's and de Nagy's follow-up data were inconsequential, only two, or 7 per cent, of their patients with “secreting” tumors having been traced for as long as five years. From their data as to axillary metastasis, however, they concluded that the presence of mucus as demonstrated by the mucicarmine stain has no particular prognostic significance.

The German pathologists who have tried to grade breast carcinoma have eschewed special staining methods and have classified their cases on an entirely different basis. In the main they have used the older grouping of scirrhous, medullary, adenocarcinoma, etc., and also in some instances have tried to correlate the degree of anaplasia with the prognosis. Salomon was one of the first to attempt this. He studied 200 cases, for which he had a 54 per cent three-year follow-up. His classification and corresponding percentages of cure were as follows: solid carcinoma, 42 per cent; medullary carcinoma, 21 per cent; infiltrating carcinoma, 13 per cent; adenocarcinoma, 71 per cent; carcinoma arising in a cyst, 67 per cent. Salomon also grouped his cases according to the degree of anaplasia, and drew the following significant conclusion: "The prognosis of mammary carcinoma is primarily dependent upon the grade of malignancy. . . . The least anaplastic forms of car-
cinoma, the adenocarcinomas, give a very favorable result, while the most highly anaplastic forms, the small-celled soft and the scirrhous forms, have a very bad prognosis."

In 1914, the year following Salomon's study, Lindenberg published an important study of breast carcinoma in which a correlation between histologic type and end-result was also attempted. Lindenberg reported the five-year results in a series of 153 cases, of which only 4.5 per cent had been lost track of. His main groups and their respective percentages of cure were as follows: adenocarcinoma, 32 per cent; scirrhous carcinoma, 25 per cent; carcinoma simplex, 28 per cent. These data suggest that the prognosis of adenocarcinoma is not much different from that of other forms of breast carcinoma.

In 1921 Boss studied the relationship of histologic type to prognosis in breast cancer along the lines laid down by Salomon. He had available a series of 127 cases, in 91 per cent of which the five-year end-results were known. His main histologic groups and their respective percentages of cure were: circumscribed scirrhous carcinoma, 46 per cent; circumscribed solid carcinoma, 36 per cent; circumscribed medullary carcinoma, 16 per cent; infiltrating carcinoma, 2.7 per cent; adenocarcinoma, 20 per cent. From these findings Boss concluded that circumscribed scirrhous carcinoma is the most favorable type of the disease, the prognosis for medullary and for infiltrating carcinoma being considerably worse. He stated that he also believed that the prognosis for gelatinous carcinoma and for adenocarcinoma was relatively favorable, although these types occurred so infrequently in his series of cases that he was able to offer no valid evidence on the point. Boss concluded that a knowledge of the histologic type of the tumor is of distinct importance in determining the outcome in breast cancer.

In the same year Hoffmann came to a similar conclusion concerning the relatively favorable prognosis of scirrhous carcinoma from his study of the results of treatment in a series of cases from Heidelberg. He had available 388 cases, the five-year results being known in 80 per cent. The data as to the histologic type of the tumor were at hand, however, for only 57 per cent of the traced cases. The percentages of cure for the different histologic types were as follows: scirrhous carcinoma, 36 per cent; medullary carcinoma, 21 per cent; squamous carcinoma, 0 per cent.

Feist and Bauer graded the 126 cases of breast carcinoma which they reported in 1922. The five-year results were known in 84 per cent of the cases. When they were classified in three groups according to degree of cellularity, the percentages of cure were as follows: cell-rich, solid, and adenocarcinoma, 50 per cent; transitional forms, 20 per cent; cell-poor, scirrhous carcinoma, 25
per cent. On this basis the cell-poor, scirrhous type appeared to have much the worst prognosis. The authors also classified their cases according to grade of anaplasia. In the group of tumors composed of immature, highly anaplastic cells, 18 per cent of cures were obtained. A transitional group, made up of those tumors which showed different grades of anaplasia in different parts, yielded 28 per cent cures; while 26 per cent of those patients with tumors showing only slight anaplasia were cured. Feist and Bauer concluded that the tumors composed of immature highly anaplastic cells have from a quarter to a third worse prognosis.

Dahl-Iversen studied the relationship of histologic type to prognosis in a series of cases from the Copenhagen City Hospital. He had the three-year results for 85 per cent of a series of 100 cases. When the tumors were classified according to their general histologic type, the following percentages of cures were obtained: medullary carcinoma, 0 per cent; carcinoma simplex, 32 per cent; adenocarcinoma, 33 per cent; scirrhous carcinoma, 43 per cent.

Present Series of Cases

From the preceding survey of previous attempts to grade breast carcinoma it is clear that there has been no agreement as to which histologic characteristics should be used as a basis for grading. It would therefore appear that our first aim in a study of the value of grading should be directed toward discovering which characteristics, if any, in the structure of breast carcinoma are associated with an increase or decrease in the grade of malignancy as shown by the end-results in a strictly compiled series of cases. Only when the true bases for grading have been determined by this sort of analysis, should formal grading be attempted.

We have approached the problem of the histologic grading of breast carcinoma from this point of view. It has been our privilege to study, for this purpose, a very exceptional series of cases, that of Dr. Frank S. Mathews. This series presents unique advantages for the investigation of the value of grading in that a number of variables have been eliminated which may well have caused confusion in other similar studies.

The series consists of 164 consecutive radical mastectomies performed for cancer by Dr. Mathews at St. Luke's Hospital, New York, from January 1913 to May 1927, inclusive. All the operations having been done by the same individual and a uniform surgical technic having been followed throughout, it may be assumed that the treatment was as uniform as it could possibly be. Secondly, the series is not a selected group. Dr. Mathews has included every case upon which he performed radical mastectomy, although in a number of these the disease was so advanced that it
would have been classed by other surgeons as inoperable. Whenever there seemed even a remote chance of benefiting the patient operation was done. Again, no separate group was set up for patients who refused operation, all of the patients in whom it was advised having ultimately submitted to it.

A most important advantage of the series is the completeness of the follow-up data. All but five, or 97 per cent, of the patients have been traced for five years or more. This follow-up is Dr. Mathews’ personal accomplishment, and the large amount of time and energy which he has personally given to tracing these patients is an indication of his interest in the matter. It should be noted that tracing patients is particularly difficult in metropolitan New York because of the shifting character of the population. Dr. Mathew’s success, however, shows that almost all patients can be traced if the required time and intelligence are devoted to the purpose.

It is of interest to note that there have been but two American series of cases of breast cancer previously reported in which the follow-up was approximately as complete: that of Halsted in 1907 (92 per cent) and that of Greenough and Simmons in 1921 (95 per cent).

From the histological aspect the present series of cases also possesses unusual advantages for grading. All the cases have been diagnosed by Dr. F. C. Wood. Not only has the technic 2

2 The technic used in preparing histologic sections at St. Luke’s Hospital is described in detail in Laboratory Technic, by F. C. Wood, Karl Vogel, and L. W. Famulener, New York, J. T. Dougherty, 1929, page 5. Briefly it is as follows:

Fixing and Embedding

1. 4 per cent formaldehyde, 12 to 24 hours
2. 80 per cent alcohol, 2 hours
3. 95 per cent alcohol, 2 hours
4. 95 per cent alcohol, overnight
5. Absolute alcohol, two changes in 24 hours
6. Equal parts of carbon disulphide and absolute alcohol, 1 to 4 hours
7. Pure carbon disulphide, 2 to 6 hours
8. Carbon disulphide saturated with paraffin at room temperature
9. Carbon disulphide saturated with paraffin at 37 to 40 C. for 1 to 2 hours
10. Stock melted and filtered paraffin at 55 C. for 1 hour, then to fresh paraffin, not previously used, for 1 hour
11. Embedded in fresh paraffin, not previously used

Staining

1. Xylol, about 2 minutes
2. Xylol, about 2 minutes
3. Absolute alcohol, 2 minutes
4. Absolute alcohol, 2 minutes
5. 80 per cent alcohol, 2 minutes
6. Water, 2 minutes
7. Hematoxylin, about 5 minutes (control with microscope)
8. Distilled water, 10 minutes
9. Tap water, 10 minutes (better 1 hour)
10. 80 per cent alcohol, 2 minutes
11. Eosin, ½ to 2 minutes
12. Absolute alcohol, 2 to 3 minutes
13. Absolute alcohol, 2 to 3 minutes
14. Absolute alcohol, 2 to 3 minutes
15. Carbol-xylol, 1 minute
16. Xylol, 1 minute
17. Mount in gum dammar
of preparing the sections been constant throughout the twenty-
year period covered by the series, but it has so happened that the
same technician has cut and stained all the sections. This con-
stant technic is a factor of great importance in a histological study
of this sort. Variation in the process of fixing, dehydrating, and
embedding tissues results in changes in the degree of shrinkage
which may prohibit an accurate comparative estimation of cell
size and character. Changes in the technic of staining likewise
interfere with a comparative estimation of hyperchromatism.

There have been an average of eight histologic sections avail-
able for study for each case in the series. It can therefore be said
that when variations existed in the structure in different portions
of the tumor they were probably seen.

Special precautions taken by Dr. Wood to prevent deteriora-
tion of the sections with age have been so effective that the sections
made twenty years ago are quite free from the yellowish discolora-
tion of the balsam usually seen in old slides, and the stains have
hardly faded at all. This has been in part the result of using
only specially prepared chemically pure xylol. Commercial xylol
contains traces of acids which cause fading of the stains due to
oxidation. Another important aid in preservation has been the
mounting in gum dammar rather than in balsam. Gum dammar,
also a variety of resin, possesses the advantage that it is naturally
free of the terpenes which contaminate balsam. It is these ter-
penes which through oxidation cause the yellowish discoloration
and fading in old sections. The advantage of such perfectly pre-
served sections for the study of the minutiae of cell morphology
is apparent.

A clinical factor tending to simplify the histologic study of this
series of tumors is the fact that only two of the patients received
preoperative radiation. Heavy preoperative radiation may pro-
duce abnormal mitosis and atypical cell forms which make grading
difficult or even impossible.

For the purposes of grading, five cases must be deducted from
the 159 in this series in which the five-year end-results of treat-
ment are known; these are two cases in which the sections have
been lost, one operative death, one carcinoma in the male breast,
and one case of sarcoma. This leaves 154 cases available for
study.

In accordance with the plan mentioned above for determining
the significance of histologic grading in any particular form of
cancer, we made no attempt at the outset of the present study to
grade formally the cases in the series. We began rather by trying

*Chemically pure benzol is equally satisfactory, and it has the advantage of being
cheaper and easily obtainable.
to find out which histologic characteristics have enough of a relationship to the prognosis in breast carcinoma to warrant their use as a basis for grading. Fifteen different characteristics were selected whose relationship to the grade of malignancy in breast carcinoma seemed to us worth while investigating. These may be conveniently grouped as relating to (1) the manner of growth of the cells, (2) the cell morphology, and (3) the reaction of the stroma, as follows:

**Manner of growth of cells**
1. Papillary character: origin in a cyst formed in a duct
2. Comedo character: growth mainly within ducts, often with central necrosis
3. Plexiform character: growth in plexiform strands
4. Adenoid arrangement of cells

**Cell morphology**
5. Size of cells
6. Size of nuclei
7. Variation in size and shape of nuclei
8. Hyperechromatism of nuclei.
9. Number of mitoses
10. Secretory activity of cells
11. Clearness of cytoplasm

**Reaction of stroma**
12. Fibrosis
13. Hyaline degeneration
14. Lymphocytic infiltration
15. Gelatinous degeneration

The histologic sections for each case were studied as to the presence, or degree of presence, of each of these different characteristics, a card being made out for each case, bearing the case record number and notations as to the occurrence of each of the characteristics. These determinations were, of course, made without knowledge of the clinical features and the end-result of the case. This step completed, the end-result was noted on the back of each card by an independent worker, and the relationship of each of the fifteen different characteristics to the end-results in the series as a whole was calculated mathematically. The findings for each characteristic deserve to be considered separately.

**Papillary Character:** Papillary adenocarcinoma arising in a cyst formed from a dilated duct in the breast (Fig. 1) has been given a favorable prognosis by most of those who have studied the question. Our experience is no exception; there were 4 such cases in the series, and all 4 patients were well after five years, as shown in Table I.

The comparatively benign character of papillary adenocarc-
cinoma cannot be satisfactorily ascribed to the circumstance that the tumor is in the main confined within the walls of a cyst. There

<table>
<thead>
<tr>
<th>Table I: Papillary Character</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
</tr>
<tr>
<td>Number of cases</td>
</tr>
<tr>
<td>Number of 5-year survivors</td>
</tr>
<tr>
<td>Per cent of 5-year survivors</td>
</tr>
<tr>
<td>Average length of life in those dying before 5 years</td>
</tr>
</tbody>
</table>

is usually some infiltration beyond the cyst wall; this was the case in all 4 of our cases. It is a striking fact that the parenchymal cells themselves in this type of carcinoma usually show but a slight degree of anaplasia. They are usually arranged in a foliate pattern as a single layer of fairly regular cuboidal cells on slender connective-tissue stalks. Mitoses are few. It would rather seem that it is this slight degree of anaplasia which is the main factor in the good prognosis of these tumors.

It is of interest to note that among the 4 cases in this series there was one of an unusual histologic type. Filling a large cyst, the tumor was composed of broad sheets and plexiform strands of comparatively regular, rather small cells with few mitoses. They were distinctly of the basal-cell type.

**Comedo Character:** Although "comedo" carcinoma is an unsatisfactory name, it is the best term which has yet been proposed to fit that comparatively small but distinct group of carcinomas of the breast in which the cells grow mainly within and fill up the ducts. The presence of a central necrotic core carries the simile
further (Fig. 2). There were 10 tumors with this type of architecture in the present series, as shown in Table II.

**Table II: Comedo Character**

<table>
<thead>
<tr>
<th></th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>10</td>
<td>144</td>
</tr>
<tr>
<td>Number of 5-year survivors</td>
<td>4</td>
<td>59</td>
</tr>
<tr>
<td>Per cent of 5-year survivors</td>
<td>40</td>
<td>41</td>
</tr>
<tr>
<td>Average length of life in those dying before 5 years</td>
<td>3.7</td>
<td>1.9</td>
</tr>
</tbody>
</table>

To judge from the percentage of five-year survivors, this type of tumor has the same prognosis as other types of carcinoma of the breast taken as a whole. It should be remembered, however, that in a group as small as this (only 10 cases) the possibility of statistical error is great. It is in order to minimize this as much as possible that we have also calculated the average length of life in those dying before five years. When this comparison is made, it is seen that the patients with "comedo" carcinoma who died before five years lived just twice as long as those with all other types of carcinoma. From a difference such as this it seems justifiable to conclude that the "comedo" character is one which should bear weight in a plan for grading breast carcinoma.

**Plexiform Character:** Occasional carcinomas of the breast are distinguished by a plexiform character (Fig. 3). The parenchymal cells are closely packed together to form long, thick bands. These bands are sharply marked off from the surrounding stroma, and are united in the form of a crude network. This type of tumor has a superficial resemblance to plexiform epidermoid carcinoma.
as it occurs in the cervix, but closer study will show that other areas of the tumor have the unmistakable features of adenocarcinoma. There were 7 cases of this type in the present series, as shown in Table III.

<table>
<thead>
<tr>
<th>Table III: Plexiform Character</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>Number of cases</td>
</tr>
<tr>
<td>Number of 5-year survivors</td>
</tr>
<tr>
<td>Per cent of 5-year survivors</td>
</tr>
<tr>
<td>Average length of life of those dying before 5 years</td>
</tr>
</tbody>
</table>

These findings suggest that the prognosis of the plexiform type of breast carcinoma is neither better nor worse than that for other types considered as a whole. We will, therefore, take no consideration of it in our plan for grading.

Adenoid Arrangement of Cells: The tendency of the cells to arrange themselves about an open space to form acini is certainly one of the most important architectural features to be considered in a study of the grading of breast carcinoma. We have distinguished three degrees to which this fundamental characteristic is preserved in the tumors in this series—marked adenoid arrangement (Fig. 4), slight adenoid arrangement (Fig. 5), and absence of adenoid arrangement (Figs. 6 and 9). The first group would correspond to adenocarcinoma in the strictest sense of the term. The third group would correspond to what is ordinarily called diffusely infiltrating carcinoma. These three groups represent
increasing degrees of anaplasia in breast carcinoma. The results of this classification in the present series of cases are shown in Table IV.

It is at once apparent from these findings that a marked

**Table IV: Adenoid Arrangement of Cells**

<table>
<thead>
<tr>
<th></th>
<th>Marked</th>
<th>Slight</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>22</td>
<td>53</td>
<td>79</td>
</tr>
<tr>
<td>Number of 5-year survivors</td>
<td>20</td>
<td>19</td>
<td>24</td>
</tr>
<tr>
<td>Per cent of 5-year survivors</td>
<td>90</td>
<td>36</td>
<td>24</td>
</tr>
<tr>
<td>Average length of life in those dying before 5 years</td>
<td>3.1</td>
<td>2.4</td>
<td>1.8</td>
</tr>
</tbody>
</table>

adenoid arrangement is a strong indication of a good prognosis, and should weigh heavily in a plan for grading breast carcinoma.

![Fig. 6. Carcinoma of the Breast, in Which an Adenoid Arrangement of the Cells is Absent. × 65](image)

Not only were there three times as high a proportion of five-year cures among the patients whose tumors showed a marked adenoid arrangement, but those in this favorable group who died before five years elapsed lived almost twice as long as those in which the adenoid arrangement was absent.

This favorable significance of a marked adenoid arrangement has been a finding of most of those who have attempted to evaluate this characteristic in their grading of breast carcinoma. Although their plans for grading were widely different, Greenough, MacCarty, Salomon, and Feist and Bauer all agreed on this point. Indeed, it can be said that this is the only point on which the majority of those who have graded breast cancer have agreed.

The fundamental significance of the preservation of an adenoid arrangement as an indicator of the degree of anaplasia in adeno-
carcinoma was long ago recognized by Hansemann himself. He placed this characteristic first among those features by which he judged the anaplasia of tumors arising from glands. The confirmation of Hansemann's theory that tumors increase in malignancy as their degree of anaplasia increases supplied by these attempts to grade breast carcinoma deserves the serious consideration of those pathologists who continue to doubt Hansemann's thesis.

If an increasing degree of anaplasia is paralleled by an increasing malignancy in carcinoma of the breast, we should expect the carcinomas which show squamous metaplasia to be the most malignant. In these rare tumors the departure from the normal form and arrangement of the duct cells which gave rise to the neoplasm, i.e. the degree of anaplasia, certainly reaches its maximum. In the present series of cases there were two cases of this type. In the first the cells had entirely lost their tendency to assume an adenoid arrangement, and grew in sheets or strands. The cells were large and round or polygonal, with an acidophilic cytoplasm; except for the absence of intercellular bridges, they bore a close resemblance to squamous cells. The patient died with metastases one year after operation. In the second case the squamous metaplasia had progressed further, for there were numerous well defined epithelial pearls, although intercellular bridges were still lacking. Pulmonary metastases caused death six months after operation. In both of these tumors the metaplastic origin of the squamoid cells from glandular epithelium was unquestionable, for in some areas the derivation from adenocarcinoma could be clearly traced.

Size of Cells: There is perhaps no more barren chapter in the history of tumor pathology than that dealing with the interpretation of cell size. In the early days of microscopic pathology Lebert and others attempted to make cell size a diagnostic criterion of cancer until the idea was ridiculed by Virchow. There have been numberless studies of the significance of the nucleo-cytoplasmic ratio, none of which has yielded any clear-cut conclusion.

In recent times both unusually large and unusually small cells have been implied by different authors to signify an unfavorable prognosis in breast carcinoma. Many pathologists regard very small cells as a grave sign. Delbet and Mendaro, however, found carcinomas with large cells to be exceptionally malignant. Stout regards both very large-celled and very small-celled carcinomas as unusually malignant. Iselin, on the other hand, concluded that

* See a discussion of this point by the writer in the American Journal of Cancer 16: abst. p. 1021, 1932.
"the larger and more numerous the cells in breast carcinoma, the better is the prognosis." Greenough, who investigated this question more critically than anyone else, found cell size (when considered as a separate characteristic apart from variation in size) to have little prognostic significance.

We have failed to find, however, any report of the measurement of the cells by micrometric methods in a series of cases of breast carcinoma which met strict statistical requirements (a series of at least 100 unselected and uniformly treated cases, in which the five-year follow-up was at least 95 per cent complete). We therefore carried out such measurements in the present series. At a magnification of 400 (Zeiss 10 x 40), an eyepiece micrometer with 100 divisions in 0.5 mm. was calibrated against a stage micrometer with 100 divisions in 1 mm. Each division on the eyepiece micrometer was thus found to equal 1.6 μ. The average diameter of the cells in each tumor was then determined by measuring at least half a dozen cells in several different portions of the tumor. When marked variation in the size and shape of cells was present it was very difficult to determine this average diameter. In many tumors, also, the limiting membrane of the cytoplasm for some obscure reason is but poorly defined, and it is impossible to determine the cell diameter with reasonable accuracy. Particularly in scirrhous carcinoma, where the cells have the appearance of being squeezed and distorted by the dense fibrous tissue in which they lie, it is often impossible to see the outlines of the cytoplasm at all.

With as much care as possible in the presence of these limitations, three classes of cell size—small, medium, and large—were established. On this basis the findings were as shown in Table V.

From these data the high percentage of cures among the patients with small-celled tumors would suggest that small cells are a favorable prognostic factor in breast carcinoma. Our judgment is, however, that the inherent difficulties and consequent inaccuracy in measuring cell diameter are so great, even when the most rigid histologic technic is used in preparing the sections, that these measurements have no practical value.

<table>
<thead>
<tr>
<th>Table V: Cell Size, In Terms of Average Diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Number of cases</strong></td>
</tr>
<tr>
<td><strong>Number of 5-year survivors</strong></td>
</tr>
<tr>
<td><strong>Per cent of 5-year survivors</strong></td>
</tr>
<tr>
<td><strong>Average length of life in those</strong></td>
</tr>
<tr>
<td><strong>dying before 5 years</strong></td>
</tr>
</tbody>
</table>
Size of Nuclei: The possibilities of accurate measurement of the size of nuclei are quite different. The outline of the nucleus is almost always sharply defined, and its diameter can readily be measured with an eyepiece micrometer such as we have used. To insure that the greatest diameter is being measured, the focus should be varied so that different planes through the nucleus are brought into view. As in the case of cell size, however, it will be found difficult to determine the average size of the nucleus when this varies greatly.

When three classes of nucleus size were established, the findings in the present series of cases were as shown in Table VI.

![Fig. 7. Carcinoma of the Breast, in Which There Is but Slight Variation in the Size and Shape of the Nuclei. \( \times 125 \)]

**TABLE VI: Nucleus Size, In Terms of Average Diameter**

<table>
<thead>
<tr>
<th></th>
<th>Large From 9.8 ( \mu ), up</th>
<th>Medium 8 ( \mu ) to 6.4 ( \mu ), inclusive</th>
<th>Small 4.8 ( \mu ) and less</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>33</td>
<td>105</td>
<td>16</td>
</tr>
<tr>
<td>Number of 5-year survivors</td>
<td>8</td>
<td>43</td>
<td>12</td>
</tr>
<tr>
<td>Per cent of 5-year survivors</td>
<td>24</td>
<td>40</td>
<td>75</td>
</tr>
<tr>
<td>Average length of life in those dying before 5 years</td>
<td>1.8</td>
<td>2.2</td>
<td>1.6</td>
</tr>
</tbody>
</table>

The high percentage of five-year survivors among the patients with tumors in which the nuclei were small suggests that the size of the nuclei, considered as a separate characteristic, may indeed have a bearing on prognosis. In view of the elaborate technic required for measurements of this type, however, it seems advisable not to include nucleus size among the criteria to be used in a practical plan for grading breast carcinoma.
Variation in Size and Shape of Nuclei: Variation in the size and shape of cells and nuclei is certainly one of the best indications of degree of anaplasia. Greenough, and those who used his system of grading, found degree of variation in size one of the best prognostic guides in breast carcinoma. He presented tables which showed the relation to curability of variation in size of both cells and nuclei separately. There was very little difference in the findings for the two factors.

Because of the greater accuracy with which the size of the nucleus can be determined, we have limited our investigation of variation in size and shape to the nucleus in the present series of cases. It would seem that this determination must be more reliable than a consideration of variation in cell size and shape. When variation in the size and shape of the nuclei was classified as slight (Fig. 7), moderate (Fig. 8), or marked (Fig. 9), the findings were as shown in Table VII.

The proportion of five-year cures in the group of tumors in which the nuclei showed but slight variation in size and shape is seen to be more than four times as great as in the group in which
there was marked variation. It would seem that this factor of variation should be given considerable weight in a plan for grading breast carcinoma.

Hyperchromatism of Nuclei: The intensity with which the nuclei take the basophile stain varies a good deal in different tumors even when the staining technic is kept perfectly constant. The presence of many deeply staining mitoses gives the effect of hyperchromatism often seen in highly anaplastic tumors. Sometimes, however, all the nuclei in a tumor are hyperchromatic, even though they appear to be in the resting stage. Whatever its cause may be, hyperchromatism has generally been regarded as a sign of increased malignancy. Greenough, in analyzing the significance of hyperchromatism in his series of cases, found this to be the case.

Most writers in discussing hyperchromatism have failed to specify whether they were referring to intense staining of the cell as a whole, including the cytoplasm, or to hyperchromatism of the nucleus only. It is our opinion that the intensity of staining of

<table>
<thead>
<tr>
<th>Table VIII: Hyperchromatism of Nuclei</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
</tr>
<tr>
<td>--------------------------------------</td>
</tr>
<tr>
<td>32</td>
</tr>
<tr>
<td>Number of 5-year survivors</td>
</tr>
<tr>
<td>Per cent of 5-year survivors</td>
</tr>
<tr>
<td>Average length of life in those</td>
</tr>
<tr>
<td>dying before 5 years</td>
</tr>
</tbody>
</table>

the cytoplasm and of the nucleus are quite unrelated characteristics, and that the former has no prognostic significance. For instance, the cytoplasm is sometimes deeply acidophilic or deeply amphophylic without any accompanying hyperchromatism of the nucleus. Such tumors do not seem to have an exceptional prognosis. In the present study we have attempted to estimate the degree of chromatism of the nuclei only, and have divided the cases into three groups according to whether the chromatism was slight, moderate, or marked. These findings are shown in Table VIII.

Both the moderately diminished percentage of five-year cures and the somewhat lessened length of life in the not cured, which appear in the group of cases with marked hyperchromatism, suggest that this factor has some prognostic significance. The evidence does not appear to be striking enough, however, to warrant considering hyperchromatism in a plan for grading breast carcinoma. It should also be remembered that if the technic of staining is varied the intensity of the stain means nothing, and, since practically this is often the case, this characteristic is of little significance.
Number of Mitoses: In some types of cancer, at least, a high grade of malignancy is ordinarily accompanied by an increase in the number of mitoses, both normal and atypical. Carcinoma of the breast seems to be one of these types. Plaut's objection to using the number of mitoses as an indicator of malignancy, because cell division in cancer so often takes place by amitosis, is less applicable to carcinoma of the breast than it is to some other types of cancer, such as lymphosarcoma, where amitosis seems to be the usual method of cell division. In breast carcinoma it would appear that, although amitosis undoubtedly occurs, a considerable proportion of the cells divide by mitosis. Certainly mitoses are frequently seen, and in the very malignant tumors they are apt to be numerous and atypical. In his series of cases Greenough found that as the number of mitoses increased the percentage of cures fell. None of his cases with a "high degree" of mitosis was cured.

To determine the number of mitoses, we used the plan suggested by Stout, which enables the expression of this characteristic in simple arithmetical terms. The average number of mitoses per high power field was calculated by counting the mitoses in at least a half a dozen different fields in various parts of the tumor. A constant magnification of 400 (Zeiss 10 × 40) was used.

Palugyay has made the interesting observation that the relative number of prophases as compared to the number of later phases of mitoses is increased in highly anaplastic cervical carcinomas. We should have liked to include such a study of the relationship of type of mitosis to grade of anaplasia in the present report, but fear to overburden the reader with statistics. We have therefore merely determined the total number of mitoses per field, including, of course, in our count all prophases. It is admitted that it was sometimes difficult to distinguish, with the magnification used (× 400 — dry), prophases from hyperchromatic but apparently resting nuclei. Care was also taken to avoid counting degenerating nuclei as atypical mitoses, for it is easy to make this
mistake. To this end the counts were made in the portions of the tumor which showed the least necrosis and round-cell infiltration.

When the tumors were classified into three groups according to the average number of mitoses per field the results were as shown in Table IX.

From these data it is seen that as the number of mitoses increases there is a striking decrease in the percentage of five-year cures and a diminution in the length of life of those dying before five years. It would seem, therefore, that an estimation of the number of mitoses should be a feature of a plan for grading breast carcinoma.

SECRETORY ACTIVITY OF CELLS

A good deal of attention has been paid to the prognostic import of secretion in breast carcinoma, and various plans have been evolved for determining this factor. Delbet and his followers have relied on the mucicarmine stain, and have claimed that the presence of mucus as shown by this stain is a distinctly favorable prognostic sign. The standard technic for the stain calls for fixation of the tissue in alcohol rather than in formalin. We have found that sections cut from old formalin-fixed tissue do not take the stain as satisfactorily as sections made from fresh tissue fixed in alcohol. In his book Delbet does not describe the technic which he used beyond the fact that he also stained sections recut from old blocks, which presumably were fixed in formalin.

It is true, however, that when the mucicarmine stain is carried out on breast carcinomas some of these tumors contain a considerable quantity of mucus, while others show none at all. Furthermore, even in our limited experience with the stain, we have found such mucus in tumors which gave no indication of it in the form of intracellular vacuoles when stained with the ordinary hematoxylin-eosin stain. Whether this mucus is secreted or whether it is a degenerative change would appear to be an open question. What its prognostic significance is would also seem to be as yet


Mayer's Mucicarmine Method

Fixation in absolute alcohol. Paraffin sections. Stain five to ten minutes in the following solution diluted for use 1 to 10 with water:

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carmine</td>
<td>1 gram</td>
</tr>
<tr>
<td>Aluminum chloride (dry)</td>
<td>0.5 gram</td>
</tr>
<tr>
<td>Water</td>
<td>2 c.c.</td>
</tr>
</tbody>
</table>

Heat over a flame for two minutes until the solution appears dark colored. Filter after twenty-four hours. Wash in water, dehydrate in alcohol, clear, and mount in xylol balsam.
undecided. Delbet has now begun to do the stain on fresh tissue (presumably alcohol fixed). Others must also have been interested by the problem. It is to be hoped that in a few years more, when enough time has elapsed to permit of five-year results on these cases, the answer will be available.

Greenough attempted to estimate the amount of "secretion" in breast cancer without the aid of a special stain. He stated: "A further light upon cell differentiation in the epithelial cells of the breast is obtained from the droplets of mucoid secretion retained in the cells as vacuoles. These occur frequently in the cells of breast cancer and give rise to many of the peculiar appearances called 'cell-inclusions,' 'secretion bodies,' etc. . . . The presence of marked secretory activity is shown to be an indication of low malignancy and its absence indicates a less degree of differentiation and thus a more malignant tumor."

In the present series of cases we made a sincere attempt to follow Greenough's plan of classifying the cases according to slight, moderate, and marked degree of secretion as shown by the number of vacuoles in the cytoplasm. It was found that it was extraordinarily difficult to distinguish such vacuoles from artefacts due to fixation and from degenerative changes in the cytoplasm. Our findings, such as they are, are shown in Table X.

It would seem justifiable to conclude from these data that the mere presence of vacuoles in the cytoplasm has no prognostic significance.

**TABLE X: Secretory Activity of Cells as Shown by Vacuoles in the Cytoplasm**

<table>
<thead>
<tr>
<th></th>
<th>Slight</th>
<th>Moderate</th>
<th>Marked</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>66</td>
<td>37</td>
<td>51</td>
</tr>
<tr>
<td>Number of 5-year survivors</td>
<td>29</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>Per cent of 5-year survivors</td>
<td>44</td>
<td>38</td>
<td>39</td>
</tr>
<tr>
<td>Average length of life in those dying before 5 years</td>
<td>2</td>
<td>2</td>
<td>2.1</td>
</tr>
</tbody>
</table>

**TABLE XI: Clearness of Cytoplasm**

<table>
<thead>
<tr>
<th></th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>11</td>
<td>143</td>
</tr>
<tr>
<td>Number of 5-year survivors</td>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>Per cent of 5-year survivors</td>
<td>27</td>
<td>41</td>
</tr>
<tr>
<td>Average length of life of those dying before 5 years</td>
<td>1.6</td>
<td>2.1</td>
</tr>
</tbody>
</table>

*Clearness of Cytoplasm:* Delbet alone has insisted on the favorable significance of cells with a clear cytoplasm in carcinoma of the breast. These tumors constituted 6.8 per cent of his cases.
One-half, *i.e.* 5, of these patients had been followed for at least five years and all survived.

Although the number of these cases which Delbet has followed is so small that this favorable result may have been due to chance, it seemed worth while to investigate this characteristic in the present series of cases. Eleven tumors in which all or a part of the cells had a clear cytoplasm (Fig. 10) were found, constituting 7.1 per cent of the cases. The end-results are shown in Table XI.

These data show that the results for clear-celled tumors did not differ significantly from those for other types of carcinoma of the breast considered as a whole.

![Fig. 10. Carcinoma of the Breast, Clear Cell Type. × 125](image)

**Fibrosis:** More than anyone else, MacCarty has emphasized fibrosis as a prognostic factor in breast carcinoma, claiming that a high degree of fibrosis is an evidence of defensive activity on the part of the host against the invading cancer. In so far as they found scirrhou carcinoma to be comparatively less malignant,

<table>
<thead>
<tr>
<th>Table XII: Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
</tr>
<tr>
<td>Number of 5-year survivors</td>
</tr>
<tr>
<td>Per cent of 5-year survivors</td>
</tr>
<tr>
<td>Average length of life of those dying before 5 years</td>
</tr>
</tbody>
</table>

Boss, Dahl-Iversen, and Hoffmann may be said to have contributed supporting evidence for this thesis.

In the present series of cases the amount of fibrosis was estimated with as much care as possible, and the cases divided into
three groups according to whether the fibrosis was marked, moderate, or slight. The findings on this basis are shown in Table XII.

These data suggest that the amount of fibrosis has no relation to prognosis, and do not justify giving this characteristic a place in a plan for grading breast carcinoma.

Hyaline Degeneration: Hyalinization is closely linked with fibrosis. Most scirrhous carcinomas of the breast show some hyaline degeneration, and in some of these it is very marked. Probably merely a degenerative change occurring in devitalized fibrous tissue, it is nevertheless not apparent why hyalinization is relatively much more prominent in some tumors than in others. MacCarty places hyalinization on a par with fibrosis as a favorable prognostic factor. Greenough, however, found that the end-results in his cases with a high degree of hyalinization differed but slightly from the results in those in which there was only slight hyalinization.

The tumors in the present series were arranged in three groups according to whether they showed marked hyalinization, slight hyalinization, or no hyalinization at all. These findings are shown in Table XIII.

<table>
<thead>
<tr>
<th>TABLE XIII: Hyaline Degeneration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marked</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>Number of cases</td>
</tr>
<tr>
<td>Number of 5-year survivors</td>
</tr>
<tr>
<td>Per cent of 5-year survivors</td>
</tr>
<tr>
<td>Average length of life of those dying before 5 years</td>
</tr>
</tbody>
</table>

From these data it seems justifiable to conclude that hyaline degeneration has no relationship to prognosis in breast carcinoma.

Lymphocytic Infiltration: Although lymphocytic infiltration in carcinoma is so often associated with the factors of infection and necrosis that an interdependence between these factors is suggested, nevertheless some pathologists give lymphocytic infiltration another meaning. MacCarty regards it as a sign of resistance against the tumor, and expects a longer postoperative life in the cases which show it. Leroux and Perrot also attribute to lymphocytic infiltration a favorable prognostic significance. Greenough, however, regards it as merely an indication of considerable degree of cell degeneration, and states that "it is not to be relied upon as an indication of the resistance of the individual to the cancer growth."

The degree of lymphocytic infiltration was carefully estimated in the tumors in the present series, and the cases classified according to whether they showed this characteristic in marked, moderate,
or slight degree. It was noted that heavy lymphocytic infiltration was most frequently seen in infected and necrotic tumors. The findings were as shown in Table XIV.

**Table XIV: Lymphocytic Infiltration**

<table>
<thead>
<tr>
<th></th>
<th>Marked</th>
<th>Moderate</th>
<th>Slight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>27</td>
<td>29</td>
<td>98</td>
</tr>
<tr>
<td>Number of 5-year survivors</td>
<td>6</td>
<td>10</td>
<td>47</td>
</tr>
<tr>
<td>Per cent of 5-year survivors</td>
<td>22</td>
<td>34</td>
<td>48</td>
</tr>
<tr>
<td>Average length of life of those dying before 5 years</td>
<td>2.2</td>
<td>1.6</td>
<td>2.1</td>
</tr>
</tbody>
</table>

If any conclusion were drawn from these data it would favor a worse rather than a better prognosis for those tumors with heavy lymphocytic infiltration. Strictly speaking, however, the differences in the percentages are too small to have any real significance. We conclude that lymphocytic infiltration has no relationship to prognosis in breast carcinoma.

**Gelatinous Degeneration:** The favorable significance of gelatinous degeneration in breast carcinoma has been widely accepted since the classical studies of Lange and Gaabe on the subject. Lange collected reports of 75 cases of this type of tumor and showed that the average total duration of the disease, on the basis of 23 case reports in which this information was available, was 63.5 months. This duration was twice that of ordinary breast carcinoma in Lange’s experience. Greenwood’s comprehensive study of the natural duration of untreated carcinoma of the breast has since confirmed Lange’s estimation of the duration of ordinary carcinoma of the breast; Greenwood found it to be 38.3 months.

Gaabe made a comprehensive review of all the information concerning gelatinous carcinoma of the breast, added one case of his own, and also came to the conclusion that this form of the disease grew with extraordinary slowness. He further pointed out that late recurrence is much more common in this type. It should not be inferred, of course, that all cases of gelatinous carcinoma of the breast grow slowly. Cheatle, for instance, in his recently reported series of 8 cases, described one in which death resulted from pulmonary metastases but two and one-half years after operation.

Plaut regards gelatinous degeneration as the only histologic characteristic in breast carcinoma which deserves recognition as a favorable prognostic sign. Nevertheless, those who have taken up the grading of breast carcinoma within recent years have, almost without exception, failed to consider gelatinous degeneration in their plans for grading. This neglect may have been due to the comparative rarity of this form of the disease; Gaabe found but
1.66 per cent among the 2944 cases of breast cancer of which he collected reports. Thus most series of cases have contained but one or two examples of it.

In the present series of cases gelatinous carcinoma was unusually frequent, there being 9 cases, or 5.8 per cent. The highest incidence of this type of the disease previously reported is 3.3 per cent, which occurred in Hildebrand's early series of cases. This high incidence of gelatinous carcinoma in the present series of cases is probably in part due to the fact that we have included in this class all carcinomas which showed this type of degeneration in even a comparatively small area. This has been done on the assumption that if this peculiar degenerative change has any prognostic significance, this should be independent of the extent to which the tumor is affected.

In the present study the distinction has been carefully made between gelatinous degeneration and myxomatous degeneration of the stroma, of which there were three instances. Myxomatous degeneration, in a standard hematoxylin and eosin stain, has a distinct bluish color, while gelatinous degeneration appears to be almost colorless. A more fundamental distinguishing feature is the fact that myxomatous degeneration affects only the stroma, while in gelatinous carcinoma not only the stroma but also the parenchymal cells are affected (Fig. 11). The latter appear to be undergoing dissolution as the result of some nutritional influence. In this respect our classification of gelatinous degeneration among the histologic characteristics of the stroma in the present study is a false one made for the sake of convenience.

The end results in the cases showing gelatinous degeneration in the present series of cases are shown in Table XV.
These data, in terms of both the percentage of five-year cures and the length of life of those dying before five years, strongly indicate that gelatinous carcinoma of the breast has a comparatively favorable prognosis, and that this characteristic should carry weight in a plan for histologic grading.

**Table XV: Gelatinous Degeneration**

<table>
<thead>
<tr>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>9</td>
</tr>
<tr>
<td>Number of 5-year survivors</td>
<td>6</td>
</tr>
<tr>
<td>Per cent of 5-year survivors</td>
<td>67</td>
</tr>
<tr>
<td>Average length of life in those dying before 5 years</td>
<td>2.9</td>
</tr>
</tbody>
</table>

**A Plan for Grading Breast Carcinoma**

Having tested the prognostic significance of the fifteen different histologic characteristics which seemed worth while studying, and having found six of them (Table XVI) to have some apparent relationship to the end-results of treatment, it becomes necessary to devise a plan in which these six significant characteristics are combined to yield a workable formula for grading the malignancy of breast carcinoma. This plan must first of all be a simple one, for too elaborate a plan would go beyond the bounds of the limited knowledge which we have of the relationship of histologic character to prognosis. To this end three rather than four grades of malignancy are used. The decision as to the relative weight which each of the six different characteristics shall be given in this plan must be made on a strictly pragmatic basis. The plan which we have finally evolved is the simplest one which it seemed possible to devise which would work well.
According to this plan tumors were arbitrarily placed in Grade I when they had a papillary or comedo character, when the adenoid arrangement of the cells was marked, when gelatinous degeneration was present, or, if lacking any of these preceding characteristics, when variation in the size and shape of the nuclei was slight and there were but few mitoses. Thus any one of the characteristics No. 1, 2, 3A, or 6 (Table XVI), or, lacking any of these, the combined presence of 4A and 5A, was considered sufficient evidence for classifying the tumor as comparatively less malignant, i.e., Grade I. The Grade III, or highly malignant tumors, were selected on the basis of only three characteristics—absence of an adenoid arrangement (3C), marked variation in the size and shape of the nuclei (4C), and numerous mitotic figures (5C). If any two of these three signs of a high degree of anaplasia were present, the tumor was classed as Grade III. All other tumors not falling into these groups were classified as Grade II. On the basis of this plan the findings in the present series of cases were as shown in Table XVII.

Relation of Lymph Node Metastases to Grading: In view of the paramount importance of lymph node metastases for the prog-
nosis of mammary carcinoma, it is of interest to compare this type of histologic grading in the group of cases in which metastases were found in the nodes, with that for the group of cases in which the nodes were not involved. Greenough made such a comparative study and found that his grading was slightly more significant in the group of cases without node involvement. The results of this computation in the present series of cases are shown in Tables XVIII A and B.

From these data it would appear that although the group of cases without node involvement gave much better results than the group in which the nodes had been involved, yet there was approximately the same relative difference between the results for

\[ \text{Graph 1. Relationship of Length of Life to Histological Grade, All Cases} \]

the Grade I and the Grade III types in each group. This leads to the conclusion that histologic grading is equally valuable whether or not the nodes be involved. By this statement we do not mean that the results of histologic grading carry as much weight in determining prognosis as the fact of whether or not lymph node metastases are present. These are two different types of evidence which should not be regarded as competing with each other, but rather as supplementing each other. Histologic grading is simply an additional prognostic guide, subordinate to the clinical data regarding the size and the location of the tumor and to the facts as to lymph node involvement. We mean to say, rather, that whatever the state of the lymph nodes may be, histologic grading adds approximately the same quota of information.
Graph 2. Relationship of Length of Life to Histological Grade, Cases without Lymph Node Metastases

Graph 3. Relationship of Length of Life to Histological Grade, Cases with Lymph Node Metastases
In order to make it possible for those who have graded breast carcinoma, and expressed their findings in graphic form, to compare their results directly with ours, Graphs 1, 2, and 3 have been made. These show the relationship of length of life to histologic grade.

Regional Variation in Structure as a Handicap to Grading: The objection most frequently advanced against histological grading is that tumors often show so much variation in different portions that they cannot be classified as conforming to any single pattern. Ribbert emphasized these regional differences in his description of breast carcinoma. We have made it a point in the present study to note and record the extent of these variations. But 11 per cent of the cases in the series showed regional differences in structure which were so marked that they made grading difficult. For instance, Figures 12 and 13 show two different areas in the same tumor which at first glance suggest very different grades of anaplasia. A dilemma of this sort was solved by classifying the tumor on the basis of what appeared to be its most fundamentally significant characteristics. In the scirrhous portion shown in Figure 12, the parenchymal cells have been so squeezed and distorted by the dense fibrous stroma in which they lie that their form can hardly be made out. The cells from another region, as shown in Figure 13, however, are seen to lie in a comparatively loose stroma, and their individual characteristics can be easily made out. They are small, quite regular, and contain but few mitoses. Since our study of the bases for grading breast carcinoma has shown that fibrosis per se has no prognostic significance, while the arrangement and the uniformity of the cells

![Image](image-url)
as well as the number of mitoses which they contain are very important, this tumor was classed as Grade I. The correctness of this grade has been verified by the fact that the patient is still alive after sixteen years, although the axillary nodes were found to be involved at operation.

It is not intended to give the impression that the problem can be as easily and as successfully solved for every mammary carcinoma showing regional variation. It would seem, however, that this difficulty of variation has been over-emphasized. It remains one of the obstacles of histologic grading, but it is not an insurmountable one. Regional variation makes it impossible to grade a single, small biopsy specimen, and it makes grading done on the basis of only one full-sized section hazardous. If three or four

sections from different portions of a given tumor are studied with care, however, a definite impression will be gained of its predominant and fundamental character in the great majority of instances. Since an average of eight sections of each tumor were studied in the present series of cases, it cannot be said that this opinion has been arrived at without a comparatively thorough investigation of the possible extent of regional variation in breast carcinoma.

Our impression that tumors, at least in the earlier phases of their life history, tend to maintain an individual character with a considerable degree of uniformity has been strengthened by a comparison of the primary tumors with their lymph node metastases in the present series of cases. In the 103 cases in which the lymph nodes were found to be involved, the tumor in the nodes was

*It should be noted that frozen sections of fresh tissues are not suitable for grading. No matter how well they are made, they fail to reveal in sufficient detail the histological characteristics which we have discussed.*
graded on the same basis as the primary tumor had been graded. This was done, of course, without knowledge of what the grade of the primary tumor was. The grade of the node metastasis was found to be the same as that of the primary tumor in 71 per cent of the cases. It was higher than that of the primary tumor in 19 per cent, and lower in 10 per cent.

The striking preservation of type which a Grade I mammary carcinoma frequently shows in its lymph node metastases is illustrated by Figures 14 and 15, which show the primary tumor and its axillary extension, respectively. Here the structure of comparatively regular, rather small, cuboidal cells arranged in well formed acini is closely reproduced in the lymph node. Similarly the individual character of highly anaplastic Grade III carcinoma is almost always maintained in its lymph node metastases. Figures 16 and 17 portray such a primary growth and its axillary metastasis. In both there is loss of an adenoid arrangement, and the cells vary greatly in size and contain many mitoses.

It should be added, of course, that malignant tumors are apt to maintain this relatively fixed individual character only in their primary growth and in their early metastases. Repeated local recurrences and later metastases often become increasingly anaplastic. This sequence is best shown in very slowly growing tumors, such as malignant mixed tumors of the parotid, for rapidly growing carcinomas often kill before they have had an opportunity to recur many times.

**Summary**

In a series of 164 cases of carcinoma of the breast, which was exceptionally advantageous for the study of the relationship of histologic structure to prognosis because of the remarkably com-
plete follow-up data and because of the superior quality and the large number of the histologic sections, a careful analysis has been made of the prognostic significance of fifteen different histologic characteristics. Six of these characteristics have been found to have a probable relationship to the end-result of treatment. These significant characteristics are, in fact, similar to those which Hansemann originally proposed for the determination of grade of anaplasia. The factors of fibrosis and lymphocytic infiltration, more recently stressed in tumor grading, have been found to be without prognostic import.

On the basis of these six significant histologic characteristics, it would appear that breast carcinomas can be classified into three grades of malignancy, in which the increasing grade of anaplasia parallels an increasing grade of malignancy as evidenced by the tendency of the tumor to metastasize and kill the patient at an early date.

It should be remembered that prognosis based on this type of histological evidence can not claim a mathematical accuracy. It should be regarded only as an approximation, and a rough one at that. The phenomenon of malignancy which we are attempting to measure is a biological one, and does not lend itself to exact measurement in mathematical terms. Moreover, the extremes, that is the Grades I and III, should be given more weight than Grade II, the less definite middle class into which a great proportion of breast carcinomas fall.

This knowledge gained from histologic grading should not be regarded as in any sense competing with the clinical data bearing on prognosis, to which it is, of course, subordinate in importance. Histologic grading should rather be considered as a new and additional form of information, as a modest but yet valuable increment to the knowledge of the disease.

BIBLIOGRAPHY


EWING, JAMES: Neoplastic Diseases, Phila., W. B. Saunders, 1928, p. 64.


Reimann, Stanley P.: The issues at stake in the grading of tumors, Arch. Path. 8: 803, 1929.
DISCUSSION

Dr. William Carpenter MacCarty (Rochester, Minn.): I cannot refrain from complimenting Dr. Haagensen on this paper. This work has formed a rather important part of my career. Many years ago I undertook to make some scientific observations on various factors which quite possibly might influence the prognosis, as I am glad to see Dr. Haagensen has done. I believe it is a very dangerous thing for anyone to "grade malignancies," and to use this grading too seriously clinically, but I do think it is perfectly scientific and justifiable to make such observations as Dr. Haagensen and I have done.

I have been studying this question for many years, taking many different factors into consideration, and I personally have never "graded" cancer. There are at least several reasons why grades, particularly based on a few factors, are of no great value. In the first place, the grades differ in different parts of the body. They differ in primary and secondary tumors. They differ in recurrences from the primary growths, and there are many other factors which are variable, as Dr. Haagensen has mentioned. In other words, whoever "grades" malignancies should do it in a purely scientific observational manner, such as Dr. Haagensen has done, but to grade tumors by any method, and then put the results into the hands of the clinician, is in my opinion an extremely dangerous thing to do. Suppose somebody has a certain grade of tumor, and 80 per cent of the patients with that grade are said to live so many years, and 20 per cent so many years. When you come to an actual case, and the patient asks: "Do I belong in the 80 per cent or the 20 per cent class?", you cannot say anything, one way or the other. To take grading too seriously, then, is a great mistake, but to make observations such as Dr. Haagensen has done is perfectly logical, and should be continued.

There is one little suggestion about hyalinization. In my own experience the percentage of those who have hyalinization varies considerably in different organs. We see a much higher percentage in rectal cancer than in the breast, and this must be taken into consideration.

Dr. E. T. Bell (Minneapolis): In my experience involvement or lack of involvement of the axillary nodes is more important than any other single factor.

Dr. James Ewing (New York): I assume that all members of the Society are aware that clinicians are very careful not to place too much emphasis on histological grading alone, and, as Dr. Haagensen has informed us, are taking into consideration the extent of the disease, the duration of the disease, the age of the patient, and other clinical factors, all of which have been lumped together into the so-called index of clinical malignancy. I do not think we are in great danger, as pathologists at least, in over-encouraging the surgeons to assume histological grading as the only matter to be taken into consideration. However, a study such as Dr. Haagensen has just shown is most impressive as showing what can be accomplished by a careful method statistically controlled, and I think it would be of great value to circulate the use of this method among pathologists in general. I should like to ask if Dr. Haagensen has been impressed by any observations relative to what we may call a specific type of breast cancer. I refer particularly to the sweat-gland carcinomas of the breast, and should like to know if he has noted that they have any peculiarities. We will occasionally encounter basal cell varieties in mammary cancer, and I wonder if they are associated with any peculiarities in grading. In addition to the ordinary grading of the usual types of cancer, it would be interesting if the pathologist could point out some specific properties of the sweat-gland cancer.

When it comes to predicting what will happen to a patient, certainly no pathologist and no clinician will ever say that histological grading will give us the information that can be obtained from the clinical index.
Dr. David P. Seeof (Cleveland): I would like to ask whether any of the cases were treated postoperatively by radiation. I remember Dr. Haagensen's saying cases were not treated preoperatively, but I do not recall whether any were treated postoperatively.

Dr. Haagensen: Dr. MacCarty's point, that tumors differ so much as they occur in different parts of the body that no single system can be used to grade all tumors, is certainly well taken. It would appear that the relationship of histological character to prognosis must be studied separately for each different form of cancer. The plan for grading which we have presented is intended solely for use with breast carcinoma.

We agree wholly with Dr. Bell's statement that the condition of the axillary nodes is the most important single prognostic factor in carcinoma of the breast. The histologic grade of the tumor is quite a different type of evidence bearing on prognosis. Although less weighty than the clinical evidence and the evidence gained from a study of the lymph nodes, nevertheless the histologic grade of the tumor adds a definite quota of information regarding the probable outcome. In dealing with such an obscure and formidable disease as breast carcinoma it would seem that all information which bears a relationship to its natural history is of value.

In answer to Dr. Ewing's question about sweat-gland carcinoma, there were 3 tumors in the present series which showed in a striking manner the characteristics which Dr. Ewing regards as being indicative of sweat-gland origin. The cells were comparatively regular, had a highly acidophile cytoplasm, and showed a marked adenoid arrangement. One of the patients died three and three-quarters years after operation, with pleural metastases. The second died of heart disease eight years postoperatively, and the third is still living ten years after operation.
It is unfortunately impossible to answer Dr. Seecof's question about the effect of postoperative radiation. A moderate number of the patients in this series of cases have, during recent years, received postoperative radiation. No effort was made, however, to estimate the bearing of this factor on the end-results.

Dr. Channing C. Simmons (Boston): At the present time we are studying the cases of cancer of the breast operated upon at the Massachusetts General Hospital during the three year period, 1924-26, to determine the results of treatment. All of these cases have been followed for at least five years, the average length of time for the entire group being seven years.

The specimens from these cases were reviewed and graded into three groups of malignancy on the microscopic appearance of the specimen. These findings were then compared with the clinical results. The grading was done by Dr. J. H. Wright, deceased, Dr. H. F. Hartwell, Dr. R. B. Greenough and myself. The criteria for determining the degree of malignancy were as follows: (1) the amount

![Chart](chart.png)

of differentiation of the cells as shown by the adenomatous arrangement of the cells, and the presence of vacuoles as evidence of secretory activity; (2) the appearance of the individual cells, taking into consideration variation in size and shape, the irregularity of the nucleus and the number of mitotic figures; (3) the tendency of the tumor to infiltrate the surrounding tissues.

If I understood Dr. Haagensen correctly, he did not consider the latter point, but we have found it an important factor in determining the prognosis.

The work is not yet completed, but at the present time we have 160 cases available for study. The results are shown graphically in Chart I, which gives the percentage of patients with the three grades of malignancy living at yearly intervals after radical operation. Chart II gives the percentage of patients in whom the
disease was limited to the breast, and Chart III the percentage of patients living in whom the axillary glands were involved. In all three charts it will be observed that the percentage of five-year cures in the cases of low malignancy is much greater than in those of medium and high malignancy.

Dr. Greenough has studied a similar group of cases of cancer of the breast observed at the Massachusetts General Hospital during the six year period, 1918-23. The two groups, comprising 358 cases, have been considered together to eliminate as far as possible the unavoidable errors that occur in dealing with small numbers of cases, and the following results obtained.

Results of Operation

<table>
<thead>
<tr>
<th>Grade</th>
<th>All Cases</th>
<th>Disease Limited to Breast</th>
<th>Axilla Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>55 cases.</td>
<td>39 cases.</td>
<td>16 cases.</td>
</tr>
<tr>
<td>Grade I</td>
<td>44 cures (80%)</td>
<td>35 cures (90%)</td>
<td>9 cures (56%)</td>
</tr>
<tr>
<td>Grade II</td>
<td>75 cures (39%)</td>
<td>41 cures (57%)</td>
<td>34 cures (28%)</td>
</tr>
<tr>
<td>Grade III</td>
<td>14 cures (13%)</td>
<td>4 cures (22%)</td>
<td>4 cures (22%)</td>
</tr>
</tbody>
</table>
We believe the pathological index of malignancy as determined by microscopic examination of the tumor is of distinct value in determining the prognosis, although in the individual case other factors have to be taken into consideration. It will also be noted that the prognosis is better in cancer of low malignancy with involvement of the axillary gland than in cancer of medium malignancy in which the disease is confined to the breast. It is found, however, that for some reason, as yet unexplained, certain cases of low malignancy metastasize early, while others, apparently of high malignancy, are cured surgically. The personal equation also enters into the grading of any group of cases to a certain extent.

**Dr. Haagensen:** As Dr. Simmons points out, the tendency of the tumor to infiltrate surrounding tissues is probably of significance. This factor is, however, difficult to evaluate quantitatively, since it is possessed to such a high degree by almost all types of carcinoma of the breast. In the plan for grading presented by us, this factor, *per se*, has not been given a place. We have, however, indirectly included it in our consideration of the *manner of growth* of the carcinoma cells. Papillary carcinoma and comedo carcinoma, in both of which the tendency to infiltrate surrounding tissues is notably slight, are graded as I in our plan. I should like to thank Dr. Simmons for his kindness in presenting his data on grading at this time.