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Bilateral Carcinoma of the Breast

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Address communications to: Staff Bulletin, 3330 Powell Hall, University of Minnesota, Minneapolis 14, Minn.

I. NON-SIMULTANEOUS BILATERAL CARCINOMA OF THE BREAST

T. Brannon Hubbard, Jr., M. D.

The occurrence of carcinoma in the remaining breast after radical removal of the first breast for cancer is a phenomenon familiar to most surgeons. For a number of years various men have discussed the question of whether or not the incidence of later carcinoma in the second breast is sufficiently great to warrant routine prophylactic removal of the contra-lateral breast at the time of treatment of the first carcinoma. However, available statistics have not made such a thesis generally acceptable, and as far as is known, there are few emphatic proponents of such a practice today.

In 1950, 2 patients who had had a cancer of one breast, underwent prophylactic simple mastectomy of the opposite breast at the University Hospitals. In both breasts minute cancers were found, the smallest being 3 mm. in diameter and being invisible grossly, having been picked up on random sectioning of the breast. Encouraged by these findings, a study of the problem was undertaken which has been composed of 3 phases:

1. Examination of a group of our own past cases to determine the incidence of non-simultaneous bilateral carcinoma of the breast.

2. Examination of the latter cases to see if they presented some common factor that would allow one to prognosticate such a happening at the time of treatment of the first breast.

3. Prophylactic simple mastectomy of the opposite breast in current cases of breast cancer, with thorough examination of these opposite breasts.

Incidence:

Although this study is primarily concerned with the problem of non-simultaneous bilateral cancer, a review of the literature quite naturally finds both simultaneous and non-simultaneous cases intermingled. William Nisbet[15] in 1800 described the case of a forty-year-old woman with simultaneous bilateral "cancer" of the breast. Velpeau[23] in 1838 wrote of excising the right breast, only to have a "scirrhous" tumor appear in the left breast shortly afterwards. Since that time case reports are found quite frequently, and early textbooks spoke of the clinical picture casually. The individual description of such patients is of no particular import today, per se. It may be said, however, that reports of 171 such cases have been found.

A number of reports of breast cancer cases appear in the literature, which give the incidence of bilateral cancer. As such, however, they are of varying significance for they have no common ground. Thus the length of follow-up varies or is not stated. Some include both simultaneous and non-simultaneous cases, or this factor is not clarified. Some include all cases of involvement of the opposite breast, while others include only those that the author (according to variable criteria) considers a probably new primary. Only those series that present the greater amount of detail, and are therefore more lucid, will be discussed.

Kilgore[10] in 1921 reviewed 1,100 unselected cases of carcinoma of the breast from the University of California Hospital and from Johns Hopkins. In 659 of these, results were known for three years or more after operation. In the entire series of 1,100 there were 37 cases (3.36%) of bilateral carcinoma, 13 simultaneous, and 24 (2.2%) consecutive. Of the latter cases he rejected 11 as being probably metastatic, based either on early occurrence in the second breast (2 - 30 months) or on occurrence in the second breast coincident with metastases elsewhere. This left 13 cases (1.17%) which developed carcinoma in the opposite breast, suggestive to him of a new and

independent neoplasm. Kilgore's overall percentages were made on the basis of his original 1,100 cases. However, it is to be noted that only 659 of these were followed three years or more. Also, he discarded those cases occurring within an interval of less than 30 months, some of which could conceivably have been due to true multifocal origin. Based on those cases living at five years (162 cases), Kilgore computed that 12 or 7.3% of them developed a carcinoma in the other breast, and 9 or 9.5% of the 96 patients living at eight years.

Lewis and Rienhoff[13] in 1931 reviewed 950 consecutive cases of carcinoma of the breast from Johns Hopkins. In 45 cases (4.7%) there was bilateral disease; 14 (1.5%) were bilateral on admission, and 31 (3.2%) had non-simultaneous involvement. Of the latter group, the second breast became involved within two years in 14 cases. The interval in the remainder ranging up to 20 years. The pros and cons of metastasis versus a new primary in these cases was not discussed. This study covered the period 1889 to 1931, the year of publication, so it is apparent that the more recent cases might well have developed a carcinoma in the other breast in ensuing years.

Harrington in 1946 reported 212 cases of operable, non-simultaneous, bilateral carcinoma of the breast. He computed this as 3.4% of a total of 6,361 cases. The interval between the occurrence of cancer in the two breasts varied up to 28 years. It should be noted, however, that he included in the series a number of patients who had been followed for only five years or less. Not listed as bilateral were that group of cases (estimated by Harrington to be an equal, if not a greater number) which developed carcinoma of the remaining breast but were inoperable due to other metastases from the first breast[8].

More recently Desaive has reviewed 1373 cases of mammary cancer seen over a 23-year period at the University of Liege. The bilateral cases are classified as "simultaneous", "bilateral" (i.e. consecutive), and "contralateral" (i.e. occurring coincident with skin, lymphatic, or visceral metastases and appearing to be metastatic themselves, rather than a new cancer). There were 46 (3.3%) consecutive, "bilateral" cancers and 44 cases in which carcinoma appeared in the opposite breast, but suggested a metastasis. A detailed description of the length of follow-up of all cases is not given[3].

In any discussion of multiple cancers, the immediate question arises as to the nature of the second tumor. Various criteria have been offered for deciding whether this second tumor is a new primary of a metastasis. Frequently quoted [7, 17] are Billroth's criteria, which are that each tumor must have a different histological picture, that they must arise in different locations, and that each tumor must produce its own metastasis. As emphasized by Warren[26], the latter stipulation is entirely too strict since many primary tumors treated today are without metastases. As related to bilateral breast carcinomas, it is also apparent that a difference or similarity in histolcgical configuration is of no significance. Any one breast carcinoma may vary markedly in any two microscopic fields, and on the other hand two breast cancers, each from a different individual, may be indistinguishable under the microscope.

It has been shown anatomically that the lymphatics of the skin of the two mammary regions are continuous across the midline[19, 4]. Oelsner also wrote of the demonstration of lymphatic collecting trunks extending from one mammary region to the supraclavicular region of the opposite side[16]. Clinical evidence of these facts is seen not infrequently in multiple skin metastases extending across the midline, or occasionally in metastatic carcinoma in the opposite axilla or supraclavicular region without apparent involvement of the adjoining breast. The possibilities of any tumor in the opposite breast being metastatic are thus always present.

It has been suggested that the second tumor is more apt to be a new primary if the interval between the appearance of the two cancers is longer. Though such a fact may be suggestive, none the less, metastases can occur after many years of quiescence, and conversely it is certainly within the realms of possibility that a tumor occurring in the second breast after only a short interval may be a new primary.

Prolonged survival without metastases, after removal of the second breast, suggests strongly that the latter was a new tumor. Such was the case in several of our cases to be presented below. Nevertheless, the occurrence of metastases shortly after or concomitant with the appearance of cancer in the second breast is by no means prima facie evidence that the second cancer is definitely metastatic.

Our original purpose in this work was to evaluate the thesis of prophylactic removal of the opposite breast when first confronted with a breast cancer. Since the question of metastasis versus a new primary cannot be answered definitely, it was felt that it would be better to include a few metastatic bilateral breast carcinomas, rather than to omit a few true bilateral primary tumors, for though surgical aggressiveness in our approach to the cancer problem must be moderated, none the less, it is probably better to veer a bit to the radical side of the ideal rather than to the inactive side. On this basis, the only criterion we have used for calling a case bilateral carcinoma of the breast is microscopic evidence of such a tumor in both breasts. To a certain extent the cases have been involuntarily chosen with an eye to the probability of the second breast being a new primary. For there were 12 other cases that developed gross carcinoma in the opposite breast, but which were treated only with radium and/or x-ray without biopsy, due to the extensive local or distant metastases from the first breast cancer. These have not been considered bilateral because the second breast tumor was not biopsied or proven pathologically. As a matter of fact, the description of the lesions in most of these cases strongly suggested direct spread from the first breast.

For the present study, the case records were examined of all microscopically proven breast carcinomas in the female which were reviewed in the Surgical Pathology Department of the University of Minnesota Hospitals from 1932 to 1939 inclusive. The records of four patients could not be found and this number is not included. The remainder constitute 275 consecutive patients with a microscopically proven carcinoma of the breast. Three cases were first seen with simultaneous bilateral involvement of both breasts. These have been deleted and henceforth the total will be considered as 272. Of this number, 17 or 6.2% were cases developing non-simultaneous, microscopically proven, carcinoma in both breasts. Eight of these cases had had the first breast treated elsewhere and came to us for treatment of the second breast. Nine cases presented with involvement of the first breast and developed carcinoma of the second breast during follow-up. In most cases the microscopic slides have been secured and the diagnosis of carcinoma confirmed. However, the slides of 12 tumors could not be found. The diagnoses in these cases are with one exception based upon the pathological reports of staff pathologists at the University of Minnesota. In one case the diagnosis was made at a neighboring hospital by a pathologist, known to us and considered capable. As stated above, there were 12 cases (4.4%), which developed clinical signs of carcinoma in the opposite breast, but which were not biopsied, and which strongly suggested metastases.

It is, of course, apparent that the 8 cases who were first seen by us after having had one breast removed previously, represent a select group in that they are patients who survived their first breast cancer and lived to develop a carcinoma of the other breast. There is also a possibility that such cases, developing a later carcinoma in the second breast, might be selectively referred to a Uni-

versity Hospital as an unusual problem. From the point of view of total risk incurred by any individual patient presenting herself with a unilateral carcinoma of the breast, it may be therefore, that a clearer picture is seen if one ignores these 8 cases and calculated the incidence of non-simultaneous bilateral breast carcinoma in the 264 patients that presented with carcinoma of the first breast. Thus of 264 patients, 9 (3.4%) developed microscopically proven carcinoma of the opposite breast, and 12 developed clinically apparent carcinoma of the opposite breast, the latter cases suggesting a metastatic origin to the attending clinicians. Such a calculation is of interest in that it takes into consideration the patients that die shortly after operation and thus from a practical viewpoint are not concerned with this problem.

This incidence is not a complete one since not all cases have been followed to death. However, that it is a representative one is suggested by the fact that of the 243 patients who have never developed a bilateral cancer while under observation, 50.6% lived 5 years and 29.2% lived 10 years. One hundred seventy-four cases have been followed to death; 69 patients were last seen alive, 59 after being followed for 10 years or more and 10 after being followed 8 - 9 years. Of these 69, 9 cases were last seen with advanced metastatic disease, leaving 60 patients who might still ultimately develop a cancer in the other breast.

Such incidence rates are, however, inadequate for comparison, nor do they give a true picture of risk, due to variation in length of follow-up in different series. For this latter purpose, the utilization of "risk years" of observation as suggested by Warren[25] seems a suitable method. Therefore, we have calculated the total number of years of observation of these 264 cases seen by us with their first cancer. The follow-up in the bilateral cases is computed only up to the development of the second tumor, ranging from 9 months to 9 years. Thus during a total of 1540.5 years of observation, cancers developed in the opposite breast in 9 cases or 5.8 cancers per 1,000 risk years of observation. If one segregates the cases according to age, those patients developing their first cancer before the age of 50 years developed 6.3 cancers in the opposite breast per 1,000 risk years. Those patients developing their first cancer after the age of 50 years, developed 5.4 bilateral cancers per 1,000 risk years.

As a control group, the total cases of breast carcinoma reported to the Connecticut State Cancer Registry for the years 1935 - 1946, were divided by 12. This number which has been classified according to age, we have assumed as a yearly occurrence rate. From the U. S. Census for the female population of Connecticut, according to age, for the year 1940[21], we have then computed the incidence of breast carcinoma for the various age groups. From the point of view of period of observation our cases likewise were observed mainly over the period 1935 - 1946. From this standpoint, then, the two groups are fairly comparable. The difference in geography has been necessarily ignored. Though by no means a perfect control group, incidence of carcinoma remains yet to be completely tabulated, and the extensive labors of the Connecticut Cancer Registry appear to present as complete a picture as is available today[14].

As may be seen then in Table I, the Connecticut female population of 30 - 49 years showed an incidence of breast cancer of 0.51 per 1,000 population. Whereas, our cases of breast carcinoma in the same age group showed an incidence of 6.3 per 1,000 risk years. The Connecticut figures for 50 years and above show an incidence of 1.2 cancers per 1,000, as compared to 5.4 per 1,000 in the breast cancer series. Grouping all ages together, there are 5.8 cancers per 1,000 risk years in our breast cancer series as compared with 0.84 cancers per 1,000 females in the Connecticut population 30 years of age and above.

TABLE I

BREAST CANCERS DEVELOPED
PER 1,000 RISK YEARS

	Total	30 - 49 Years	50 - Years
Breast Cancer Cases	5.8	6.3	5.4
Connecticut Population	0.84	0.51	1.2
	$X^2 = 4.517$ P =<0.05	$X^2 = 4.9$ P =<.05	$X^2 = 2.58$ P =>0.10

The above findings are not incompatible with those of Kilgore, Harrington, Lewis and Rienhoff, and Desaive, though the period of observation in all series is not known and an exact comparison cannot be made. The evidence suggests that there is an increased risk of cancer of the opposite breast in those patients developing their first cancer before the age of 50 years; but there is no evidence that these women over 50 years experience an increased risk.

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To the 17 cases of non-simultaneous bilateral carcinoma found in our 1932-1939 series, we have added 9 cases that occurred among hospital admissions since 1939. This total of 26 consecutive cases has been analysed from various standpoints. The information to be recorded has been gleaned mainly from the case histories, the pathological specimens, or from correspondence with the patient or her family.

Location of the tumors:

In only one case were both cancers in the medial quadrants of the breast. In 7 cases either the first or second cancer was in the medial quadrant, but the contralateral cancer was then in either the lateral hemisphere or in the nipple line. Twenty-two cancers were in the lateral quadrants, 16 were in the nipple line, and the location of 5 tumors could not be ascertained.

Since location in the medial quadrants might be suspected as evidence of metastasis rather than a new primary, it is of interest that that patient with 2 medial tumors is living and well 17 years after her second mastectomy. The 3 patients, in whom the second tumor occurred in the medial quadrants, lived 4, 5, and 16 years after their second cancer, the latter two patients being still alive.

Interval Between the Two Carcinomas:

The interval between the occurrence of carcinoma in the two breasts varied from four weeks to 32 years, the second cancer occurring within 5 years or less in 16 cases, and within 10 years in 22 cases (84%). The time of occurrence was considered the time of pathological diagnosis. The date when the tumor was first noticed by the patient or doctor was not used due to the known subjective variations in this regard. A carcinoma occurring within a short period in the opposite breast would certainly suggest a metastasis[10]. However, a number of those cases having short intervals between the two cancers have lived for prolonged periods without recurrence. Such a course tends to rule against the second breast being metastatic.

Node Involvement and Survival:

In relation to the first breast, there was axillary node involvement in 12 cases, no node involvement in six cases, and in 8 cases the nodes were either not described or sectioned, or only a simple mastectomy was done without removal of the axillary nodes. In regard to the second breast, there was no node involvement detected in 10 cases, positive node involvement in 9 cases, and in 7 cases the nodes were not mentioned or sectioned or a simple mastectomy had been done. In those where the lymph nodes were described as uninvolved, only three or four nodes were usually sectioned; so this negative finding must be considered

with reservations.

Treatment consisted of radical mastectomy in all cases but three. In the latter, simple mastectomy was done. Prophylactic postoperative x-ray therapy was utilized in a number of cases. The whole group presents an average survival time of 5.27 years from time of operation on the second breast. Twenty cases had their second mastectomy five or more years ago, and of these 11 (55%) lived five years. Such a survival rate suggests that these lesions were seperate primaries rather than metastases in many instances. As would be expected the survival time following the first cancer was unusually long. Twenty-three patients had had their first cancer removed five or more years ago, and 19 (82.6%) of these survived 5 years after the first cancer. Of those whose first cancer was removed ten or more years ago, there were 20 of whom 15 (75%) lived ten years.

Age at First and Second Breast:

Kraus and Kline in 1926 reported a case of consecutive bilateral breast cancer in a 16 year old girl[11]. As regards age at time of occurrence of the first breast cancer, the youngest patient in our series was 32 years, and the oldest was 67. Sixteen of the 23 cases were under 50 years when their first cancer developed. This proportion, 61.5% is somewhat larger than the proportion of the 249 unilateral cases under 50 years, 96 cases or 39.5%. Similarly the mean age of the bilateral cancers was 47.9 years, as contrasted with a mean age of 54.2 years for the 243 patients in our original series with unilateral carcinoma.

These findings are consistent with those of Desaive[3] who found that of 46 non-simultaneous bilateral breast cancers the peak of incidence in regard to the first breast was at 45 years as compared to 55 years for a control group of 1,318 cases. Likewise, he found the mean age of his bilateral breast cases to be 48.09 years at time of occurrence of the first carcinoma, as compared to 54.55 years in the case of the unilateral carcinomas.

One might, therefore, expect patients in the younger age groups to show a greater risk of developing carcinoma of the opposite breast. Of those cases seen by us with their first breast cancer before the age of 50, there were 100, of whom 4 or 4.0% developed a carcinoma of the opposite breast. These findings show a slight, but certainly not significant, increase over the incidence rates in the 164 patients who developed their first cancer after the age of 50 years (3% bilateral cancers).

From the point of view of risk years of observation, the 100 patients under 50 years at the time of their first cancer, were followed for a total of 628 years or with the development of 6.3 cancers in the opposite breast per 1,000 risk years. The 164 patients over 50 years were followed for a total of 912.5 years or with 5.4 cancers per 1,000 risk years.

One is unable, therefore, to draw any conclusions as to a greater risk per unit of time of non-simultaneous bilateral cancer in those patients developing their first cancer at an early age. It is suggestive, however, to note that those 6 bilateral cancers, wherein the interval between the two cancers was 10 years or more (12-32 years), all developed their first cancer before the age of 46 years. It might be that a relatively large proportion of the bilateral cases develop their first cancer at any early age, because such cases are the ones that live long enough to develop their second cancer.

Sexual History:

The menstrual histories regarding menarche, frequency, dysmonnorhea, et cetera, presented nothing unusual.

As regards the time of menopause and its relation to the occurrence of the two breast cancers, a slight shift to a younger age group than usual is again reflected here, the first breast becoming

involved before the menopause in 15 of the 26 cases (57.7%), as compared with 39.0% in the unilateral cases. This finding coincides with that of Desaive, who reported that of 46 patients with non-simultaneous bilateral cancers, 59% developed their first breast cancer before the menopause, whereas 1259 unilateral breast cancers occurred before the menopause in 29% of the cases.

If one separates our original series of cases as regards the relation of the first cancer to the menopause, one finds again a slight, but not significant, increase in risk. The 92 cancer patients before the menopause developed 4 (4.3%) bilateral cancers; the 172 patients developing their cancer after the menopause developed 5 (2.9%) bilateral cancers.

All patients were married. Twenty-four patients had had from one to ten children, an average of 2.7 children. Two patients were nulliparous. Of the 176 unilateral cancer patients, of whom the information was available, 140 parous patients had an average of 3.2 children, with 29 nulliparous patients, and 7 single patients. These findings are interesting in light of the suggestion not infrequently seen in the literature that patients with cancer of the breast include an inordinately large proportion of single women and that cancer patients have fewer children than the population at large[12, 24].

In any discussion of the development of non-simultaneous bilateral breast carcinoma, the influence of pregnancy occurring after the first breast is a factor of interest. Trout[22] in 1921 reported 31 cases of breast carcinoma below 40 years of age. Two of these patients became pregnant after treatment of the first breast. Both cases developed carcinoma of the opposite breast during or following their pregnancy, although in only one case was the second tumor examined microscopically. Trout also wrote to a number of physicians, and received reports of 15 cases where pregnancy occurred after a primary breast carcinoma was removed. Thirteen of these subsequently developed carcinoma in the opposite breast, there ensuing from 2 to 10 years between the first breast cancer and the pregnancy.

Brooks and Proffit[2] have recently concluded that there is no evidence that pregnancy is influential in originating a breast cnacer; and, therefore, that, if a unilateral breast cancer is completely extripated, pregnancy can be permitted without fear for the other breast. They present 5 patients who became pregnant after operative removal of a cancer of one breast. None of these developed a carcinoma of the opposite breast. However, it should be noted that the one case, that had been followed for 5 years after pregnancy, had an original lesion, the malignancy of which was admittedly in dispute. Of the other 4 cases, one died 2 months after delivery, one was pregnant at the time of writing, and the other 2 had been followed 2 months and 1 year , respectively.

Of the 46 cases of non-simultaneous bilateral breast carcinoma reported by Desaive[3], there were 2 cases in which he observed "the coincidence of a pregnancy and the development of a cancer in the second breast". One of our cases developed her first breast cancer in 1944 at the age of 37 years, had two children in 1946 and 1948 respectively, and developed a carcinoma of the opposite breast in 1951.

Such isolated cases are, of course, of little significance, the rather striking report by Trout presents all the hazards of any investigation carried out by mail, and microscopic verification was not confirmed in the paper. Nevertheless, until more evidence is available to confirm or deny the possibility, it would seem well to look upon pregnancy, following apparent "cure" of a breast cancer, with some qualms in relation to the other breast, if for no other reason.

Of the 15 bilateral cases developing their first cancer before the menopause, none were sterilized. However, of the 82 unilateral cancers, which occurred be-

fore the menopause, only 18 were sterilized, so this finding is of little significance alone.

Heredity:

That there is a familial factor in the development of breast cancer is generally agreed upon today. However, the study of this subject in the human has necessarily been based upon isolated case reports or on statistical data. The conclusiveness of the latter has suffered due to lack of completely comparable control groups, and moreover the reported cases of breast cancer in relatives are in most papers unconfirmed. Nevertheless, fairly large statistical studies by several workers strongly suggest that breast cancer occurs more frequently among the relatives of breast cancer patients than would be expected in the population at large[1, 9, 18].

Should there be a familial predisposition to breast cancer, however, one might expect both breasts to be equally sensitive. It is interesting to note, in this regard, two isolated case reports, which, while they are alone inconclusive, are none the less suggestive. Handley[6] in 1938 told of a family of 5 sisters, of whom 2 had bilateral carcinoma of the breast, one a probable (unbiopsied) unilateral carcinoma of the breast, and one had both breasts amputated for "proliferative mastitis", and the fifth had x-ray and radium treatment for "mastitic induration". Wood and Darling in 1943[27] reported an incomplete pedigree of 4 generations of one family. There were 4 cases of bilateral breast carcinoma. In the third generation all three sisters had breast cancer, two bilateral and one unilateral. A family has recently been called to our attention in Saint Paul, in which there are 6 sisters, of whom 5 have had breast cancer, 2 bilateral and one probably bilateral.

An effort has been made to find how many of our 23 cases of bilateral breast cancer present a family history of the disease. The latter finding has been compared with the pedigrees of a group of unilateral breast cancers.

In the case of the bilateral cancers, family histories were obtained by correspondence or personal interview with as many members of the 26 families as possible. Most reported cases of cancer in relatives were confirmed by either the death certificate or the pathological report or a letter from the attending physician.

As a control group, 306 consecutive cases of breast cancer were studied from the files of the Dight Institute. Six of these were bilateral cancers and as such have been deleted as controls. Five of these bilateral cancers were also patients previously included in our 26 original cases. The cases on the files at the Dight Institute are patients seen consecutively in the Out-patient Department of the University Hospitals. The diagnosis of cancer in relatives has been confirmed in most cases. The patients are quite comparable to ours in regard to background and environment. The age distribution is similar to that of the unilateral cancers in our original series.

In neither our 23 cases nor the pedigrees of the Dight Institute is the information felt to be sufficiently complete to compare all members of the family. The information regarding mothers and sisters however, is felt to be sufficiently reliable to allow for statistical analysis. In 2 of our bilateral cases the fate of the patient's family is unknown and untraceable due to their location behind the Iron Curtain. Therefore, these 2 cases have been deleted from our series, leaving a total of 24 bilateral breast cancers in the ensuing discussion. Such a number is small but may be accepted as adequate for biological statistical analysis.

Of these 24 bilateral breast cancers, 11 patients had a mother or sister with carcinoma of the breast, (10 proven, 1 probable but unconfirmed). Of the 300 cases of unilateral breast cancer, 27 pa-

tients had a mother or sister with breast cnacer (24 confirmed, 3 probable but unconfirmed). This difference in incidence, 45.8 per 100 as compared to 9.0 per 100, is striking. However, there is a possible fallacy in that the number of the sisters and their ages could influence such results considerably. Therefore, the sisters have been segregated according to age.

Among the bilateral cancers there were 28 sisters, at least 60 years of age or over with cancer. Of these 28, there were 6 breast cancers (21.4%). Among the unilateral cases there were 318 sisters of 60 or over with cancer, of whom 22 (6.8%) had breast cancer (X^2 = 5.46; P = < 0.02).

Among the mothers, 24 mothers in the bilateral group developed 6 breast cancers (25.0%); while in the unilateral group 300 mothers developed 9 breast cancers (3%) (X^2 = 24.64; P = <0.001).

It is striking that 20 (83.3%) of the bilateral cases showed cancer in one or more members of their immediate family (mother, father, brother, or sister). Among the 300 unilateral cases, 116 (38%) showed a similar picture. When calculated, taking into consideration the number of brothers and sisters of at least 60 yrs. or over with cancer, the difference is less impressive however, (21.5% in the bilateral cases, 13.4% among the unilateral cases).

Of the 24 mothers of the bilateral cases, 12 (50%) developed cancer of some kind, as compared to 15% of the mothers of the unilateral cases. However, if one deletes the breast cancers, there is not then a significant difference in the incidence of cancers other than the breast (25% of mothers in the bilateral cases, 12% of mothers of the unilateral cases). (X^2 = 3.33; P = <0.1)

As previously stated, records are not felt to be complete as regards more distant members of the family. However, it is of interest that of the 24 bilateral cancer cases, 15 (62.5%) showed a family history of breast cancers in any relative. Of these 15, 3 gave a family history of bilateral breast cancer, and 2 had more than one relative with breast cancer. This proportion (62.5%) contrasts with the unilateral cancers, who gave a family history of breast cancer in any relative in 46 cases (15.3%).

Twenty-three of the 24 patients gave a family history of some kind of cancer, and 20 of the 24 patients presented multiple occurrence of cancer in their pedigrees.

One hesitates to make conclusions from such small numbers. However, the above findings suggest strongly that patients with bilateral breast cancer show an increase in breast cancer among their relatives, especially in regard to mothers. One might infer that that case who presents herself with a first breast cancer and with a family history of breast cancer suffers a greater risk of developing cancer in the opposite breast. Though such generalizations are fallible in such a small series, none the less, prophylactic removal of the opposite breast in such a patient would in our cases have taken care of 62.5% of the patients.

Pathology:

Handley[5] in 1936 wrote that "when a breast has suffered from chronic mastitis and cancer, the other breast is likely in the course of years to follow the same course". He described such a case, and suggested that when carcinoma and "chronic mastitis" occurred in one breast, the other breast should be treated by either simple mastectomy or x-ray. Sistrunk[20] in 1921 stated that if carcinoma appeared in one breast and the other breast was the seat of "definite mastitis", he did a prophylactic simple mastectomy of the latter breast.

From the point of view of clinical evaluation, however, in only one of our cases was the first breast noted to contain other masses or cysts, or described in any way that would suggest the presence

of cystic disease. The second breast (i.e. the breast which later developed the second tumor) was described in a similar fashion in only 3 of the 26 cases. In only one case were both the first and the second breast described as involved. This case, included in the above listings, was also the only case in which the cystic disease was described as "massive, involving the whole breast"; the patient also gave a history of breast cancer in 2 maternal cousins.

An evaluation of our cases from the point of view of microscopic "cystic disease" is handicapped by the fact that in only one or two cases were the gross specimens of the entire breast available. Original pathologist's reports described gross and/or microscopic "cystic disease" in 3 cases in relation to the first breast and in 3 cases in relation to the second breast. However, the fact that such pathology was not mentioned does not rule out its presence, since such additional description in relation to a cancer may well seem superfluous to a pathologist, not particularly interested in this aspect.

The microscopic slides were available on 50 of the 52 breasts. These sections in any individual case usually consisted of one or two sections through various parts of the tumor. Views of the non-malignant breast tissue were relegated to isolated lobules found at the edge of the tumor sections, and in only one or two cases had sections been cut of breast tissue away from the area of the tumor. The microscopic sections were compared with similar slides of the breasts of those patients in our original series who had lived 9 years or more without developing a tumor in the other breast and who were of the same age group. In relation to ductal dilatation, epithelial hyperplasia, and the presence of "apocrine" epithelium, there was a slight preponderance in the bilateral breasts especially as regards "apocrine" epithelium. This difference was not marked, however, and it is apparent that any such comparison should include very careful examination of the whole breast, and conclusions based on a less thorough examination would be dangerous.

The tumor types presented nothing unusual or characteristic. Of the 26 cancers of the first breast, the sections were available in 18 cases. One of these was a Paget's cancer with intraductal carcinoma, one was a low grade adenocarcinoma of the nipple, and the remaining 17 cases showed adenocarcinoma of varying degrees of differentiation and with stroma containing varying degrees of fibrous tissue. Of the latter, 3 cases presented a picture consistent with a "medullary" carcinoma. The other 14 cancers were adenocarcinomas, growing in a rather abundant fibrous stroma, and consistent with the picture seen in scirrhous tumors. The 8 cancers of the first breast, on which slides were not available, were described only as "adenocarcinoma" or "scirrhous carcinoma".

Of the 26 cancers of the second breast, sections were available on 22. One of these was a mucinous carcinoma; 20 were adenocarcinomas of a scirrhous type, and one was a medullary carcinoma. The 4 tumors of which we have not viewed the slides, were described by the original pathologists as "scirrhous carcinoma" or "adenocarcinoma".

In two patients the second breast revealed 2 distinct small tumor nodules. In one case both were poorly differentiated adenocarcinomas; in the other, one tumor was scirrhous, the other medullary. Though such multiplicity might suggest metastasis, these 2 patients are living without apparent recurrence at 13 and 1.5 years, respectively following the second cancer.

In an attempt to evaluate the problem of breast pathology, a study is being carried out in which breasts are being sectioned throughout their extent at intervals of no greater than 1 cm. It is felt that such a study would give a more complete picture of the presence or absence of disease.

In three recent cases of bilateral

carcinoma, the breasts have been examined in this manner. Fifteen prophylactic simple mastectomies following unilateral cancer are also being examined. Nine have been examined in the above more complete manner, and 6 thus far in a routine way. To date our findings have been essentially negative. That pathology usually grouped under the heading of "cystic disease" has been remarkably absent. Nor have any lesions been found in the "bilateral cancer" breasts which are suggestive of a precancerous lesion.

As might be expected from the incidence found on follow-up studies, except for the small carcinomas found early in the series of prophylactic simple mastectomies, no other cancers have been found in a total of 17 mastectomies.

Summary:

1. A follow-up study of patients operated on for carcinoma of the breast at least ten years ago reveals an incidence of non-simultaneous bilateral cancer of 3.4%.

2. This incidence is greater than that found in the population at large as regards women under 50 years of age at the time of their first cancer.

3. Age distribution shows a slight shift to the younger age groups in bilateral cancers, compared to unilateral cancers.

4. Patients with bilateral cancer appear to have a significantly greater number of mothers and sisters with breast cancer than do those with unilateral cancer.

5. We have found no evidence that "cystic disease" of one or both breasts predisposes to bilateral cancer.

6. A program of prophylactic simple mastectomies has revealed 2 patients with microscopic bilateral cancer in 17 such procedures.

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II. MEDICAL SCHOOL NEWS

Coming Events

Jan. 15 George Chase Christian Cancer Lecture; "Current Thoughts on Viruses and Cancer"; Dr. C. H. Andrewes, Head, Department of Bacteriology and Virus Research, National Institute for Medical Research, London; Owre Amphitheater, 8:00 p.m.

Jan. 18 Special Lecture; "Biochemistry of Bone Formation"; Dr. Marcel J. Dallemagne, University of Liege, Belgium; Owre Amphitheater; 4:00 p.m.

Jan. 21-25 Continuation Course in Electrocardiography for General Physicians

Jan. 22 Minnesota Pathological Society Meeting; "The Problem of Intracellular Parasitism in Brucellosis," Dr. Wesley W. Spink; Owre Amphitheater, 8:00 p.m.

Jan. 28 - Feb. 9 Continuation Course in Clinical Neurology for General Physicians and Specialists

Feb. 14-16 Continuation Course in Therapy of Cardiovascular Diseases for General Physicians

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Continuation Course in Electrocardiography

A continuation course in Electrocardiography for general physicians will be presented January 21-25, 1952, at the Center for Continuation Study. Each registrant for the course will be given an opportunity to interpret, under supervision, approximately 200 electrocardiograms. The faculty for the course will be made up of full-time and clinical members of the staff of the University of Minnesota Medical School and the Mayo Foundation. In the past this has always been one of the most popular courses, and another excellent session is expected.

Faculty News

Dr. David Glick, Professor of Physiological Chemistry, attended the meeting of the American Academy of Dermatology in Chicago as a guest lecturer. Dr. Glick presented a paper on "The Histochemical Approach to Studies on the Skin" on December 10.

Dr. E. H. Rynearson, Professor of Medicine, Mayo Foundation, Rochester, addressed the Hennepin County Medical Society on Monday evening, January 7, on the subject, "Diseases of the Adrenal Glands."

Special Lectureship

On January 15, the University will welcome Professor C. H. Andrewes, Head, Department of Bacteriology and Virus Research, National Institute for Medical Research, London, as the George Chase Christian lecturer. He will speak on, "Current Thoughts on Viruses and Cancer," at 8:00 p.m. in 15 Owre Hall (Medical Sciences Amphitheater). Dr. Andrewes has also consented to speak on "New Techniques for the Study of Mouse Tumors" at 4:30 p.m. on Monday, January 14, in 111 Owre Hall.

New Minnesota Medical Foundation Members

Thomas Polley, M.D., St. Joliet, Ill.
L. G. Ericksen, M.D., South Bend, Ind.
Louis L. Freidman, M.D., St. Paul
H. M. Berg, M.D., Bismarck, N. Dak.
Mr. Robert A. Rice, Minneapolis
Mr. Joe Soiney, Thief River Falls
Mr. E. E. Crabb, Minneapolis
Samuel Miller, M.D., Albert Lea
David V. Habif, M.D., New York
A. S. Midthune, M.D., Lake Park
B. D. Elliott, M.D., Oskaloosa, Iowa

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On January 1, 1952, Dr. George N. Aagaard, former Director of the Department of Continuation Medical Education and editor of this bulletin, assumed his new duties as Dean, Southwestern Medical School of the University of Texas, Dallas. His outstanding qualities as physician, leader, teacher, and administrator fit him admirably for this task. The entire faculty of the medical school bids him every wish for success and happiness in his new position.

R. B. H.

III. UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
WEEKLY CALENDAR OF EVENTS

Physicians Welcome

January 14 - 19, 1952

Monday, January 14

Medical School and University Hospitals

9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; M-109, U. H.

10:00 - 12:00 Neurology Rounds; A. B. Baker and Staff; Station 50, U. H.

11:30 - Tumor Conference; Doctors Kremen, Moore, and Stenstrom, Todd Amphitheater, U. H.

12:15 - 1:20 Obstetrics and Gynecology Journal Club; Staff Dining Room, U. H.

12:30 - Physiology Seminar: Forms and Shapes in the Electrical Activity of the Brain: Spontaneous and Evoked Traveling Apparitions; Dr. John C. Lilly, Johnson Foundation for Medical Physics, University of Pennsylvania; 214 Millard Hall.

1:30 - 2:30 Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U. H.

4:00 - Pediatric Seminar; Infectious Hepatitis; Theresa Haddy; 6th Floor West, U. H.

4:30 - 5:30 Dermatological Seminar; M-346, U. H.

4:30 - Public Health Seminar; 15 Owre Hall.

5:00 - 6:00 Urology-Roentgenology Conference; C. D. Creevy, O. J. Baggenstoss, and Staff; Eustis Amphitheater.

Minneapolis General Hospital

7:30 a.m. Fracture Grand Rounds; Dr. Zierold; Station A.

11:00 - Pediatric Rounds; F. H. Top; 7th Floor.

12:30 p.m. Surgery Grand Rounds; Dr. Zierold; Station E.

1:00 - 2:00 X-ray Conference; Classroom, 4th Floor.

1:30 - Pediatric Rounds; R. Ulstrom; 4th Floor.

Monday, January 14 (Cont.)

Veterans Administration Hospital

9:00 - G. I. Rounds; R. V. Ebert, J. A. Wilson, Norman Shrifter; Bldg. I.

11:30 - X-ray Conference; Conference Room; Bldg. I.

2:00 - Psychosomatic Rounds; Bldg. 5.

3:30 - Psychosomatic Rounds; Bldg. 1, C. K. Aldrich.

Tuesday, January 15

Medical School and University Hospitals

8:30 - Conference on Diet Endocrines and Cancer; M. B. Visscher; Physiology Library.

9:00 - 9:50 Roentgenology-Pediatric Conference; L. G. Rigler, I. McQuarrie and Staff; Eustis Amphitheater, U. H.

9:00 - 12:00 Cardiovascular Rounds; Station 30, U. H.

12:30 - 1:20 Pathology Conference; Autopsies; J. R. Dawson and Staff; 102 I. A.

12:30 - Selected Topics, Permeability and Metabolism; Nathan Lifson; Physiology Library.

3:15 - 4:20 Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U. H.

4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.

4:30 - Clinical-Medical-Pathological Conference; Todd Amphitheater, U. H.

5:00 - 6:00 X-ray Conference; Presentation of Cases by Veterans Hospital Staff; Drs. Fink, O'Loughlin, et al., Eustis Amphitheater, U. H.

*8:00 p.m. George Chase Christian Cancer Lecture; Current Thoughts on Viruses and Cancer; Dr. C. H. Andrewes, Head, Department of Bacteriology and Virus Research, National Institute for Medical Research, London; Owre Amphitheater.

Ancker Hospital

8:00 - 9:00 Fracture Conference; Auditorium.

1:00 - 2:30 X-ray Surgery Conference; Auditorium.

Minneapolis General Hospital

8:00 - Pediatric Rounds; Dr. Gibbs; 5th Floor Annex.

Tuesday, January 15 (Cont.)

Minneapolis General Hospital (Cont.)

10:00 - Psychiatric Grand Rounds; J. C. Michael and Staff; 3rd Floor Annex.

11:00 - Pediatric Rounds; E. S. Platou; 7th Floor.

Veterans Administration Hospital

7:30 - Anesthesiology Conference; Conference Room, Bldg. I.

8:30 - Infectious Disease Rounds; Dr. Hall.

8:45 - Surgery Journal Club; Conference Room, Bldg. I.

9:00 - Liver Rounds; Drs. Nesbitt and MacDonald.

9:30 - Surgery-Pathology Conference; Conference Room, Bldg. I.

10:30 - Surgery Tumor Conference; Conference Room, Bldg. I.

1:00 - Surgery Chest Conference; T. Kinsella and Wm. Tucker; Conference Room, Bldg. I.

2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III.

3:30 - 4:20 Autopsy Conference; E. T. Bell and Donald Gleason; Conference Room, Bldg. I.

Wednesday, January 16

Medical School and University Hospitals

8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-109, U. H.

8:00 - 9:00 Roentgenology-Surgical-Pathological Conference; Allen Judd and L. G. Rigler; Todd Amphitheater, U. H.

11:00 - 12:00 Pathology-Medicine-Surgery Conference; Medicine Case; O. H. Wangensteen, C. J. Watson and Staffs; Todd Amphitheater, U. H.

12:30 - 1:20 Radio-Isotope Seminar; James F. Marvin; 12 Owre Hall.

1:30 - Conference on Circulatory and Renal Systems Problems; M. B. Visscher; 116 Millard Hall.

5:00 - 5:50 Urology-Pathological Conference; C. D. Creevy and Staff; Eustis Amphitheater, U. H.

5:00 - 6:00 Vascular Conference; Todd Amphitheater, U. H.

5:00 - 7:00 Dermatology Clinical Seminar; Dining Room, U. H.

Wednesday, January 16 (Cont.)

Medical School and University Hospitals (Cont.)

7:00 - 8:00 Dermatology Journal Club; Dining Room, U. H.

8:00 - 10:00 Dermatological-Pathology Conference; Review of Histopathology Section; R. Goltz; Todd Amphitheater, U. H.

Ancker Hospital

8:30 - 9:30 Clinico-Pathological Conference; Auditorium.

3:30 - 4:30 Journal Club; Surgery Office.

Minneapolis General Hospital

9:30 - Pediatric Rounds; E. S. Platou; 7th Floor Annex.

11:00 - Pediatric Rounds; F. H. Top; 7th Floor.

12:15 - Pediatric Conference; 4th Floor Annex.

1:30 - Pediatric Rounds; E. J. Huenekens and R. Ulstrom; 4th Floor Annex.

2:00 - 4:00 Infectious Disease Rounds; 8th Floor.

4:00 - 5:00 Infectious Disease Conference; Classroom, 8th Floor.

Veterans Administration Hospital

8:30 - 10:00 Orthopedic X-ray Conference; Conference Room, Bldg. I.

8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker.

7:00 p.m. Lectures in Basic Science of Orthopedics; Conference Room, Bldg. I.

Thursday, January 17

Medical School and University Hospitals

9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Todd Amphitheater, U. H.

1:30 - 4:00 Cardiology X-ray Conference; Heart Hospital Theater.

4:00 - 5:00 Physiology-Surgery Conference; Todd Amphitheater, U. H.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.

5:00 - 6:00 X-ray Seminar; Report of Meeting of Radiological Society of North America; Eustis Amphitheater, U. H.

Thursday, January 17 (Cont.)

Medical School and University Hospitals (Cont.)

7:30 - 9:30 Pediatric Cardiology Conference and Journal Club; Review of Current Literature 1st hour and Review of Patients 2nd hour; 206 Temporary West Hospital.

Minneapolis General Hospital

8:00 - Pediatric Rounds; Dr. Gibbs; 5th Floor.

8:30 - Neurology Rounds; Dr. Heilig; 4th Floor Annex.

9:00 - Neurology Grand Rounds; J. C. Michael and Staff; Station A.

11:00 - Pediatric Rounds; E. S. Platou; 7th Floor.

11:30 - Pathology Conference; Main Classroom.

1:00 - 2:00 Fracture - X-ray Conference; Dr. Zierold; Classroom, 4th Floor Annex.

2:00 - Psychiatry Rounds; P. Benton; 4th Floor Annex.

Veterans Administration Hospital

8:00 - Surgery Ward Rounds; Lyle Hay and Staff; Ward 11.

9:15 - Surgery Grand Rounds; Conference Room, Bldg. I.

11:00 - Surgery Roentgen Conference; Conference Room, Bldg. I.

Friday, January 18

Medical School and University Hospitals

8:30 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:30 - 11:50 Medicine Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:30 - 11:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.

11:45 - 12:50 University of Minnesota Hospitals Staff Meeting; Metabolic Functions of the Vitamin B Complex; Herman C. Lichstein; Powell Hall Amphitheater.

1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

2:00 - 3:00 Dermatology and Syphilology Conference; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-312, U. H.

3:00 - 4:00 Neuropathological Conference; F. Tichy; Todd Amphitheater, U. H.

Friday, January 18 (Cont.)

Medical School and University Hospitals (Cont.)

4:00 - 5:00 Dermatology Seminar; W-312, U. H.

4:00 - Neurophysiology Seminar; 113 Owre Hall.

*4:00 - Special Lecture; Biochemistry of Bone Formation; Dr. Marcel J. Dallemagne; University of Liege, Belgium; 15 Owre Hall.

5:00 - Urology Semiar and X-ray Conference; Eustis Amphitheater, U. H.

Ancker Hospital

1:00 - 3:00 Pathology-Surgery Conference; Auditorium.

Minneapolis General Hospital

8:00 - Pediatric Allergy Rounds; Dr. Nelson; 4th Floor.

11:00 - Pediatric Rounds; F. H. Top; 7th Floor.

11:00 - Pediatric-Surgery Conference; Drs. Wyatt and F. H. Adams; Classroom, Sta. I.

12:00 - Surgery-Pathology Conference; Drs. Zierold and Coe; Classroom.

1:30 - Pediatric Rounds; R. Ulstrom, 4th Floor.

Veterans Administration Hospital

10:30 - 11:20 Medicine Grand Rounds; Conference Room, Bldg. I.

1:00 - Microscopic-Pathology Conference; E. T. Bell; Conference Room, Bldg. I.

1:30 - Chest Conference; Wm. Tucker and J. A. Meyers; Ward 62, Day Room.

3:00 - Renal Pathology; E. T. Bell; Conference Room, Bldg. I.

Saturday, January 19

Medical School and University Hospitals

7:45 - 8:50 Orthopedic X-ray Conference; W. H. Cole and Staff; M-109, U. H.

9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater, U. H.

9:15 - 10:00 Surgery-Roentgenology Conference; J. Friedman, O. H. Wangensteen and Staff; Todd Amphitheater, U. H.

9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; Heart Hospital Amphitheater.

Saturday, January 19 (Cont.)

Medical School and University Hospitals (Cont.)

10:00 - 11:30 Surgery Conference; Todd Amphitheater, U. H.

10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

11:30 - Anatomy Seminar; Recent Literature on Prenatal and Postnatal Growth, L. J. Wells; Growth, Jennifer Sullivan; 226 Institute of Anatomy.

Minneapolis General Hospital

8:00 - Pediatric Rounds; Dr. Gibbs; 5th Floor.

11:00 - 12:00 Pediatric Clinic; L. Thomas and C. D. May; Classroom, 4th Floor Annex.

Veterans Administration Hospital

8:00 - Proctology Rounds; W. C. Bernstein and Staff; Bldg. III.

8:30 - Hematology Rounds; P. Hagen and E. F. Englund.

* Indicates special meeting. All other meetings occur regularly each week at the same time on the same day. Meeting place may vary from week to week for some conferences.