PAPERS AND ORIGINALS

Prognostic Typing in Breast Cancer

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Summary

Infiltrating breast carcinomas in which recurrence takes place 10 years or more after operation are reported to contain tumour cells of characteristic morphology. The cytological features of these tumour cells form the basis of the system of classification described here. Three cytological types are recognized, prognosis being best in type III. Typing is carried out on specimens stained with haematoxylin and eosin. The results of typing were reproducible in over 90% of cases and independent of the histology of the lesion. Correlation to survival time was shown in a total of 222 cases.

Introduction

Late recurrence following breast cancer has been variously defined as recurrence from two years (Henneford *et al.*, 1962) and upwards after removal of the primary cancer. The longest interval on record is 51 years (Chauffard, 1932). The longer the interval between the primary and the recurrence the less likely it is that histology of the primary tumour is described. The few cases with histology have been reviewed by Dankers *et al.* (1960) and Sutton (1960). They reached the conclusion that the histological findings are not characteristic.

These primary tumours are not as rare as our lack of information on them would suggest. At present we pass over them as we have no means of recognizing them, but we do see late recurrences regularly among our surgical specimens.

In an attempt to be "wise after the event" the primary tumours that gave rise to such late recurrences were traced (Hartveit and Wiig, 1971; Hartveit, submitted for publication) to see if they had any morphological characteristics in common. This being so the series was extended. *The recognition of these features enabled a typing system to be evolved* and their prognostic value to be assessed.

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Material and methods

Cases from the necropsy and surgical files of the Gade Institute, Department of Pathology, were studied. Cancers of the female breast alone were investigated. (1) The primary breast cancer was traced from the surgical records in 20 cases giving recurrence 10 years or more after operation between 1953 and 1970.* (2) The primary breast tumour was also traced in 57 cases with recurrence within 10 years of operation, between the years 1963 and 1970. (3) The necropsy material yielded 89 cases of patients dying of breast cancer, in the years 1963-70, in which the primary could be traced from the surgical records. (4) This necropsy material also contained 28 cases in which a primary breast cancer was traced, but the patient died of an unrelated cause. (5) There were 14 cases with bilateral breast cancer in the total material.

Slides of formalin-fixed paraffin-embedded material stained with haematoxylin and eosin were used, new slides being prepared from the blocks if the original was unsatisfactory.

The following criteria that emerged in the course of the investigation were recorded in connexion with the tumour cell morphology:

Cell borders	Clearly defined	..	..	..	..	..	+
	Partly defined	..	..	..	..	..	±
	Ill defined	..	..	..	..	..	−
Nuclear crowding	Marked	..	..	..	..	..	+
	Present	..	..	..	..	..	±
	Absent	..	..	..	..	..	−
Nuclear lobulation	Marked	..	..	..	..	..	+
	Slight	..	..	..	..	..	±
	Absent	..	..	..	..	..	−
Nuclear diameter	Over half total cell diameter		..	..	..	1
	Approximately half		..	..	..	2
	Under half	..	..	..	..	..	3

These criteria, which are described in detail below, form the basis of the typing system that evolved from this study. It will be noted that + and − are used for recording cytological criteria that can be assessed on a present/absent scale, while arbitrary figures are used for the nucleocytoplasmic ratio.

* A detailed report of the first 10 of the cases has been submitted for publication.

Results

(1) *Twenty primary breast carcinomas with recurrence more than 10 years after operation.* These were all infiltrating carcinomas of various histological type. All contained areas of in situ growth. The tumour cells in these areas had the following characteristics in common (see Fig. 1, type III): the cell borders were well defined, they had plenty of cytoplasm, the nuclei seemed to be well separated from each other, and the nuclear membrane was smooth.
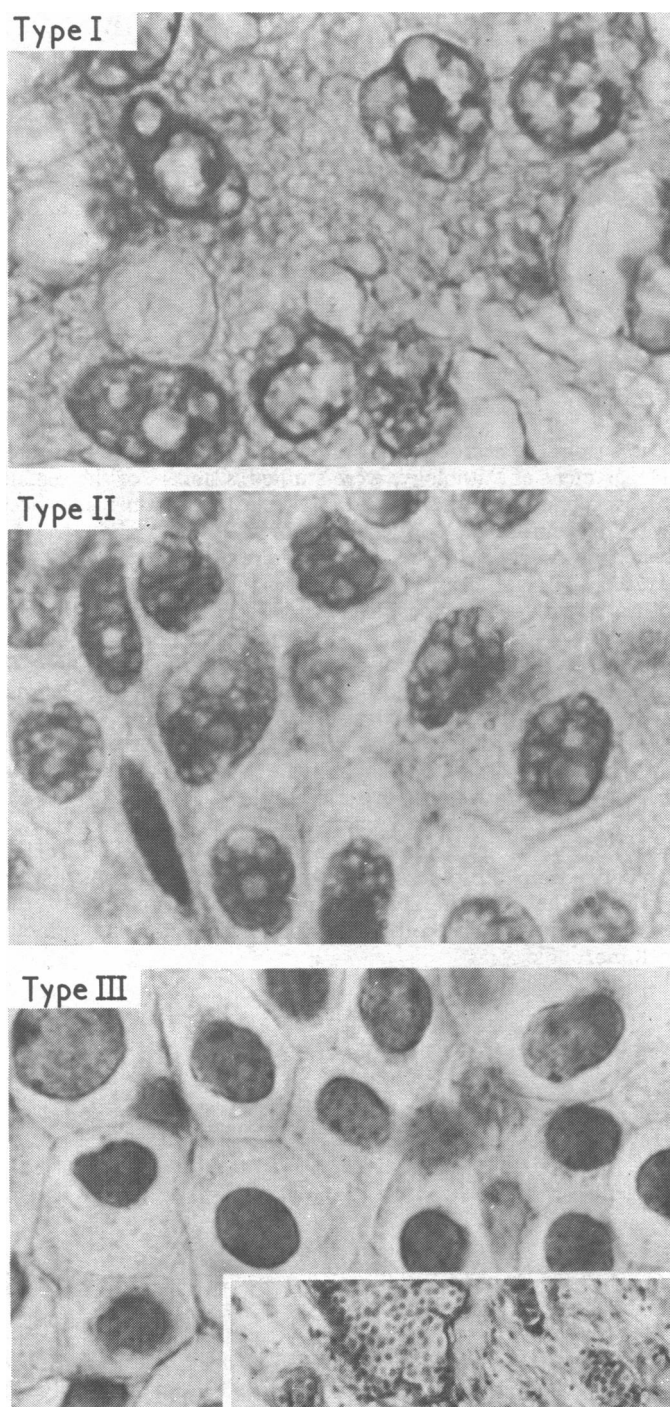

FIG. 1—Example of breast tumours of each of the three cytological types. Note: in type I, irregular grouping (crowding) of the nuclei, irregularity of nuclear outline, and ill-defined cell borders; in type III, well-defined cell borders, smooth nuclear outline, and plenty of cytoplasm (inset, low-power view of such cells—"frog spawn"—see Text (×150)); in type II, intermediate features, approximating to type III apart from marked irregularity of nuclear outline. Haematoxylin and eosin. (×1,300.)

(2) *Fifty-seven primary breast carcinomas with recurrence within 10 years of operation.* This material contained no examples of the tumour cell type described above. However, the cells present in in situ areas or in larger groups of infiltrating tumour cells, in primaries that recurred within two years, had the opposite characteristics in common (see Fig. 1, type I). The cell borders were ill defined and the amount of cytoplasm per cell was difficult to define. The nuclei were crowded in irregular groups and the nuclear membrane was irregular, or "lobulated."

On the basis of the grading of the criteria described above, these primaries could be characterized by their *cytological patterns*. Those recurring within two years can be represented as $-++1$ (type I). Those recurring after 10 years or more $+--3$ (type III) (see Fig. 1). The tumours were *classified from groups of cells that stood out on low power as cells nearest to the type seen in tumours recurring 10 years or more after operation*, irrespective of the findings elsewhere on the slide. On low-power examination these stood out as areas of "frog spawn" (see Fig. 1, inset). In the absence of such areas groups of cancer cells, as opposed to single infiltrating cells, were used (see Appendix, Table III).

On classification of a series of slides it was found that a difference of 1 grade, for example ± to +, occurred in about half the cases, but more than this was rare (see Appendix). An intermediate pattern was accepted as type I or type III if it differed by 1 grade only.

For example: $-+\pm1$ would be accepted as type I ($-++1$), $+-\pm2$ would be accepted as type III ($+--3$), while $+\pm+2$ stays type II whatever (see Fig. 1).

(3) To test this method the *89 primary breast carcinomas traced in patients dying of breast cancer* were typed. The results are shown in Fig. 2, in which the findings are related to the histological type. Type I cancers predominated when the survival time was five years or less. Type III predominated with a survival time of 10 years or more. Type II showed a survival time that varied from one to nine years. There were few cases of this type. The cytological type was not related to any particular histological type. Table I shows the percentage postoperative survival time in this material for the three cytological types. Of patients with type I tumours 28% were alive
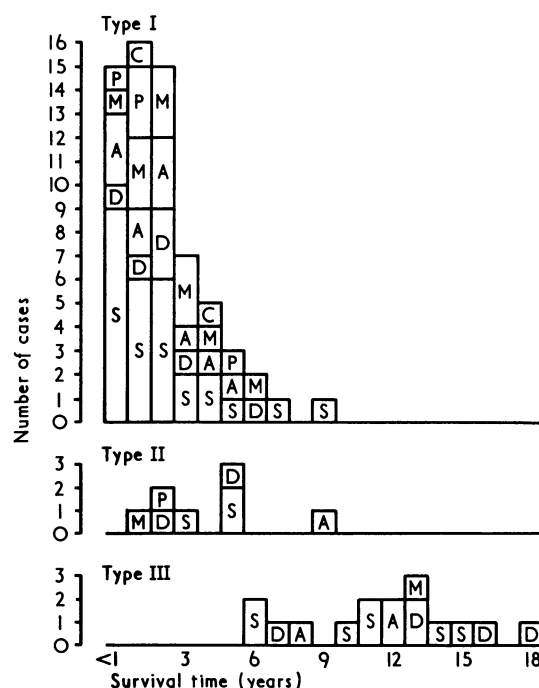

FIG. 2—Cytological type in 89 primary breast cancers, related to the histological type and the survival time after operation. (S = Scirrhous. D = Duct. A = Adenocarcinoma. M = Medullary. P = Papillary. C = Colloid.

TABLE I—*Percentage Postoperative Survival Related to Cytological Type in 89 Primary Breast Carcinomas*

Survival Time				Cytological Type		
				I	II	III
2 years	..	..	..	28	58	100
5 „	..	..	..	7	8	100
10 „	..	..	..	0	0	69

at two years, 7% at five years, while none survived 10 years. With type II tumours 58% survived two years, 8% five years, none 10 years. So differentiation between types I and II was of value only with regard to short-term prognosis. In contrast all type III tumours showed a survival time of over five years, and 69% over 10 years.

(4) *The primaries from 28 patients who did not die of their breast cancer* (Fig. 3) contained more type II tumours than would be expected from their distribution in the patients
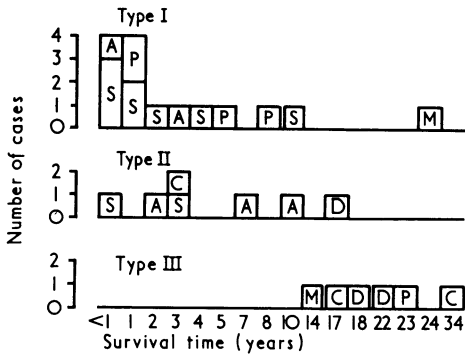

FIG. 3—Cytological type in 28 primary breast cancers, related to the histological type (see legend to Fig. 2), and the survival time in patients dying of an unrelated cause.

dying of their cancers. Once again the type III tumours were related to a long survival time, this time without recurrence.

(5) *In the 14 cases of bilateral breast cancer in the total material* there were five with a clinically tumour-free interval of 10 years or more between the two tumours. In all cases this interval followed the removal of a type III tumour.

Discussion

In the present work an attempt was first made to define the morphology of the tumour cells in breast cancers of good prognosis. All the tumours were infiltrating carcinomas and showed a wide variety of morphological signs of their anaplastic nature. But only a few characteristics seemed to be common to these tumours of good prognosis. From this grew the idea of describing other breast cancer cells in terms of these criteria.

Grading of malignancy in breast cancer is usually carried out from the infiltrating zone at the periphery of the tumour (Black and Speer, 1957; Hultborn and Törnberg, 1960; Schiödt, 1966). In the present work characteristic tumour cells were found in situ in type III tumours, and it was at first felt to be imperative to judge all the tumour cells from in situ areas. However, it was later found (see Appendix) that groups of cells in type I and II tumours, whether in situ or in tissue spaces, expressed their characteristic morphology. Infiltrating single cells did not (see example in Appendix, Table III).

From a study of 650 cases of breast cancer Schiödt (1966) concluded that histological grading is of no prognostic value in 90% of cases. Further, having used Bloom and Richardson's (1957) system of grading malignancy, based on the degree of structural differentiation, variation in size, shape, and staining of the nuclei, and the frequency of hyperchromatic and mitotic

figures, he concluded: "The individual case of mammary carcinoma presumably has its specific biological character, in most cases with a predetermined further course. Grading of malignancy cannot at present characterise this course with such accuracy that histologic prognosis can be said to be of use in the daily clinico-pathological routine." However, the present method of prognostic typing seems to cut across other histological classifications (see Fig. 2).

In trying to arrive at a prognosis in breast cancer we are attempting to judge the growth rate of one malignant tumour cell population as opposed to others, not to compare the growth rate of malignant cells with that of normal cells. The criteria needed are therefore not necessarily the accepted criteria of malignancy, but factors associated with a slow as opposed to a rapid growth rate.

RATE OF GROWTH

In the present work a start has been made to define some of the features associated with a slow growth rate in routine histological sections. The presence of distinct cell borders has been used previously as a criterion of low malignancy (Hueper and Schmitz, 1929), as has the nucelocytoplasmic ratio. Nuclear crowding does not seem to have attracted attention in the past. It is intimately associated with the nucleocytoplasmic ratio and ill-defined cell borders. Its presence in the higher degrees of malignancy has been well shown by Cutler et al. (1966). Their figure also shows the clear angular cell borders characteristic of tumours of slow growth rate. Nuclear lobulation should probably come under the heading of an artefact, like the nuclear changes described by Black and Speer (1950) as related to the endocrine status of the host. They suggest that such "formalin artefacts" are indicative of a change in the colloid structure of the nucleus. Nuclear lobulation was absent in tumours of good prognosis and marked in those that killed within a few years. It is not a sign of malignancy as it is often seen in normal tissues, such as the basal layer of the squamous epithelium of the uterine cervix. Here it is often associated with hyperplasia. It may thus be a potential measure of growth rate.

In the past the concept of anaplasia (Hansemann, 1893) has been used as a basis for the grading of malignancy. This is a static rather than a dynamic concept. The stages in progression from benign to malignant represent a discontinuous process that may stop at any intermediate point (see Foulds, 1958). In these stages the cells can be expected to show varying degrees of anaplasia—that is, differences in morphology from the parent cell type. Once malignant change has supervened we have no evidence that the process is still discontinuous. The evidence we have indicates that growth is then progressive and the growth rate constant (see Gershon-Cohen et al., 1963). Grading of the degree of anaplasia may tell us how far along the road to neoplasia a cell has come—hence its use in exfoliative cytology. The same criteria used on histological sections may tell us whether a cell is neoplastic or not. These criteria cannot be used to measure the growth rate, though as most anaplastic breast carcinomas have a rapid growth rate we may get the impression that to some extent they can. As Schiödt (1966) stressed, grading of malignancy on this basis gives at best a "group prognosis." The differences are not sharply enough defined to give more than a rough estimate in the individual case.

Conclusion

All infiltrating breast cancers are malignant, but some take longer to kill than others. This is dependent on their intrinsic growth rate, a chronometer that seems to be set at the time of onset of the malignant change. The present typing system clearly defines breast carcinomas with a prognosis of five

years or more in all cases and 10 years or more in most cases. It also gives an indication of the short-term prognosis in the remaining tumours by picking out some of those in which a survival time of over two years can be expected. Further work is needed to define these cases more precisely. It should perhaps be stressed that the prognosis with this typing system seems to be independent of the histological type of the primary. The origin of the type III cells is open to discussion, particularly with regard to their relationship to intralobular carcinoma in which a similar "Pagetoid" cell type has been described in both ducts and lobuli (Hutter et al., 1970). However, while a lobular carcinoma may be classified as type III in some cases, not all type III tumours are lobular carcinomas. The finding of a similar type III cell type in the regional nodes and other metastases (Harveit and Wiig, 1971) indicates that these are truly malignant cells and not associated areas of duct hyperplasia.

Appendix

Reliability of Classification of Cytological Patterns and Distribution of Individual Factors

The cytological features in the primary tumours from the 117 necropsy patients were first recorded in the order the tumours were retrieved from the files, without knowledge of their clinical history. One slide from each tumour was used. When more than one block was available that numbered "1" was chosen. After an interval of two weeks these slides were mixed. The labels were covered and new code numbers applied at random. They were then classified again, and the results of the two readings compared. The histological type of the tumour, the presence of in situ areas, and the age of the patient at operation were also recorded.

The results obtained from *comparison of the two readings* are shown in Fig. 4. The first column gives the percentage of all cases in which complete agreement was recorded. Next come the individual factors in the following order: the degree
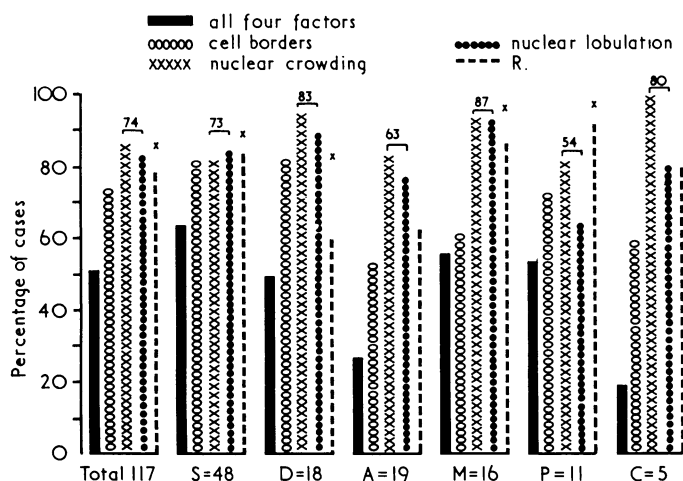

FIG. 4—Percentage of cases showing agreement on comparison of two readings on classification of tumour cell type according to the cytological pattern (see Text), for the total series of 117 cases and for the different histological tumour types (see Fig. 5).

of definition of the tumour cell borders, nuclear crowding, nuclear lobulation, and the nucleocytoplasmic ratio (R). The subsequent sets of columns refer to the results for tumours of different histological type. Complete agreement at the two readings, that is to say in all degrees of each of the four factors, giving a possible 12 factors, was recorded in 52% of the total series. This is similar to the figures obtained for duct, papillary, and medullary carcinomas alone. Scirrhous carcinoma gave 63% agreement, adenocarcinomas and colloid carcinomas showed most variation.

As Fig. 4 shows, this variation came mainly from disagreement over the definition of the cell borders. Agreement on nuclear crowding was high in all cases, 87% in the total series, varying from 82 to 100% in the different histological types. Nuclear lobulation gave a value of 83% in the total series, agreement being best in medullary, duct, and scirrhous carcinomas. If these last two factors are taken together, agreement was reached in 74% of the total series, over 80% in duct, medullary, and colloid carcinomas. Finally the factor R gave total agreement in 78% of cases, or 84% if only two grades—that is, 1 and 2 or 3—are recognized. Agreement was best in scirrhous, medullary, and papillary carcinomas. From these figures it seems that adenocarcinoma is the most difficult to characterize, while scirrhous and duct carcinomas are easiest when all factors are considered.

The above data recorded the number of times agreement was reached for the individual factors when readings were obtained on two different occasions. Table II records the

TABLE II—Number of Factors in Cytological Pattern Classified Differently on Two Occasions (i.e., Number of Points of Discord) from 117 Primary Tumours Classified either from in situ Areas or Infiltrating Cell Groups

Tumour Cells	Points of Discord				No. of Cases	%
	0	1	2	3		
In situ	40	20	11	3	74	62
Not in situ	21	14	6	2	43	38
Total	61	34	17	5	117	
%	52	29	15	4		100

extent of the disagreement—that is, how many factors showed discord in each individual case, one point of discord signifying disagreement in the classification of one of the four factors. In the total series of 117 cases, one point of discord was recorded in 29%, two in 15%, and three in 4%. There was little difference in the discord recorded in in situ areas and that from groups of infiltrating cells. When the cells are not in groups they do not express their characteristic morphology (see Table III). These points of discord were usually from

TABLE III—Cytological Patterns (see Text) from Groups of Tumour Cells in in Situ Areas in 10 Primary Breast Carcinomas Giving Recurrence more than 10 Years after Operation Compared with Infiltrating Cells in the Same Tumours

Case No.	Cytological Pattern (C.B., N.C., Lob., R)*	
	In Situ	Infiltrating
1	+ − − 2	− + − 1
2	+ − − 3	+ + − 1
3	+ − − 3	+ + − 2
4	+ − − 3	− + − 1
5	+ − − 3	+ + − 2
6	+ ± ± 3	− + − + 1
7	+ − ± 3	− + − 1
8	+ ± ± 3	− + ± 1
9	+ − − 2	− + ± 1
10	+ − − 3	± + − 1

* Cell borders, nuclear crowding, nuclear lobulation, and nucleocytoplasmic ratio.

one grade to the next—that is, one degree of discord—but on occasion a difference of two degrees was recorded. Such variation occurred only with cell borders and the factor R, not with the nuclear factors.

Analysis with regard to the age of the patients at operation showed that there was a slight excess of the type III cytological pattern in younger patients with scirrhous carcinoma and adenocarcinoma. No relationship was found with duct carcinomas where the two factors—age and pattern—appear to segregate independently. It thus seems that while this cell type may be more common in younger patients with certain histological types of tumour, the pattern is of favourable

prognosis irrespective of the histological type or the age of the patient.

Fig. 5 gives a *summary of the cytological patterns* from the first reading for the total series of 89 cases grouped according to the time between primary operation and death. For those dying within two years of operation the tumours cell borders were ill defined in 74% of cases (see upper right of Fig. 5). At three to five years there was more variation in the readings,
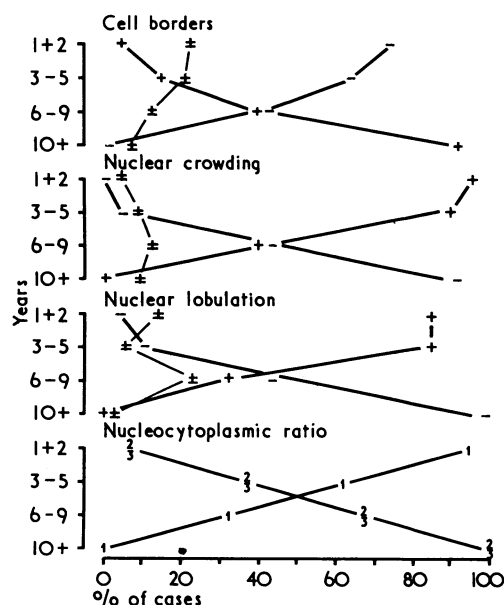

FIG. 5—Cytological patterns (see Text) in 89 cases grouped according to the time (years) between the primary operation and death. The percentage of cases showing each grade of each factor is given, the factor R being recorded as 1 and 2 or 3 (see Text).

but 63% still showed ill-defined cell borders. At six to nine years this figure dropped to 44%, while at 10 years it reached 0%. Well-defined cell borders showed an inverse relationship, being positive in 4% after two years, 16% at three to five years, rising to 44% and reaching 92% in 10 years or more. Intermediate values occurred mainly in the two low survival time groups.

Nuclear crowding also showed a clear difference in distribution related to the survival time. Crowding was present in 96% at one to two years, 89% at three to five years, 44% at six to nine years, and finally dropped to 0% at 10 years or more. The converse was seen with lack of crowding as intermediate values were not common. Nuclear lobulation showed similar results to nuclear crowding, except that the drop did

not occur until six to nine years. The factor R was recorded as either 1 or 2+3. The readings gave a linear course. At one to two years 94% of cases were recorded as 1—that is, the nuclear diameter more than half the total cell diameter—while 100% of cases showed a nuclear diameter of under half the cell diameter at 10 years or more.

When the cytological patterns in the 89 cases of known survival time are approximated to type, as described previously, disagreement occurred in only five cases, two of these had asymmetric nuclei. Typing for each of the four factors separately was also tried, again allowing half a grade of difference between the two readings. Factor R alone was of little help, 20 of the 89 cases changing type. With cell borders alone 22 changed type. Nuclear crowding and nuclear lobulation alone were more reliable, 12 of the former and 14 of the latter changing type.

Cytological typing thus gave 94% agreement in this material. Black (see Cutler *et al.*, 1966) recorded 70% agreement concerning grade on two independent readings of nuclear grade. This is in keeping with the 74% agreement recorded here for the two nuclear factors, though nuclear crowding alone gave 87% and nuclear lobulation 83%. Bloom and Richardson (1957) record over 90% agreement in grading by independent observers. This corresponds more to typing after approximation to pattern recorded here than to total agreement on all factors, as they used a points system in which the difference of one point does not necessarily lead to a change in grade. The patterns described in the present work would also lend themselves to a points system. As yet, however, there is not sufficient information to justify precise formulation of the requirements within each histological type.

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