Complication and sequelae of carcinoma of the breast

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COMPPLICATION AND SEQUELAE OF CARCINOMA
OF THE BREAST

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Introduction

Since time immemorial cancer of the breast has been the most dreaded disease of the female sex. Cancer of the breast is next to cancer of the uterus in frequency among women and holds third place of all cancers in both men and women.

Ewing has shown that cancer is definitely on the increase. However, he believes this increase is due to an improvement in diagnosis and registration and not due to any more cancer being present than has been formerly.

Cancer of the breast has long held the interest of the medical profession, an enormous amount of material has been written on all phases of the subject, men have devoted their lives to its study and in recent years many hospitals have established special breast clinics in order that it might be studied in more detail.

The complications and sequelae of carcinoma of the breast are of interest to me chiefly because the disease is already established and as has been shown, already advanced to the axilla in sixty per cent of the patients at the time they present themselves in the office for their first examination.

Many men have suggested that to successfully combat the condition, it will be necessary first to educate the medical profession to the seriousness of a lump in the breast and the careful study which it demands and second, the education of the public to the fact that cancer, when taken early and properly treated, is not an incurable disease.
Review of the Literature

Lee (59) states that the antiquity of cancer was proved long before medical history was written. In the Mesozoic era or age of reptiles, the bones show evidence of osteoma, osteosarcoma and hemangioma of the bone. The evidence of bone cancer increases with each succeeding geological period through the Cenozoic and Paleozoic era until in the Egyptian period, benign and malignant tumors were discovered.

The earliest medical document yet discovered, according to Lee (59), the Evers papyrus (Circa B.C. 1500), contains a reference to tumors. Cancer of the breast is described with some detail in an inscription from Ninevah (B.C. 800). Democedes (B.C. 520) describes the cure of Atossa, the daughter of Darius Hystaspis, of breast cancer.

Hippocrates (460 - 375 B.C.) employed terms of cancer and carcinoma, described cancer of the skin, breast, stomach, uterus and rectum, and gave a description of recurrent cancer of the neck treated by cautery. Celsus devised a plastic operation for cancer of the lip and practiced excision of the cancer of the breast, advising against the removal of the underlying pectoral muscles. Galen (A.D. 131 - 203) believed that the body was composed of four fluids; blood, mucous, yellow and black bile. He held that the concentration of black bile at any part of the body would cause cancer. He also advised removal of the cancer by radical operation (60).
Paul (63) of Aegina 625 - 690 writes chiefly on the cause of cancer of the breast. He states that cancer occurs in every part of the body, but is most frequent in the breasts of women. He explained this as being due to the laxity of the breasts, readily admitting the thick humour which causes it. He agreed with Galen as to cause of cancer being due to black bile and states cancers were formed by black bile being overheated and if particularly acrid, it would be attended by ulceration. He further states that cancer was an incurable disease for it can neither be repelled nor dispersed, not yielding to purging of the whole body, resisting the milder applications and being exasperated by the stronger.

Lee (59) further states that Leonides, who lived in Alexandria in latter part of the second century, was apparently the first surgeon to carry out a dissection for cancer of the breast approaching modern technique. Walsh (97) refers to the writings of Aetius in which he refers to Leonides and his operation for cancer of the breast. Leonides insists on the external removal of tissue and free application of the cautery to aid in stopping bleeding and also to further destroy cancerous tissue. Kaplan (47) refers to radical mastectomy being practiced 50 B.C. Thorne (94) states that the earliest records speak of operation being complete which consisted of removing the breast and of freely applying the cautery to the exposed chest wall. In preanaesthetic days this operation was only undertaken in advanced cases to prevent the presence of
foul-smelling discharge. At this time it was thought a constitutional disease and only the lump in the breast was removed and the skin with it.

Following (59) the period of Leonides there was an elapse of a thousand years when little was added to our knowledge of cancer. The operative treatment of cancer did not advance as the practice of surgery was held in disrepute. The council of Tombs (1162) placed the ban of the church on the practice of surgery. An outstanding physician of this period was Guy De Chauliac (1300 - 1368), author of the classical treatise "Chirurgia Magna", who employed caustic pastes, also thought and practiced that cancer of the breast should be treated surgically.

The (58) development of the microscope (1592) and the recognition of cellular structure by Schleiden and Schwann, gave the first impulses to the dissemination of medical knowledge and the intelligent study of the histology of tumors. Ambrose Pere (1510 - 1590), a French army surgeon, attempted to treat cancer employing diet and purgation as routine measures and occasional surgical excision for small early cancers. The treatment proved very ineffective. Fabricious Hildamus (1560 - 1634), the father of German surgery, was the first to practice a complete axillary dissection in the treatment of mammary cancer.

Marco Aurelio Severins (1580 - 1656) (63) classified tumors of the breast stating that the breast was subject to four severe affections or tumors. They were glandular,
strumous, scirrhous, and cancerous. He states cancerous tumors were caused by a perpetual heating of the juices and for this reason it is both most offensive and displays the most severe symptoms. All the rest not arising from heated humors are less injurious. He advises surgery for the condition.

With the advent (58) of the nineteenth century came the beginning of effective histological study of tumors. Johannes Muller (1801 - 1858), who has been called the founder of cellular pathology, made the first comprehensive study of the histology of tumors. This was made possible by the discovery of the achromatic microscope by Silligues in Paris in 1824.

Karl Virchow (1821 - 1902), a pupil of Muller, is perhaps the greatest figure in the history of pathology. His books, "Die Cellular Pathologie", and the unfinished "Die Krankhaften Gerschwulste", contributed more to the theoretical and histological knowledge of cancer than any other source (59).

Cooke (13) in 1857 reported a case of carcinoma of the breast which proved fatal. The disease had metastasized widely and, therefore, he took this to mean it was a constitutional disease and used this case as an example of the utter impossibility of eradicating it by local measures. This case had a large ulcerated left breast and refused operation.

Cooke (14) was appointed on staff of cancer hospital in 1851 and at that time there was a rule that the scalpel
was the treatment. Dr. Carswell agreed with Cooke in thinking cancer was a constitutional disease. He gave the invariable return of the disease after extirpation as his reason for believing it so.

Hird (39), about the same time, expressed the belief that if any medicine retarded the growth of cancer it was arsenic given in cod liver oil. Also arsenic was given with iodine believing it would prevent secondary deposits.

Ewing (27) gives Moore the credit for having introduced the modern operation for mammary carcinoma in 1867 when he contended recurrences were due not to blood infection but to incomplete extirpation of the tumor. He recommended general removal of the breast, skin, fat, axillary nodes and pectoral muscles. His views were supported by Lister and Banks.

In 1875, Von Volkmann (70) removed enlarged axillary glands and fat with the breast. He observed that if cancerous tissue was dissected off of fascia of pectoral muscles, local recurrences often occurred. Therefore, he advised further removal, not only of the entire breast, but with a liberal piece of skin, axillary glands, also the entire fascia of the pectoralis major muscle. Kuester of Berlin, in 1883, generalized Von Volkmann's advice and demanded cleaning out of the axilla in every case of breast tumor whether the glands were palpable or not. In 1885,
Gerster in New York reversed the procedure because he was of the opinion that handling the breast caused tumor cells to be forced into the blood stream, therefore, he cleaned out the axilla first and then removed breast and fascia. However, the end result in relation to recurrences did not change a great deal.

In 1889, Heidenhain, on the basis of careful microscopical examination of eighteen specimens removed by Kuester, substantiated Von Volkman's findings in every detail, and showed that in a great number of cases, the pectoralis major muscle was already involved by carcinomatous cells and he advised either the removal of the top layer of muscle or all of it.

In 1894, there were two radical operations introduced at the same time by Meyer and W. T. Halstead in which they advocated the removal of both pectoral muscles with the tumor plus the lymphatic glands and fat in one piece, thus leaving cancerously infected area undisturbed and all parts in normal anatomical relation to each other. This method has lessened the time of operation, loss of blood and chance of dissemination of cancer cells.

Following the discovery of x-ray and radium, they have been used either supplementing radical surgery or by themselves on inoperable cancer. Opinions are divided as to the value of x-ray. Since 1920, heavier x-ray machines giving deeper therapy have been used possibly to to better end results. It was (23) been stated that ra-
dical surgery for carcinoma of the breast reached its limits twenty-five years ago. This same author happens to be one who favors the use of x-ray and states that based on theoretical and clinical evidence, five-year survivals can be made more frequent by properly applied x-ray and radium therapy.
Complications and Sequelae of Carcinoma of the Breast

We (29) are far from any accurate knowledge of the cause of cancer of the breast, but surgical opinion is agreed that it begins as a local process, that there must be a precancerous stage and from the standpoint of effective therapy, the recognition of the precancerous stage is important. Chestle (16) believes it is impossible to decide how far back in date the biological conditions of epithelial cells destined to become carcinoma are precancerous. Tentative opinion is that the precancerous state may be set back even to embryonic life which may contain a decisive element of truth if the claim by Maud Slye upon hereditary influence of cancer is a correct one. An idea (27) as to the difficulty in recognizing this precancerous stage may be drawn from the statement which Ribbert makes to the effect that, "no one has ever seen a beginning carcinoma of the breast." He further states that when the lymph nodes or blood vessels are once involved, the further course of the disease, while extremely varied, may be much the same with tumors of very divergent antecedent history. The only indisputable test there is of the presence of carcinoma is the presence of living, multiplying and invading epithelial cells in parts where they have no normal right to be. Several authors, including Taylor (91) and Bunts (5), agree with Maud Slye in that even if cancer is not inherited, there is a family predisposition to it.
Ewing (27) believes that extension in the mammary parenchyma must be interpreted in some cases as a local evolution of the tumor and in others as a dissemination. It has been found that the remainder of the breast tissue varies widely, but is almost never normal. Most distant portions will usually show diffuse or cystic mastitis with periacinar infiltration and overnutrition or proliferation of epithelium.

Handley (36) states it is an axiom that the skin is early infected and carcinoma extends along it in all directions from the primary growth. After reviewing several cases, Velpeau is of the opinion that skin nodules always appear earliest in the immediate neighborhood of the primary lesion and the smaller ones are at the periphery.

There (27) are three methods by which the skin may become involved. First by the subpapillary lymphatic plexus from the periductal plexus, therefore, extensive cutaneous cancer of the breast may be observed in central duct cancers. In such cases the derma is infiltrated by nodules and masses, discrete or diffuse, encroaching more and more upon the subcutaneous fat. The area of skin involved may be much wider than the underlying tumor. The second method of skin invasion is by the ligament of Cooper and the third by destruction of the epidermis by carcinoma.

Cancer encuirasse (36) is at present considered to be a cancerous infiltration of the skin by spread of the disease along the deep cutaneous plexus of lymphatics.
Ewing (27) agrees with this; however, not all authors do. The skin has the same appearance as in elephantiasis which is due to lymphatic obstruction. Cheyne, in Handley's book, says the prodromal stage in encuirasse of the skin doesn't show any cancerous infiltration. Involvement of the skin may possibly be caused by an obstruction to the return of lymph from the skin.

There (36) are several theories as to the method of spread of carcinoma by lymphatics, whether by permeation or emboli. There is, also, some disagreement as to whether cancer metastasizes by lymph channels or blood stream. First I shall consider the involvement of the lymphatics and then present the discussion on metastases by blood stream. The involvement of the axillary glands has already occurred in a rather large percentage of cases when the patient first presents himself for examination, and it will later be shown that this has a very important bearing on the prognosis of the case. Handley (36) gives a rather detailed discussion on the involvement of the lymph glands. He states that embolic invasion of the axillary glands almost invariably occurs in an early stage of breast cancer. In the first stage of gland invasion a few cancer cells are seen lying in the subcapsular lymph sinus at the point of entry of afferent lymphatics along which the cancer cells have been swept by the lymph stream. The cancer cells penetrate the substance of the gland by
a process of actual growth. After considerable time, they reach the efferent channels and pass on to the next set of glands either embolically or by actual growth. After a period of time, the lymph glands will become foci of infection themselves. At first, they act as filters for the cancerous cells and delay the progress of the cells that reach them and may even cause some destruction of the cancerous cells, but after a long period of time, they succumb to the invasion. There may be dissemination without the enlargement of the glands. Simpson (89) agrees with Handley in that the axillary glands are the chief filters of the breast; therefore, are the most important. Primrose (78) believes the axillary lymph nodes may be demonstrated in practically every case by a pathologist. Portman (77) is of the opinion that once the axilla is involved it is impossible to rid it of all cancer cells and that some of the remaining cells lay dormant for a long period of time. It is on the theory of dormant cells being present that he accounts for late recurrences and metastases. Cheatle (15) agrees with the preceding ideas as regards axillary involvement. However, he is of the opinion that the rapidity with which the axillary glands become the seat of metastases varies in wide limits. He adds that the axillary glands contain tumor cells long before they are palpably enlarged so that clinical indications are not always an accurate index to the presence or
absence of carcinomatous invasion of these parts. Neither is there as much chance for error in a thin subject as there is in a fat one.

Whether the axillary glands are involved or not has been more or less used as a dividing line in offering a prognosis as to freedom from recurrence following operation. Their (66) involvement has been placed next to early operation in importance. Salvin (82) finds that sixty per cent of the cases presenting themselves for treatment have axillary glands which are palpable in many instances, and in others they are not palpable but are found microscopically to be already involved. Sistrunk (86) found the axillary glands involved in 60.5 per cent of the patients he had and he classes these cases as a late stage of the disease. Greenough (30) in a series of 135 cases in which axillary glands were recorded as not enlarged, found during pathological examination, following operation, involvement in 55 of them. This supports Cleveland's statement that involvement may be present but glands not palpable. He also classes these cases as inoperable as far as cure is concerned, as it is hard to conceive that spread ceases here.

Deaver (21) warns that palpably enlarged axillary or supraclavicular lymph nodes in presence of a mammary growth does not mean necessarily carcinomatous involvement. In both chronic cystic mastitis and cancer these nodes hypertrophy. The microscope proved the absence of metastases
in 6.5 per cent of the 37 per cent of malignant cases in which axillary enlargement was found by palpation. The glands were found microscopically to be involved in 62 per cent of cases. Saltzstein (81) states that axillary glands are uniformly involved in twelve months.

Involvement (80) of the axillary glands of the opposite side is an occurrence of considerable frequency and is prone to recur in late cases. Possibly due to spread by superficial lymph channels interlacing with those of the opposite side. Handley, however, attributes it to involvement of trunk lymphatics of the opposite side due to permeation of the malignant process beyond the mid line, the disease advancing along minute vessels of the fascial lymphatic plexus.

Supraclavicular (80) glands may become infected through the efferent lymphatic channels from the axillary glands or by way of the set of cutaneous vessels which drain the upper half of the breast and pass directly over the clavicle to empty into the glands above that bone. Handley (36) found in a series of 328 cases from the Middlesex Hospital, the supraclavicular and cervical glands, taken together, were involved in 18 per cent of the cases. In a series of 93 cases from Guy's Hospital, they were found involved in 13 per cent of the cases. These glands may be involved, but are not necessarily palpable. As a rule, only the glands on the side of the primary growth were involved. However, in 3 cases, the glands of the opposite
side were found to be involved, and in 4 cases the involvement was bilateral. They may be involved independent of the axillary glands due to spread by fascia and, if this were true, it would be found with presence of subcutaneous nodules. However, this theory has not worked out and it still seems that the former opinion, that the efferent lymphatics which pass from the axilla to supraclavicular gland, are the channels of infection. The involvement of the supraclavicular gland has been considered as a more advanced stage than axillary involvement, and carries a more grave prognosis. Kaplan and Rosh (46) are of the opinion that involvement of these glands may be regarded as a contraindication to a radical mastectomy.

Salvin (82) reports a case in which there was malignant involvement of a group of glands which are frequently overlooked. It is the group of glands lying along the third digitation of the serratus magnus muscle. He makes the statement that this region includes the great majority of mammary lymphatics and drains the area of the breast which is most frequently involved and should be considered as much or more than the axillary glands. The diagnosis of the case was gelatinous cystadenoma of the breast, with metastatic colloid carcinoma of lymph gland in segment of third digitation of the serratus magnus. The case was operated on, no enlargement of glands was found in any other location, and the patient made an uneventful recovery.
The (50) incidence of cancer in the second breast is of interest both on practical and theoretical grounds in that does its occurrence in the second breast mean individual susceptibility or a cancer diathesis? Deciding if it is a cancer diathesis is made difficult by the impossibility of deciding with certainty in a given case whether a cancer developing in the second breast after an interval of years is a true primary growth or simply a late metastasis. In many instances, cancer in the second breast arises independently of metastases in other regions and runs courses exactly comparable to courses expected of a primary cancer in length of life and metastases to axillary nodes on the side of the cancer. Johnson (42) believes that where both breasts are involved that the one involved later is the result of lymphatic spread and not a primary condition. He believes they spread by retro-mammary lymphatics and points out that axillary lymphatics may be involved which are located on the opposite side of the involvement. Paget (72) alluded to predisposition to cancer several years ago in which he stated he believed that certain parts of the body are more susceptible to metastases from cancer of the breast, and that women with cancer of the breast have more complicating diseases as fibroids of the uterus, dermoid cysts of the ovary, uterine polyps, bronchiocele, rodent ulcer, and cysts in the cerebellum. Carcinoma of the uterus and alimentary tract did not show these complications.
The question of cancer in the second breast was studied to determine whether it was advisable to remove the second breast at the time of the removal of the first as a prophylaxis the same as clearing the axilla; also studied to ascertain frequency of carcinoma in the second breast and time elapsing between first and second involvement of the breast. The results in 659 of 1100 unselected cases studied were known three or more years after operation.

In the entire series both breasts were involved in 37 (3.38 per cent) of the cases. In 13 of these cases the patient presented herself with both breasts involved. The histories would indicate cancer arose in one breast and metastasized to the other. Of the remaining 24 cases, the post-operative history in 11 suggested that the second breast cancer was metastatic on account of its appearance within a short interval of time after the removal of the first breast or its development coincidently with other metastases in the axilla of the side of the first cancer. The interval of time from operation and appearance of cancer in the second breast in these 11 cases was from 2 to 30 months averaging 12½ months. In the remaining 13 cases, the cancer in the second breast presented a clinical history suggesting a new and independent neoplasm on account of long interval of time after removal of the first breast with freedom from metastases or in 2 cases a comparatively short interval with freedom from other metastases and cure by operations on the second breast. 12 of this group of 13
cancers which behaved as primary tumors in the second breast, occurred in patients living five or more years after the first operation. In this series it is indicated that a woman who lives five years after a complete operation for cancer of the breast is approximately four times as likely to develop carcinoma in the second breast as in the previously normal woman of same age to have cancer of either breast. An interesting point in the series was that the patient did not profit by one experience, but presented herself after the metastases to the axilla of the same side had occurred and the mortality was 70 to 80 per cent.

Handley (36) in a series of 422 cases found involvement of the second breast occurred in 15 per cent of the cases. It was present in 18 per cent of the Middlesex Hospital cases and in only 5 per cent of the Guy's Hospital record. It was considered a late event. Handley uses this as proof that involvement occurs by a process of permeation through lymphatics.

There (36) are two views as to method of bone infection. One is by the blood stream and the other theory is the extension of growth of the cancer along the deep fascial lymphatic plexus. If the bone metastases were due to blood borne infection, then it would be reasonable for the lung to be involved which was the case in only 24 per cent of the 37 cases showing extensive bone deposits; while pulmonary metastases are recorded in 26 per cent of the entire series of 329 cases. Another argument used against blood
Stream infection is the escape of the fibula, tibia, radius and ulna, as well as bones of the hands and feet from metastases. Carnett and Howell (9) explain the lack of involvement of the lower part of the extremities is not due to any immunity, but due to the fact death occurs before these areas have time to become invaded.

A study made by Paget (72) on 735 fatal cases of carcinoma found there were metastases in 241 cases in the liver while there were only 17 cases in which the spleen was involved. Compare this with 340 cases of pyemia in which abscess of the liver occurred in 66 cases and in the spleen 39 times.

Simpson (89) believes cancer cells may be carried to distant parts of the body by the blood stream and lymph stream. He believes cells may enter the blood stream by direct erosion of the wall of the vessel situated in the tumor, involvement of veins lying close to a metastatic lymph node that is breaking down and cancer emboli which have reached the lung and erode a vein.

Handley (34) says centrifugal permeation of the fascial lymphatics must be taken as proved and this process must carry carcinoma cells to periosteal lymphatics at the subcutaneous areas where fascia is attached directly to bone. Furthermore, since lymphatics follow veins, infiltration of the wall of the concomitant vein is a likely event and subsequent extension in bone may follow by blood channels. Dr. Piney could not demonstrate lymph channels in bone marrow.
but could in periosteum. Cancer cells in marrow were growing in the blood channels. He believes the involvement of the bone marrow is by the blood emboli and the distal part of the bone immunity is due to lack of red bone marrow. Handley believes in dissemination by lymphatics and Dr. Carnett's study supports him.

It (36) has been given as a general law that, "the liability of a bone to cancerous metastases increases with its proximity to the site of primary growth". The clavicle is an exception to this. The (52) lower most axillary nodes connect with lymphatics down the arm to the vicinity of the nutrient foramen of the humerus so that an invasion of the humerus above this point might be accounted for by lymphatic extension. Lymphatic permeation to the bone from a cancer of the breast would appear a probable mode of extension if the most reasonable line of lymphatic permeation is found in the majority of cases, which is not always found to be true as will be shown by a series of cases from the Memorial Hospital. Dr. George Semken of New York says it is highly improbable that the bony metastases that occur in cases of carcinoma of the breast can be ascribed to permeation via the lymphatic channels mainly because of the absence of any demonstrable lymphatic connection of this type. He seems to ascribe these metastases more to emboli of cancer cells which are carried to the bones by the blood stream. This was conclusively demonstrated by Schmidt in his monograph on methods of dissemination of cancer, the
significant finding in which was the frequent and widespread occurrence of such emboli in the small arteries of the lung parenchyma. The apparent predilection of cancer metastases for sites within the substance of bones may be explained by the relative quiescence of the region.

There still remains two schools of thought as to the method of cancer dissemination, and there have been series of cases reported which supports each one. Nevertheless, (52) the subject of cancer emboli, transmitted by the blood stream has received little consideration, but deserves greatest emphasis and should be borne in mind by those who palpate the breast in making a diagnosis and who handle the breast in a radical removal. Breast carcinoma may invade veins and fill their lumen with cancer thrombi which do not require much force to become dislodged and send the emboli into the blood stream. Many of the emboli fail to survive, especially if enclosed in a blood clot, but others not enclosed or that grow through the clot result in distant metastases.

Handley (36) found during 30 years time at the Middlesex Hospital, between 1872 and 1901, there were 329 autopsies on cases of mammary carcinoma. Excluding cases in which only the sternum or ribs were involved, there were 37 cases in which the bones were the seat of secondary deposits or of spontaneous fracture. If the sternum and ribs are included the total is raised to 73 cases. However, he admits this is not very reliable because a complete skeletal
examination is rarely made, and only those bones liable to spontaneous fracture are examined. The flat bones of the skull and scapula and pelvic bones are not so liable to fracture. Therefore, metastases to these bones are not found very often. In the case of the skull it is quite often the seat of secondary growth, discovered when the brain is examined. In this series of cases, 9 were recorded in which one or both femurs were seats of definite deposits with or without fracture and 5 others in which spontaneous fracture alone occurred. In all these cases, if the deposit was local or the fracture single, the pathological condition was in the upper third of the femur, most often a little below the base of the great trochanter. There were indications that the base of the great trochanter was the site of entrance, but the bone was thicker and fracture occurs lower down. In this series, there were 6 in which one or both humeri were the seat of deposits. In 5 cases attention was directed to bone by fracture occurring, and in 4 other cases, there was fracture without proof of growth. In 2 of the 10 cases, fracture was bilateral. Point of fracture was mid point at insertion of the deltoid muscle. Fracture of the humerus occurs less often than would be expected because the arm is bound by firm edema, does not have much weight, and is bound down by the growth in the axilla.

Lee (52) in a survey of 100 cases of carcinoma of the breast with metastases to the osseous system, made in Mem-
oril Hospital in New York, found that 14 cases had involvement of the humerus, upper portion of the sternum or clavicle. 3 of these cases showed metastases to one or more of these bones on the same side as the lesion of the breast, while in 11 cases carcinoma of the breast was on the opposite side to the lesion or lesions in the bones. It is due to these findings of involvement of the bones on the opposite side of the involved breast which causes some argument as to the probability of invasion being via the lymphatics.

Carnett and Howell (9) made a study of a series of 101 cases which were in the late stage of the disease. They are of the opinion that the earliest bone invasion is in the shoulder girdle, homolateral to the breast carcinoma. In the earliest cases, the head of the humerus and glenoid process and adjacent region of the scapula were involved. Later the acromial process and still later the outer end of the clavicle is affected. In only 6 cases did the carcinoma extend below the elbow. Invasion of the shoulder, they think, occurs by way of the axilla.

Copeland (12) says that carcinoma of the breast is one of the most frequent primary tumors metastasizing to the bones. Rodman (80) agrees with Carnett to a certain extent in that the humerus may be invaded by direct extension of the carcinoma from the axilla. The sternum and ribs, he says, may be involved by direct extension of the malignant process. Rodman does not believe that statistics on the osseous system are very reliable as quite often no symptoms have presented
themselves, consequently, bones are not examined carefully at autopsy. Türck and Wittelshöfer examined cranial bones in nearly every case of 336 necropsies and as a result they found involvement in 33 cases or 9 per cent. In contrast, Munn and Williams, in a series of cases examined, the cranial bones only in evidence of disease and found involvement in only 1.8 per cent. Involvement of the bones has been discovered in some cases when the patients return following operation to receive x-ray treatments.

Cheatle (15) also states that involvement of the osseous system from carcinoma of the breast is common and spontaneous fractures from this cause are frequently observed. In fact, secondary deposits from carcinoma of the breast are the usual cause of spontaneous fractures of the humerus or femur in women. In rare cases, spontaneous fractures may be first indication of the disease, and examination of the breast should never be omitted under these conditions.

The number of cases in which involvement of the osseous system complicates carcinoma of the breast is variable because in most instances, as has been stated previously, attention is not given the bones unless a fracture has occurred. Downs (22) gives a report on 106 cases of breast carcinoma which came under observation at Jeanes Hospital in Philadelphia. In this series of 106 cases metastases were found by x-ray in 57 or 53.8 per cent of the cases. He states that metastatic bone lesions secondary to breast cancer are computed in many clinics is from 5.2 to 53 per
cent. It is rather difficult to obtain accurate data as to the per cent of cases in which bone metastases has occurred.

Lymphatic (80) involvement of the pectoral fascia may occur before the breast becomes adherent to it. Lymphatics of the pectoral fascia are merely a part of the deep fascial lymphatic plexus. Schmidt (52) believes metastases to skeletal muscle is rare because they are in active motion. Wainwright (85) believes that muscle involvement occurs earlier and more frequent in men than in women, however, muscle involvement in women is more serious. Moore (69) believes it is pretty definitely proved that dissemination takes place through fascial coverings of the muscle. He has never seen muscle involved except by direct extension. He states that first the fascis is involved and then the muscle secondarily. However, (96) due to a newer method of study, muscle involvement is more frequently found now than formerly. When strips of muscle adequately studied in relation to primary growth on the same side, involvement is found in about 60 per cent of the cases. Wainwright studied a series of 158 cases. This number included cases with actual infiltration of muscle and cases in which microscope showed cancer cells lying within two millimeters of the muscle surface. He calls attention to the fact that the first stage of involvement for lymphatic glands in the breast cancer is on the anterior surface of the muscle and not behind the muscle in the axilla as was previously supposed.
The (80) pleura may be infected by direct growth from the primary neoplasm in the breast, from the mediastinum, and from the supraclavicular glands by extension of the growth directly downward through Sibson's fascia and, no doubt, in cases in which the lungs are involved, further dissemination to the pleura may take place from these latter organs. The pleura usually involved before the lungs and Handley found secondary nodules on the pleura in 38 per cent of 422 cases. Simpson (89) states that the lungs, pleura and mediastinum are all involved in the same manner. The parietal pleura may be involved by way of the intercostal lymphatics through permeation. In other cases the visceral pleura becomes involved and then the lungs. Lymphatics at the periphery of the lung drain into the peribronchial nodes and thus these nodes are ultimately involved. Thoracic (36) metastases without any invasion of the abdomen occurs in 10 per cent of cases of early and 22 per cent of late cases. Abdominal metastases without involvement of the thorax occurred in 17 per cent of early cases and 16 per cent of the late cases. This statement should be of interest to anyone who thinks cancer spreads by emboli from pulmonary vessels because if true, the abdomen should be secondary to thoracic involvement. When metastases have occurred in the lungs, it is considered as a late case and there is nothing in a curative way to be done.

The liver (89) is the most common site of abdominal metastases in cases of carcinoma of the breast. Cheatle (15)
also agrees with this statement. Probably (36) the most direct connection between the breast and liver is by efferent lymphatics which run along the umbilical fissure from the portal glands. Turning upward at the umbilical notch they pass between the layers of the falciform ligament to pierce the diaphragm and terminate in the glands lying on its upper surface to the left of the midline between the pericardium and anterior wall of the chest. Efferent lymphatics pass from these glands to the internal mammary chain. Another route is by efferent lymphatics originating on the anterior part of the convex surface of either lobe of liver and then pass into the falciform ligament at the level of its attachment to the abdominal wall. They curve downward and backward and entering the umbilical notch above the round ligament pass back to the portal glands. The portal glands connect with the subserous lymphatic plexus in the epigastric angle and through the linea alba by fascial plexus with the mammary lymphatics. In 2 out of 53 cases of pure epigastric invasion, abdominal secondary deposits were present only in the ovaries. Among 8 cases of epigastric invasion showing multiple abdominal metastases the ovaries were involved. Due to rich vascular supply, embolic theory might explain the metastases here, but then if this is accepted, it is hard to explain how the ovaries are spared in some cases of abdominal involvement. A case was reported as a double primary cancer of the breast and uterus, but probably primary in the breast and secondary in the uterus.
Carcinoma of the omentum occurred in only 1 per cent of the cases. This is not due so much to the omentum escaping cancer cells, but more to its power of protecting itself against them. It has an encysting power and cancerous cells have been found surrounded by an organized layer of lymph. The cells were probably destroyed in some cases and in others a pedunculated growth was produced. White (100) found the liver involved in 12.5 per cent of the cases in a series of 85 cases. Warren and Witham (92) made a study of distribution of metastases based on a series of 162 autopsied cases. 8 cases at autopsy failed to show metastases leaving 154 cases with metastases which averaged 5 organs or tissues per case, one or both ovaries were found involved 15 times, and they found liver was next to lungs in frequency of involvement. The adrenals were involved in 50 cases which was far more frequent than any other ductless gland. They believe it to be due to lymph drainage more than blood as the thyroid, which is more vascular, was involved 4 times. The spleen was involved in 23 cases, but as a rule, these are small. Cheatle and Cutler (15) reported 17 out of 193 cases (18 per cent) from Guy’s Hospital, 98 out of 329 cases (29 per cent) from the Middlesex Hospital and 115 out of 422 cases (27 per cent) by Daves and McFarland.

A (92) swollen arm known as brawny arm and lymphedema may complicate the inoperable, recurrent, and post-operative case of mammary carcinoma. The arm often becomes swollen and edematous, at first pits on pressure, and then soon becomes brawny and solid. In about 10 per cent of the cases
with mammary carcinoma, edema of the arm may occur on the side of involvement of the breast. It is more common where recurrence has followed surgery, and is most frequently observed as sequel to the radical operation, even if there has been no return of the disease. Lee (54) believes lymphedema following radical amputation of the breast to be due to the presence of a low grade infection in or about the wound more frequently than being due to the cutting of small lymphatics coming up the arm. He has encountered it in 12.5 per cent of the cases. Five of the most serious cases have been accounted for as an extensive fibrosis from over-irradiation of the supraclavicular region. Handley (36) states the arm may become 2 or 3 times its normal size, muscle pain present, and the patient will gradually lose muscular power until complete paralysis results. He explains the phenomena as being due to permeation of the cancer along the lymphatic system and may completely encircle the arm, producing a fibrosis along the lymph vessels and prevent return of the lymph from the distal portion of the arm, and a swelling occurs. The return of lymph in this case would be through the tissue interspaces which is inadequate. Lymphedema (54) may begin shortly after operation or may appear several months or a year post-operative. When it develops later, one should suspect a recurrence high in the axilla or in the supraclavicular fossa. In two patients, an abscess developed on the inner aspect of the
elbow and following drainage of this abscess, the arm in one case went to normal size while the other one markedly decreased in size. Lee is of the opinion that lymphedema will develop in certain percentage of cases in spite of meticulous surgical technique, and the patient should be warned that there may be a slight swelling of the arm following operation.

Neal and Simpson (71) found carcinoma of the breast in the male is comparatively rare. They believe this to be due to the arrest of development of the mammary gland at the age of puberty, atrophy at thirty and is never called upon in functional activity. They found that only 1 per cent of carcinomata were in the male breast. Cheatle (15) agrees with this, and offers as explanation for the marked disproportion between incidence of cancer in the male breast and that in the female breast being due to a physiological factor in relation to the tumor and the gland. There are two points, one would be absence of physiological function to explain the immunity of the male breast and the physiological function which is related to the female breast may be a factor in the tumor's development. At (32) Memorial Hospital, Pack and LeFevre found the male breast cancer comprised 1.24 per cent or .41 per cent of all cancer in males. Mammary hypertrophy has been studied by Pigot, Schuchardt, Imbert, and Villon who report cases of concurrent cancer and gynecomastia. Examinations have been made, and, it has been found that the male breast contains abundant glandular
tissue and not merely adipose tissue. In a case of gynec- 
comastia, the connective tissue is only slightly increased 
while the gland tissue is enormously increased. All patients 
alive at the time of the report (18), 9 have no evidence 
of recurrence or metastatic disease, however, only 33 per 
cent of the 9 patients were observed before January 1928.
Axillary lymph nodes were involved in 10 of the 23 patients 
at the time of the radical operation. Distribution of me-
tastases was as follows: skin 2; axilla 30 (4 times bilat-
eral); supraclavicular fossa 17; lungs 21; bones 5. 38 of 
the cases had some surgical procedure while 9 were treated 
by some other method. Radical mastectomy performed 24 times, 
local mastectomy 8 times, and local removal of tumors 6 
times. The majority of the cases received some irradiation 
therapy. Five patients or 10 per cent developed non-specific 
elephantiasis of the arm. Three patients are alive without 
evidence of the disease after five years or more following 
mastectomy. Two now dead lived over five years from the date 
of the operation. Another case lived seven years and died 
of pulmonary metastases and recurrence. 18 per cent of the 
patients or 36 per cent were classified as primarily oper-
able. 18 or 55 per cent, now alive, are without disease. Of 
10 or 21 per cent classed inoperable none lived five years. 
Wainwright (85) finds as to type the tumors of male breasts 
are very similar to those found in the female breast. Also 
he finds that only 14 per cent of the patients survive a 
period of five years. Schneiner (85) found that among 17486
cases seen in the tumor clinic of New York State Institute for study of malignant disease, there were 1864 diseases of the breast of which 31 occurred in the male. Of these 16 were malignant. Only 8 per cent of the cases were available for five-year study and of these only one has no lymphatic involvement. The others were all dead.

Adair (1) reports that each year cases of carcinomatous invasion of the brachial plexus are seen which are rather baffling. Cases are typical as to facial expression and position of the affected shoulder, inability to obtain relief from the intense pain, atrophy of the hand, painful arm, increasing paralysis of the hand muscles and a dusky color of the hand. The chief complaint is pain so severe and so intractable that they go for nights without sleep and morphine gives no relief, the entire arm, shoulder and hand are painful and stiff, the arm is enlarged due to impediment of lymph return, an atrophy of the thumb and interossei muscles. The only relief has been by cordotomy. This may not give complete relief, but aid.

When (58) pregnancy accompanies mammary carcinoma, the outlook for the patient is very unfavorable. Lee (58) gives a series of 506 cases in which there were 11 instances where the women were pregnant. Three of these were inoperable. In one case, the woman died 2½ months after beginning of symptoms. Seven were operated radically, received pre- and post-operative irradiation, one survived more than three years. Lee advises therapeutic abortion and sterilization preformed. In another (87) report it is
stated that carcinoma developing during pregnancy or the lactating period invariably proves fatal within five years, following the operation. Orile (11) finds the younger the patient the less favorable the prognosis and the older the patient, the more favorable the prognosis. Cancer during the lactating period is especially serious. Harrington (37) found in this series of 1859 cases that 5 were pregnant at the time of operation, 3 died within one year and 2 died within two years. He advises against operating. 28 carcinomas were present during the lactating period. 19 lived less than one year, 5 less than two years, 1 lived five years, and 1 lived six years. 2 are living at the present time, 1 two and one-half years after operation and 1 four years after operation.

Before very much emphasis can be placed on what to expect following treatment of carcinoma of the breast, it would probably be well to consider the course the disease takes when it is not treated. Sistrunk and MacCarty (87) state that it is impossible to foretell the duration of life of all patients with carcinoma of the breast. Malignancy varies widely and patients react differently to the disease. Bunts (4) states that a point of prime importance in its relation to prognosis in breast cancer is the length of time which the patient was allowed to escape or elapse between her first discovery of the presence of a tumor and the operation. In 84 per cent of his cases, attention was called to the breast because of a lump and not because of
pain. Blackburn (2) gives the following points to consider in giving a prognosis on cancer of the breast: (1) Age and physical condition of the patient, (2) pregnancy and lactation, (3) type of tumor, (4) location, (5) glandular involvement, metastases and recurrence, (6) time of operation, (7) type of operation, and (8) radiation. Jacobson (40) agrees with the preceding statements and is of the opinion that the rapidity of development of disease is important, period or duration and extent of involvement are all contributing factors to the final result.

Daland (18) reports a series of 100 cases selected from Collis P. Huntington and Good Samaritan Hospitals, Boston. None of these 100 cases had ever received any treatment. This series includes 98 women and 2 men. There was no record of any spontaneous regression. The average duration of life from the onset of the first symptoms to death was 40.5 months. In cases where cancer was detected early and operation was advised, the average length of life was 42.8 months. Patients with inoperable cancers at the time of the first examination lived on the average, 29 months. In this series he found deaths began as early as 3 months. 21 per cent of the cases died the first year, 20 per cent the second year, 19 per cent of the cases died the third year, and 40 per cent were alive with cancer at the end of 3 years. 10 per cent died the 4th year and 8 per cent the 5th year, leaving 22 per cent living at the end of 5 years. 8 per cent died the 6th year and 5 per cent the 7th year,
and at the end of 10 years, 5 patients were alive. 22 patients developed swollen arms usually accompanied by glandular metastases either axillary or supraclavicular. Bone metastases occurred and there were 3 cases of spontaneous fractures, but none of the patients had any involvement below the knee or elbow. He found the longest duration of life was between the ages of 60 to 64 and the shortest was between 55 and 59 years except one patient who died at the age of 33. Gottesman (33) states the average duration of life of patients suffering from all types of inoperated cancer varies from 3.2 to 4 years after the discovery of the tumor. After radical operation, life is increased to 5 years; therefore, patients gain about one year by operation. It seems to be generally recognized that there is no hope for a patient with carcinoma who does not receive treatment.

Cheyne (16) does not consider it necessary to discuss the advisability of operation for cancer of the breast, but gives three points to carry out in treating the disease, and these are: (a) to remove the disease thoroughly, (b) to avoid dissemination of the cancer cells, and (c) to obtain a good functional result afterward.

The recurrence of cancer in the skin was not taken up in any detail in the literature, probably due to the fact that if cancer recurs at the site of operation, metastases of more importance has occurred in other parts of the body. Summers (88) states that an operable cancer which recurs
locally indicates that either the technic was incomplete or else its lymphatic extension had passed beyond the limits of the field of operation. Eggers (25) states it has been customary to hold a surgeon responsible for local recurrences for it has been felt and been shown by experience that in properly performed radical operations, they are rare. Metastases on the other hand, both regional and distant, have been considered beyond the surgeon's control. If metastases are not present at the time of operation, the surgeon may be held responsible for them due to rough handling of the breast during the operation.

Cheyne (16) believes that the amount of skin to remove varies in each case as to whether skin is involved or not, and the amount of involvement. He believes the fascia should be removed more extensively than the skin. Davis (19) agrees with Cheyne in the amount of skin to remove and removal of fascia should be more extensive than the skin, and he also states that any tissue which is abundant in lymphatics should be removed. He believes that cancer is microscopically present much farther than macroscopically.

Sistrunk (86) reports in a series of 218 cases, local recurrences occurred in only 10.8 per cent of patients in those who did not have glandular involvement. A (51) return of cancer in the scar has been classed as a recurrence of the primary tumor. Lee (55) reports that small local metastases are amendable to treatment by radium and in larger areas, irradiation has been successful in prolonging life.
It has been almost universally accepted and agreed upon, that one of the most important points to consider is whether the axillary glands are involved. Cheatle (15) probably expressed a number of other men's opinions when he expressed the opinion that when axillary glands are involved, carcinoma is inoperable as far as cure is concerned, as it is hard to conceive that the spread ceases here. Sis-trunk and McCarty (86) found the axillary glands involved in 60.5 per cent of the cases at the time they presented themselves for operation. Seltzstein (81) found that axillary glands were already involved in 80 per cent of the admissions to Harper Hospital. Harrington (38) reported 72 per cent.

Lewis, Dean and Rienhoff (51) found that where regional metastases were present, axillary and supraclavicular glands, 23 patients in a series of 379 cases died in the hospital following operation, while not a single case without axillary metastases contributed to the immediate operative mortality. Harrington (37) studied a large series of cases from different angles and he found that cases which did not have axillary involvement at the time of operation, 80.23 per cent were living after 3 years, 67.44 per cent living after 5 years, and 52.94 per cent living after 10 years. In cases in which lymphatic involvement was present at the time of operation, 41.71 per cent of the cases live 3 years, 25.75 per cent live 5 years, and 12.23 per cent live 10 years. Clapton (17) traced 126 patients out of a
series of 197 cases treated by radical operation. In 37 cases the cancer was confined to the breast and he reports 64 per cent of the cases living 5 years, and 27 per cent alive 10 years. In 89 cases, the cancer was beyond the breast and only 30 per cent of the patients were alive 5 years and 9 per cent alive 10 years. Harrington (38) following a series of 2257 cases operated on between 1910 and 1927 inclusive, found that of the cases operated in which there was not any nodal involvement, 71.2 per cent of the patients lived 5 years following operation, 52.9 per cent lived 10 years, and 40.7 per cent lived 15 years. Of the cases in which the nodes were involved, 26.3 per cent lived 5 years, 14.6 per cent lived 10 years, and 10.5 per cent lived 15 years. Potts (76) in a series of 375 cases shows that where operation was performed before axillary involvement, 72 per cent of the cases were alive at the end of 10 years and where the regional lymph glands were involved, only 15 per cent are alive at the end of 10 years. Portman (77) is of the opinion that 70 per cent of the patients operated on before the axilla is involved will survive the 5 year period while in cases of axillary involvement only 22 per cent will survive the same period. Lee (54) gave, in a brief outline, results of several surgeons over a 5 year period. First is the per cent of patients alive at the end of 5 years. Greenough and Simmons, 18 cases, 56 per cent; Sistrunk and McCarty, 88 cases, 65 per cent; Mathews, 45 cases, 64 per cent; Harrington, 332
cases, 67 per cent; Smith and Bartlett, 21 cases, 67 per cent; Peck and White, 26 cases, 85 per cent; Lee, 55 cases, 72 per cent. Same report of cases over 5 year period with axillary glands involved: Greenough and Simmons, 46 cases, 24 per cent; Sistrunk and MacCarty, 132 cases, 22 per cent; Mathews, 99 cases, 29 per cent; Harrington, 1092 cases, 26 per cent; Smith and Bartlett, 27 cases, 28 per cent; Peck and White, 42 cases, 23 per cent; Lee, 103 cases, 23 per cent.

Several other references could be given, but I am of the opinion this is a sufficient number to show there is a definite bearing on the length of life depending upon the involvement of axillary glands. Not a great deal of importance has been attached to statistics as to their accuracy, in that not every patient reacts the same to carcinoma and it is difficult to give accurately the extent of involvement; and there is a difference in whether the same surgeon did all the operations in the series, or if different men did them, also the stage of the disease when they were done. However, I think there is a very close similarity in results in the cases reported here. In very few instances was there evidently any attempt made to classify the carcinoma.

Lee (56) in commenting on 5 year "cures" said at the time of writing he had 90 patients who were operated on for carcinoma of the breast 5 or more years ago. In all of the histories, verification of the diagnosis of carcinoma was
obtained microscopically, and, at the present time, they are all living and are entirely free of the disease. These women came for treatment early while there was hope. He is of the opinion that the reason why there are not more 5 year cures is that women will persist in not consulting a physician at frequent intervals and will not adopt the plan of careful, complete physical examination by their physician every 6 months. Neither do they see the physician the moment an abnormal condition develops. In some cases the women mention a lump in the breast in an off-hand way, mainly wishing assurance it is not important. The other reason, not infrequently the physician, in his lack of wisdom, assures the patient that a painless lump in the breast is of no importance and is not serious.

Handley (35) believes that enlargement of the axillary glands is not in itself the lethal factor, but by the time the axillary glands are enlarged, the disease has frequently and perhaps usually obtained access through the inner ends of the intercostal spaces to the internal mammary glands, and, that quite early and in still operable cases these glands contain microscopic deposits of cancer cells. More than half of his recurrent cases were manifested either by an enlargement of the glands at the lower and inner angle of the posterior triangle or by the appearance of nodules, later merging in sternal recurrence upon the deep fascia at the inner end of the first, second, and third intercostal spaces. This position of recurrence is due to invasion of
the lymphatic glands along the mammary artery. He has excised these glands in 5 operations, but it makes the operation too long and severe; however, radium may be buried in them. It is easy and does not prolong the operation. He says it has been definitely proved that this use can destroy microscopic and even massive deposits in the internal mammary glands. He concludes that in order to find the reason for the increased gravity of prognosis associated with enlargement of the axillary glands, it will be necessary to consider the parasternal glands of the internal mammary chain. If axillary glands are infected, then probably so are the parasternal glands. Clearance of the axilla is easy, but results have been marred by failure to recognize and deal with the parasternal invasion of the carcinomatous process.

Perry (74) in a series of cases found the first recurrences were in the supraclavicular glands in 15 per cent of the cases. No case of supraclavicular gland involvement treated either by excision or X-ray could be traced as having survived more than 18 months. Deaver (21) agrees with this in a series of 40 cases with supraclavicular glands involved, only 2 survived.

Kaplan and Roser (46) state that the presence of supraclavicular metastases has been regarded as contraindicating radical mastectomy and the presence of pulmonary and skeletal metastases as precluding possibility of any surgical procedure. Involvement of any of the other systems beyond those already mentioned are late stages of the disease.
and palliative measures are used, and the length of life varies.

There have been a few series of cases reported in which an attempt was made to classify the tumor. Lewis, Dean, and Rienhoff (51) in the series of 379 cases, encountered three main types of tumors. They were the scirrhou, medullary, and adeno-carcinoma. The post-operative length of life of patients suffering from medullary carcinoma was on the whole shorter than that of patients with scirrhou or adeno-carcinoma. At the end of two years 53.9 per cent scirrhou, 21.9 per cent adeno-carcinoma and 59.3 per cent of the patients with medullary carcinoma were dead. At the end of five years three fourths of the patients with scirrhou and medullary carcinoma were dead while only three fifths of the adeno-carcinoma patients were dead.

Warren and Witham (98) classified tumors in 132 autopsied cases. They made a division into three groups histologically. The least differentiated tumor they classed as carcinoma simplex and stated in their opinion the tumor may be either scirrhou or medullary in its local lesion, and metastases with all gradations between. They state no significant variation has been detected in the behavior of the scirrhou and the medullary, so they were not separately considered in this study. The second group contained the more highly differentiated adeno-carcinoma. The third group was of colloid carcinoma which was characterized by the presence of a great amount of mucinous secretion, absence of early metastases, limited late metastases, and,
as a rule, large local lesions. This classification covered 153 of the cases. They found the average age of death was 57 years for the adeno-carcinoma and carcinoma simplex group. The total duration of life from the onset of symptoms was 3.1 years for the adeno-carcinoma; 3.1 years for carcinoma simplex, and 8 years for the colloid.

Bunts (6) found that the life expectancy in respect to clinical character of the tumor was shortest in the medullary, while cases of adeno-carcinoma seemed to have the most favorable outlook. A very brief summary of his findings show that at the end of five years 26.9 per cent of the patients with scirrhous carcinoma, 34.7 per cent with adeno-carcinoma, 20 per cent with carcinoma simplex, 16 per cent with medullary, 26.3 per cent with ductile, and 75 per cent with colloid carcinoma are living. At the end of 10 years, the following per centages of patients with different types of carcinoma are living: scirrhous, 12 per cent; adeno-carcinoma, 17.3 per cent; simplex, 16.6 per cent; medullary, 2 per cent; ductile, 5.2 per cent; and colloid, 50 per cent. In this series, there were 141 cases of scirrhous, 75 cases of adeno-carcinoma, 60 cases of simplex, 50 of medullary, 19 of ductile, and 4 of colloid.

Studies have been made in an attempt to determine the effect the size of tumor has on the longevity of life. Bunts(6) finds there was not a marked difference in life expectancy between large and small tumors during the first five years, however, a much larger group of patients with small tumors are living 10 and 15 years following operation.
Warren and Witham (38) differ from Bunte in that they point out, not infrequently, a large colloid carcinoma of the breast may be present for a year or more without even involvement of the regional lymph nodes, whereas, in other cases, a small inconspicuous mass of short duration may show widespread metastases. In some cases the first symptoms are of those due to metastases as pathological fracture or intracranial pressure. They are of the opinion that their findings bear out the clinical observations that the larger and more bulky the local lesion the less extensive the distribution of metastases is apt to be.

Blackburn (2) adds one other point in this attempt to determine the end results when he states that the younger the patient the greater is the probability of recurrence and in the older patient the tumor is much slower growing due to the fact that in younger patients, usually cells predominate while in the older patients, stroma predominates.

Furthermore, the size of cells have been considered in an attempt to correlate, if possible, any relation this might have to the malignancy of the tumor. Reiman (79) considers the smaller cells more malignant than the larger cells, however, he adds that the small cells may result from lack of room to grow or compression and might not represent a high rate of proliferation. He found that an attempt to grade the relative malignancy of 100 cases of carcinoma of the breast from histologic picture of speci-
man at the time for operation gave false results as determined by later history and the follow up reports. As far as the recurrence of cancer is concerned, Reiman believes the answer lies in the gross aspects and not the microscopical picture. If any particles are left behind, the cancer will recur unless these particles perish.

Sistrunk and MacCarty (87) have worked on this more from the angle of cellular differentiation and found this to be unfavorable to continued growth of carcinoma as based on the unwritten law of biology, in that power of cellular reproduction is inversely proportional to cellular differentiation. If this is true, cancer cells which showed partial differentiation as in 15 per cent of the cases of mammary cancer studied, must of necessity grow slower than cells without differentiation. Fleethow (28) agrees with Sistrunk and MacCarty and classes cellular differentiation as a body defense against cancer, also including fibrosis, hyalinization, and lymphocytic infiltration. Fleethow states that there is a tendency to differentiate in approximately 65 per cent of the cases. Patay and Scarff (73) considered the nuclei in relation to malignancy. They contend that a marked inequality in size and outline of nuclei is indicative of a high degree of malignancy and the presence of many hyperchromatic nuclei affect the prognosis adversely. They consider the irregularity in size of cells with irregular nuclei.

Taylor (91) considered the quadrant of the breast in which the tumor is located and the effect on length of 5
year "cures". He found the upper, outer quadrant involved 21.3 per cent; upper, inner quadrant 38.1 per cent; lower, outer quadrant 34 per cent; lower, inner quadrant 25 per cent; and central 39.3 per cent. He stated Abell and Graves believes that the prognosis is more favorable in cases of outer quadrant growths than in cases of inner quadrant growths. Sistrunk believes the best results are in cases of growths being located in the upper inner quadrant. Points to be considered in this are that growths in the outer quadrants metastasize first to the axillary nodes which has been proved by clinical experience. Also these growths will remain movable in relation to the chest wall longer than inner quadrant growths. Inner quadrant growths may form their first metastases in the supraclavicular region, in the thorax or even in the liver.

Surgery has been accepted as the best treatment for carcinoma of the breast when the tumor has been discovered before extensive metastases have occurred. X-ray has been added to surgery in treatment. Lee (58), in discussing therapeutic value of x-ray, stated that prior to 1920 a low voltage type of x-ray was used. This type had good effect on skin lesions, but deeper lesions were not affected except when used over a long period of time. In 1921 the low voltage apparatus was modified and the treatment was then more effective as a larger dose might be administered to a tumor at a greater depth and during the past five years, high voltage therapy has been utilized as one
of the methods of treatment in dealing with mammary carcinoma. The regressions obtained have been more pronounced than any of the previous low voltage methods. He used the divided dose instead of massive dose method. The x-ray and radium treatment both have limitations. The general condition of the patient must be borne in mind in planning any form of treatment. A patient in poor general condition should not be subjected to prolonged or heavy irradiation for they do not react well and the local lesion regresses less satisfactorily. Adjacent normal tissue has a limit of tolerance and the skin will stand only a certain amount at any single dose, but continued repetitions will cause skin destruction. Also the subcutaneous tissue atrophies with prolonged irradiation associated with diminishing blood supply.

At first x-ray was used considerably pre-operatively and post-operatively, but the pre-operative x-ray treatment (56) has not been generally approved. The chief reasons are the delay in surgical intervention, the irradiation hyperemia may cause more active bleeding, wound heals more slowly and less satisfactorily and better end results are not obtained. Chestle (15) agrees with Lee and valuable time is lost, especially if dealing with a radio-resistant tumor. Enfield (23) abandoned pre-operative x-ray treatment also. Trout (83) gives no pre-operative x-ray because when the patients thought they benefitted they would delay operation and the axilla, by that time, had become involved.
This is a new thought which was not given by any of the preceding men. Trout also sent out questionnaires to 149 surgeons and received 139 replies. He found that 124 of these surgeons never employed pre-operative irradiation and 83 uses it post-operatively.

There have been several studies made on the effect that post-operative treatment by x-ray has on the length of life of patients. Harrington (37) followed cases on which x-ray was used since 1915. In a series of 1859 cases, it was used in 1092, in 776 when lymph nodes were involved at the time of operation, and 332 which it was not. The end results in these cases were compared with end results in 767 cases in which roentgen ray was not given. In this latter group 490 cases operated between 1910 and 1915 and 277 cases between 1915 and 1923. Results show that of the cases in which there was lymphatic involvement and roentgen-ray treatment was used, 41.31 per cent lived 3 years; 25.78 lived 5 years; and 8.24 per cent lived 10 years. Where roentgen-ray was not used, 35.66 per cent of the patients lived 3 years; 21.67 per cent lived 5 years; and 15.84 per cent lived 10 years. In cases without lymphatic involvement in which roentgen-ray treatment was given, 9 per cent more have lived 3 years; 4 per cent more 5 years; and 1.5 per cent more have lived 10 years. This series was then compared to a similar group of cases in which radical amputation had been performed since 1915. In cases where lymph nodes were involved and x-ray was used, 4.75 per cent
more patients lived 3 years than those not x-rayed; 3.49 per cent more lived 5 years; and 10.31 per cent less lived 10 years. When lymph nodes not involved and x-ray was used, 1.7 per cent more patients lived 3 years; 4.35 per cent less patients lived 5 years; and 11.14 per cent less patients lived 10 years after operation. He believes x-ray does not have a great deal of value on the remaining malignant tissue and if a radical operation is done, a wide excision should be done, removing all diseased tissue and not depending upon x-ray. Enfield (2) uses x-ray post-operatively in two series six weeks apart and has not had a recurrence in the scar nor skin in 10 years. Young (103) is an advocate of early post-operative x-ray therapy started preferably within two weeks of operation.

Lee (57) states that recurrent inoperable carcinoma of the breast comprises a large group and x-ray is by far the agent most often employed. In comparing a series of 3 year cases with those of another New York hospital where no radiation was used after operation or for recurrence, he found the period of life following recurrence was three times as long when x-ray was used. He also (55) followed a series of 218 cases between 1918 and 1920 which were recurrent mammary cancer. When radical and x-ray treatment were given following recurrence, the average life was 6.5 months, while cases in which irradiation was used following recurrence, the length of life was 2.5 years. Of a series of 124 cases in whom a favorable result might be expected,
are alive at present. Summers (88) explains irradiation
of cancer in accessible locations, if a sufficient dose is
given, results in destruction of pathologic cells and their
replacement by fibrosis and hyalinization, both inhibitive
to extension of cancer; hence, employment of irradiation
before and after operation is rational. Lee (53) in com-
paring inoperable patients with untreated cases found that
length of life was increased 4 months where x-ray was used.
It will also give relief from pain, healing of superficial
carcinomatous ulcers, improvement of general condition,
and prolongation of life.

In dealing with chest metastases, the lung tissue was
irradiated and numerous cases have been reported in liter-
ature of diffuse and maybe fatal pulmonary fibrosis. Treat-
ing metastases to the supraclavicular glands, an intract-
able neuritis of the brachial plexus may follow. Late skin
changes may occur in which there is atrophy and in some
cases, areas of ulceration may appear, and cases of squamous
cell epithelioma developed.

Lee (55) states that small localized lesions in the
infraclavicular region or adherent to or involving the
chest wall, small localized skin metastases or small ac-
cessible nodes are most amenable to treatment by radium
itself.
Summary

1. The percentage of 5 year "cures" is much higher when adequate treatment has been given before axillary glands are involved than afterwards.

2. Lymph nodes which are not palpable are not necessarily free of involvement.

3. A patient who has survived a 5 year period following operation is four times as likely to develop carcinoma in the second breast as is a normal woman of the same age to have carcinoma of either breast.

4. Regardless of the method of spread to the osseous system, it would probably be found to be involved in many cases if a complete x-ray study were made in cases which were considered to be free of metastases because of lack of symptoms.

5. Muscles are involved more frequently than previously thought to be, especially the pectoral muscles.

6. The liver is the most common site of abdominal metastases.

7. Carcinoma of the male breast occurs in approximately one per cent of the cases.

8. When pregnancy accompanies carcinoma of the breast, the prognosis is very unfavorable.

9. Carcinoma of the breast which is not treated is invariably fatal.

10. Probably the chief reason for the higher mortality following involvement of the axillary glands is that by the time these glands have become involved, other glands...
are also involved which are overlooked.

II. X-ray used chiefly in post-operative treatment and probably has a definite place at this point in the treatment of carcinoma of the breast.


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