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HISTORY OF ONCOLOGY

Milestones in the treatment of breast cancer

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Summary

With this paper the author briefly presents some historical notes concerning breast cancer: first recorded mastectomies for non medical reasons in the Antiquity, and evolution of medical and surgical treatment methods, as well as radiotherapy as treatment modality for breast cancer.

Key words: breast cancer, hormonotherapy, mastectomy, radiotherapy

Intoduction

Diseases of the breast have been studied and documented since the earliest days of surgery. Long before any surgeon could even dream of tackling other cancers, indeed before he was aware that many even existed, he could hardly fail to observe the growth, ulceration and spread of a breast cancer with the ultimate inevitable destruction of the patient.

It is practically certain that, since his origin, man has been subject to disturbances in the biological controls on cell growth that are manifested clinically as malignant tumors and the like. However, the frequency of these ailments has not necessarily been the same in different eras or throughout the range of geographic and sociocultural environments.

Mastectomy in the Antiquity

Though cancer has nearly always been the reason for amputating breasts (mastectomy), a quite different motive led to the earliest record of this operation in Babylonian times. Paragraph 194 of Hammurabi's code prescribed that, if a wet nurse committed a crime, "they shall cut off her breasts" -a double punishment, since she thereby lost her job [1].

Breast ulcers and tumours were known in ancient Egypt, as shown by the papyri of Ebers and Smith. A successful operation on a "knot of fat" was also mentioned, and the treatment for a breast boil was the same as it is today: " If you find a swelling over the breast's surface, clearly defined and round in shape, it is a purulent tumour growing in the flesh. It must be dealt with by the knife"[2].

The Hippocratic corpus describes with accuracy a case of breast cancer in a few lines: In a woman, at Abdera, a carcinoma developed on the breast; its appearance was so: a bloody *ikhor* (fluid) flowed (ran) from the nipple; once the flow (discharge) stopped, she died [3].

Modern medicine confirms the diagnosis of *karkinoma* proposed by the Greek physician Hippocrates. Breast cancer, with typical lymphatic spread and cachexia, is well described in another text from the Hippocratic corpus. Indeed, it looks as though then, as now, it was a relatively common disease in women of a certain age [4].

Our knowledge of the Greco-Roman concept of cancer and its treatment is derived from Cornelius Celsus (42 BC-38 AD), whose *De re Medicina* [5] is a compendium of what was known of medicine at the time. He records the various methods of dealing with breast and other superficial tumours and the poor prognosis of the disease.

According to Herodotus (484-420 BC), the Greeek historian, a famous patient at the end of the 6th century BC, Queen Atossa, daughter of Cyrus and wife of Darius, is thought to have suffered from breast cancer [6]. Herodotus tells us that Queen Atossa "had a *phûma* (tumor) on her breast that burst open and was slowly spreading". However, the complete cure that was effected without mutilation of the breast by the physician Democedes of Croton leads one to suppose that Atossa's disease was a mastitis, not a malignant tumor [7]. In fact Herodotus, who is always very precise in his choice of technical terms, avoids speaking of cancer in this instance and instead uses the term *phûma,* which can designate an abscess as well as a neoplasm [8]. As for the *ikhor,* the word signifies the sero-purulent discharge from a wound, the exudation from a sore, the juice of animal

flesh, that is, what flows when fleshy parts of the body are liquefied (to be sure, this last part of the definition is not a description of reality but the way the ancient Greeks represented it to themselves); recent philological research has shown that even in Homer the word *ikhor* refers to such a liquid and not to "the blood of the gods," as is commonly thought [9].

The Amazons (Figure 1) supposedly cut off their right breast to facilitate shooting with bow and arrow. Warrior women from the Caucasus, who invaded Asia Minor, maintained their numbers by mating annually with men from a neighbouring tribe, while killing boy babies. Nobody knows if the tale is true : it may be a memory of well-armed priestesses who served some goddess, like Artemis, in that region. But their breast operation was accepted by Gerolamo Cardano (1501-76), a great Italian physician and mathematician. He claimed that it was performed at age 18, the blood being stanched by cauterization with hot copper, which was thought better than iron for this purpose [10].

Breasts were long a symbol of fertility, and women who lost them were not only maimed but regarded as inferior. Such a view was exploited by medieval punishment, which often made one or both breasts the price for actual or suspected crimes. When the "crime" was being an early Christian, several of these martyrs became, not surprisingly, saints. Famous examples are Barbara, Christina, Foya, Apollonia – who turned into the patron saint of dentistry – and primarily Agatha (Figure 2), the protectress of all who suffered from breast diseases. Agatha was a beautiful girl from Catania in Sicily, during the third century AD when the Romans persecuted Christians. She rejected an amorous consul, who then condemned her to lose both breasts "because she was Christian". The deed was done with red-hot tongs, and she was cast into prison to die, but Saint Peter appeared to her and restored her breasts as well as her health. So the consul had her fried over a slow fire, and Heaven avenged her by killing his two best friends with an earthquake, which was enough to earn Agatha canonization [11]. Catanians celebrate her memory every year, carrying a triumphant image of her breasts through the streets!

The first therapeutic mastectomies

Over the centuries, removal of a breast tumour by knife, cautery, a combination of the two or by means of caustics has been carried out.

Operations for breast cancer were done at an early date by Aetius of Amida (502-571 AD), who was a pioneer of gynaecological surgery [12]. He emphasized that the knife should cut around a tumour in healthy tissue, and that a cauterizing iron should stanch the blood. His method was used in late medieval times, occasionally replacing cauterization with etching salves of arsenic and zinc chloride. The famous French surgeon Henri de Mondeville (1260-1320) advocated the use of a paste made up of arsenic and zinc chloride [13]. In those pre-



Figure 1. An Amazon without her right breast. Engraving of unknown artist.



Figure 2. St Agatha offering to God her breasts cut off, symbol of her martyrdom. A painting of Lorenzo Lippi (1606-1665).

anaesthetic days, amputation of the breast had to be performed as swiftly as possible. Wilhelm Fabry von Hilden (1560-1624), the leading German surgeon at the time, invented an instrument that constricted the base of the breast while an attached blade amputated the organ. He stressed the importance of ensuring that the tumour was mobile before he would operate [14]. Johannes Scultetus (1595-1645) passed heavy ligatures through the base of the breast to serve as traction, amputated the breast with the sweep of a knife and then used the cautery to stop the bleeding [15]. The full horror of this operation is vividly shown in his illustration of this procedure in his *Armamentarium Chirurgicum* (Figure 3). Andreas Vesalius (1514-1564) was apparently the first to control the bleeding from the large vessels by using ligatures [16].

It has long been known, too, that a less than radical operation for breast cancer may not only fail to cure the patient, but also to hasten the disease's spread through the body. Despite the lack of good anaesthesia, reliable methods of completely removing a tumour were soon sought. Barthelemy Cabrol, a student of Ambroise Paré (1509-1590), was the first to take away the pectoralis major muscle as well as the breast itself [17]. A little later, in the early 1600s, Marco Aurelio Severino (1580-1656) did a radical mastectomy – also removing the lymph nodes in the axilla, which are usually the initial structures to which this cancer spreads [18].

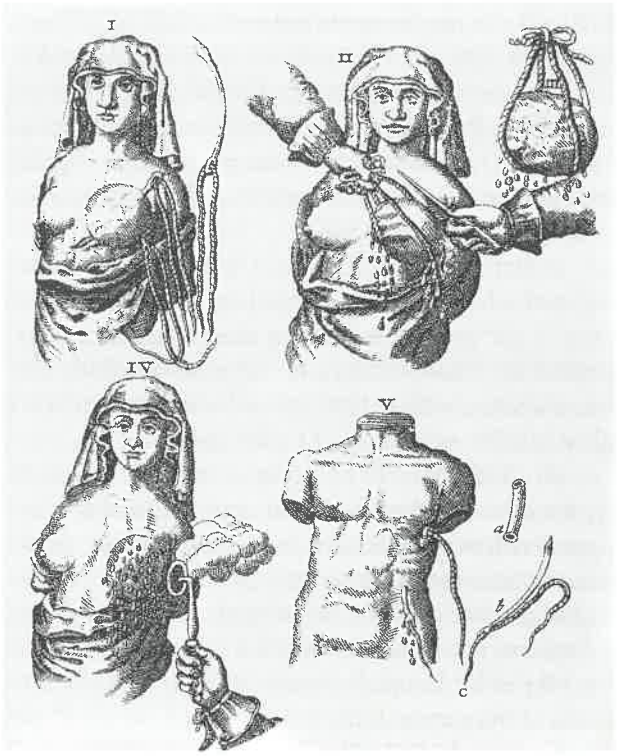


Figure 3. Amputation of the breast using the knife followed by the cautery, as illustrated by Scultetus in his *Armamentarium Chirurgicum* (1741).

Breast cancer therapy after the 18th century

Angelo Nannoni (1715-90), a Florentine doctor, published a book in 1746 about the surgical treatment of breast cancer, with ideas amazingly like our own. He recommended immediate operation to remove the tumour with a wide margin, along with the underlying fascia, pectoralis major muscle and axillary lymph nodes [19].

Two 18th century French surgeons made important contributions to our concept of the pathology and adequate surgical treatment of breast cancer. Henri Le Dran (1685-1770) of the *Charité* Hospital, Paris, taught that cancer of the breast was a local lesion in its earliest stage which then would spread through the lymphatics to the regional lymph nodes. Once there was involvement of the axillary lymph nodes, the prognosis would be considerably worse [20].

But the greatest influence on future breast surgery was from the French Jean-Louis Petit (1674-1760), first Director of the French Academy of Surgery, who described the basic guidelines of an adequate mastectomy – wide excision of the tumour and removal of the axillary lymph nodes. While his great *Treatise on Surgical Ailments and Operations* [21] advocated radical removal of the breast muscle and lymph nodes, he left the nipple area alone as a cosmetic measure. Petit was the first to show how breast cancer spreads to a woman's axillary lymph nodes.

The description by Lorenz Heister (1683-1758) of a mastectomy that he performed in 1720 gives us a vivid idea of what this operation comprised in those days [22]. He discusses the careful preoperative preparation, the mastectomy itself, performed at maximum speed, and the tedious postoperative dressings of the invariably suppurating wound (if the patient was lucky enough to survive the operation) (Figure 4). Although Heister was convinced his patient had cancer, the description of the tumour – its mobility, the colour of the overlying skin, the bosselations, the absence of secondary deposits in the axilla, and the long survival of the patient – suggests that the lesion was, in fact, an example of cystosarcoma phyllodes, a slowly growing benign tumour of the breast which may reach enormous size although it may eventually turn malignant.

Reading descriptions of mastectomy such as these in the preanaesthetic era, it is not surprising that surgeons, as well as quacks, tried every conceivable nonsurgical procedure in an attempt to treat cancer of the breast.

Thus the eminent French surgeon Alfred Velpeau (1795-1867), who held the Chair of Clinical Surgery in the Faculty of Medicine in Paris, gives an extensive list

of remedies or medicines for breast cancer in his *A Treatise on the Diseases of the Breast and Mammary Region* [23] which include: repeated application of leeches, cure by hunger, hemlock, iron, ammoniac solution of copper, arsenic, mercury, Vichy water, preparations of gold, quinine, iodine, sarsaparilla and bitters. Many of these he tried himself without success.

A step backward was taken in the early 19th century, with a belief that superficial tumours would wither away if the arteries supplying them were just compressed. By contrast, the radical operation's value was scientifically established by Charles Hewitt Moore (1821-70) at Middlesex Hospital, London [24].

In 1825, Sir Astley Cooper (1768-1841) wrote in his *Lectures on the Principles and Practice of Surgery*: "It will be sometimes necessary to remove the whole breast, where much is apparently contaminated; for there is more generally diseased than is perceived and it is best not to leave any small portions of it..."[25].

By 1844, Joseph Pancoast (1805-1882) [26], Professor of Surgery at Jefferson Medical College, Philadelphia, was advising still more radical surgery: involved muscles should be removed, even affected portions of ribs should be resected with the cutting forceps or a saw, and also the axillary nodes should be removed, as they are supposed to be scirrhous, or are even indurated and enlarged (Figure 5).

Over the 19th century, many surgeons advocated complete mastectomy together with removal of the axillary lymph nodes. In 1874, Benjamin Bell (1749-1806), surgeon at the Edinburgh Royal Infirmary, in his six-volume textbook, wrote: "Even when only a small portion of the breast is diseased, the whole mamma should be removed. The axillary glands should be dissected by opening up the armpit, but as much skin as possible should be preserved " [27].

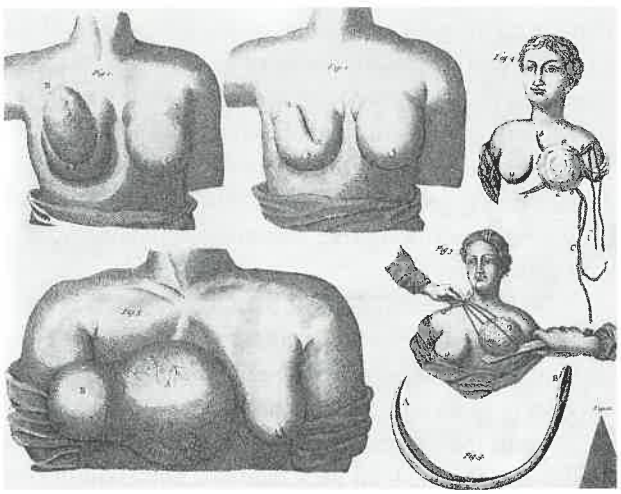


Figure 4. Heister's mastectomy.

However, many deaths and complications still resulted. Theodor Billroth's Clinic in Vienna reported in 1879 that 34 out of 143 women had died from the operation – mostly of infection – and a mere 35 survived it for any length of time. When the operation was introduced by surgeons like William Halsted in America, the patients usually had advanced tumours which could be removed only by extensive operation [28].

Many experienced surgeons, however, appalled at the early recurrences they saw following removal of the breast tumour, wondered whether surgery was indicated at all in many cases and whether, in fact, it often did more harm than good. Robert Liston (1794-1847), Professor of Surgery at the University College Hospital, London, and the first surgeon to operate using ether anaesthesia in England wrote: "Recourse may be had to the knife in some cases, but the circumstances must be very favourable indeed to induce a surgeon to recommend or warrant him in undertaking any operation for removal of malignant disease of the breast..."[29].

Sir James Paget (1814-1899), of St Bartholomew's Hospital, London, wrote in his *Lectures on Surgical Pathology* in 1853: "We have come to ask ourselves whether it is probable that the operation will add to the length or comfort of life enough to justify incurring the risk for its own consequences. I cannot doubt that the answer may be often in the affirmative in some cases..." Much of this philoso-



Figure 5. Pancoast's mastectomy technique.

phy, written 150 years ago, is relevant to surgical practice today [30].

Sir James Paget went on to show that in 235 cases he had had an operative mortality of 10% and he said that he had not seen a case where recurrence was delayed beyond 8 years. He had followed the life histories of 139 patients with scirrhous carcinoma of the breast for as much as 9 years and had found that, except for a few cases, those who had had no operation lived longer than those who had had surgery. It must be remembered, of course, that in those days patients would rarely present themselves to the surgeon with the small tumour of 1 cm or less that is so commonly seen in the clinics today; one has only to read the case descriptions or look at the clinical photographs of patients in the last century to realise that the so-called "early" breast tumours in the 19th and early 20th century were often actually visible, with dimpling of the skin and often already ulcerated – todays' T4 tumours [31].

Of course, the early mastectomies were performed without any form of anaesthesia and without the benefit of antiseptic surgery. Once these twin blessings had been introduced, mastectomies could be carried out by means of careful dissection and without the fear of almost inevitable suppuration of the wound. Thus, in 1870, Sir Joseph Lister (1827-1912) wrote: "I have at present a patient about to leave the Infirmary 3 weeks after the removal of the entire mamma for scirrhous, all the axillary glands having been at the same time cleared out..."[32].

In Germany, the concept of cancer dissemination via the lymphatics developed thanks to the work of Richard von Volkmann (1830-1889) and of Lothar Heidenhain (1860-1940) of Berlin, who published a detailed study on the spread of breast cancer in 1889. Volkmann himself, by 1875, was advocating routine removal of the fascia over the pectoralis major together with the entire breast and an extensive portion of the overlying skin, together with removal of the entire fatty tissue of the axilla. If the underlying muscle was bound to the tumour a thick layer of muscle was also excised [33].

Gradually, surgeons were moving to the concept of the radical mastectomy, whose detailed technique was evolved by Willy Meyer (1858-1932) of the New York Hospital and William Stewart Halsted (1852-1922).

Meyer drew attention to the danger of dissemination of the cancer cells in the wound if the tumour was handled during the operation. He included removal of the pectoralis minor in his operative procedure, a technique later adopted by Halsted. The large wound defect was treated by skin grafting about 8-10 days after the initial mastectomy [34].

Halsted did much to pioneer the operation of radical mastectomy which, in the United States, was often termed "the Halsted mastectomy" (Figure 6). By 1898, Halsted was advising dissection of the supraclavicular nodes in the majority of cases and even removal of the mediastinal nodes, although, in later years, he abandoned the supraclavicular part of the dissection. Halsted was also performing immediate skin grafting to the resultant large raw area, having used the available skin to cover the axillary contents (Figure 7). By 1907, Halsted was able to demonstrate the well known relationship between the stage of the tumour and its prognosis [35].

At about this time, William Sampson Handley (1872-1962) of the Middlesex Hospital, London, published his monograph on *Cancer of the Breast and its Operative Treatment*. His philosophy was to affect the therapy of breast cancer over the next half century and certainly deeply influenced Halsted. This was the cancer permeation hypothesis – that breast cancer spreads centrifugally, primarily in the plane of the subcutaneous tissues and along lymphatics. Blood spread was considered to be unimportant; bone spread occurred by way of the lymphatic plexus of the deep fascia, and even intra-abdominal spread was due to permeation along the sheath of the rectus muscle of the abdominal wall. It was this concept that led to the feeling that if only a sufficiently wide sweep could be made around the tumour the chances of a cure could be increased (Figure 8). Handley himself employed not only a very wide radical mastectomy but also, from 1920 onwards, implanted radium needles into the anterior intercostal spaces in order to deal with the internal mammary lymph nodes [19].

The apparent logical extension of these pathological findings was to attempt to increase the radicality of the radical mastectomy. Erling Dahl-Iverson (1892-1978) at the Rigshospitalet, Copenhagen, in 1951 performed an extrapleural dissection of the internal mammary nodes, as did Mario Margottini (1897-1970) of the National Cancer Institute, Roma, the following year, while Owen Wangensteen (1898-1981) in Minneapolis advised splitting the sternum to remove the internal mammary nodes

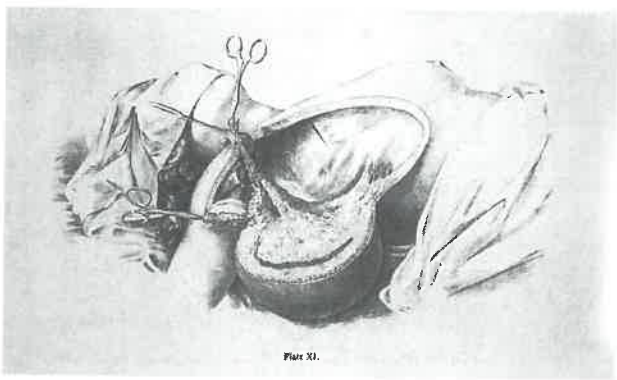


Figure 6. Halsted radical mastectomy.

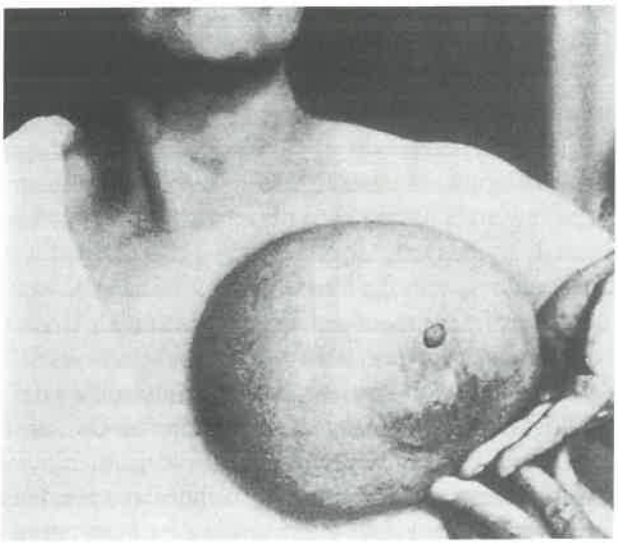


Figure 7. Patient submitted to radical mastectomy by Halsted in 1912.

and dissection of the nodes above the clavicle [36]. But it was Jerry Urban (1914-1991) [37] at the Memorial Hospital, New York, who perfected a massive operation that combined radical mastectomy with en bloc resection of the internal mammary chain by removal of part of the sternum together with the inner ends of the 2nd to the 5th rib and with repair of the resultant defect with fascia taken from the thigh (Figure 9).

So, for the first half of the 20th century, the concept of centrifugal spread of breast cancer held sway and with it the cult of radical mastectomy. Indeed, any progress seemed to depend on developing still more radical ablations of the breast and its surroundings. It has only been in comparatively recent years that the development of controlled clinical trials has shown that survival bears no relationship to the radicality of the operation. The permeation theory of the spread of the tumour has long since been displaced by the realisation that it is blood-borne dissemination of the tumour that is the vitally important clue to prognosis. This in turn has made us realise that the answer to progress in breast cancer lies not with still more radical mastectomies but must have two aims in mind: first, adequate control of local disease and, second, the prevention or treatment of secondary spread of the tumour.

Even in those early days there were occasional pioneers, usually regarded as dangerous heretics, who were ready to try less mutilating procedures. Robert Mc Whirter (1904-1994), Professor of Radiotherapy at the Edinburgh Royal Infirmary, treated a series of 757 patients between 1941 and 1945 by simple mastectomy followed by radiotherapy. He compared these cases with 411 patients treated by radical surgery together with postoperative radiotherapy between 1935 and 1940 and showed, if anything, that survival was greater in the more conservatively treated group [38].

Meanwhile, David Patey (1899-1977), at the Middlesex Hospital, was experimenting with preservation of the pectoralis, except in those few cases where it was invaded by the tumour. In 1948 he reviewed his mastectomies performed between 1930 and 1943. Comparing his radical mastectomies with patients treated by his modified

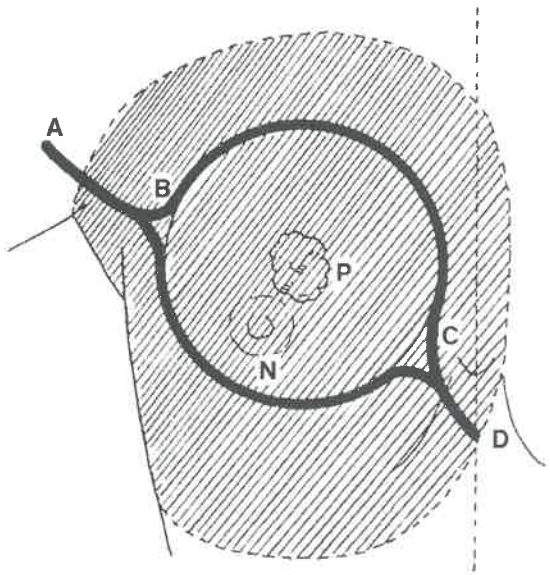


Figure 8. Sampson Handley's diagram of the area to be removed for adequate clearance in breast cancer.

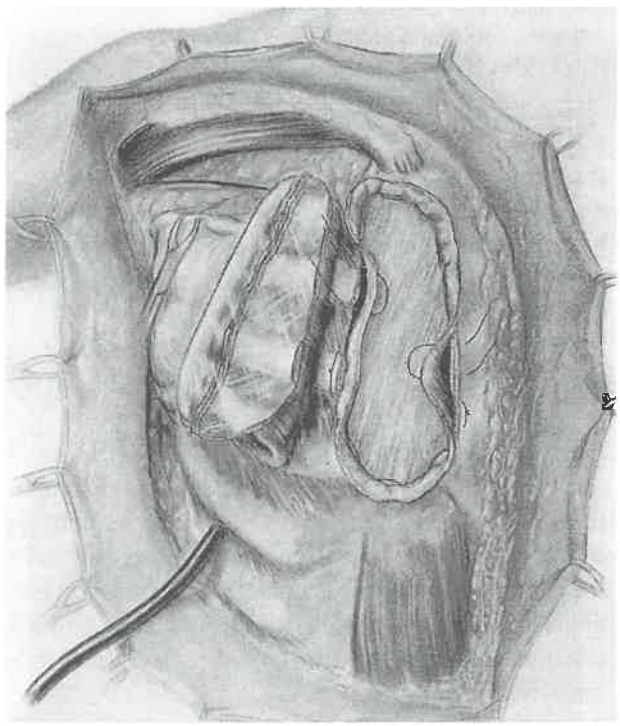


Figure 9. The chest-wall defect left by Urban's super-radical mastectomy.

operation, now often called the Patey mastectomy, he showed that there was no difference in the survival rate or local reccurrence rate between the two groups [1].

Radiotherapy and breast cancer

The beginning of 20th century brought a wholly new technique for treating tumours: radiotherapy. Its use before and /or after a radical mastectomy was the classical treatment for many years, but now it is an individualized postoperative tool.

Radiation therapy in the treatment of early breast cancer was pioneered at the Curie Institute in Paris around 1936. In recent years published results from many major centres have encouraged surgeons and radiotherapists around the world to use local excision of the tumour combined with radiotherapy as a substitute for mastectomy. In numerous trials, the survival rate for women treated by this technique has been shown to be exactly comparable to that achieved by mastectomy, and this is not difficult to understand. Death from breast cancer results not from local disease but from the effects of secondary spread of the tumour. Once the primary lesion has been controlled, whether this is by local excision, radiotherapy, or the most radical surgery that surgeons can devise, the patient's fate depends on whether or not subclinical dissemination of the disease had taken place before the primary lesion was removed. The means by which the tumour is treated locally can in no way influence this vital issue [39].

Long before these clinical experiments, however, a still more unconventional form of treatment was being developed at St Bartholomew's Hospital, London. After the First World War, Geoffrey Keynes (1887-1982), a pioneer of blood transfusion, returned to Bart's and investigated the use of the newly developed radium needles in the treatment of advanced and inoperable breast cancer (Figure 10). By 1927, he was able to report a 5-year experience in which he had shown that good local control of the disease could often be obtained. Keynes' results were entirely comparable with those obtained by mastectomy but unfortunately his work was interrupted by the outbreak of the Second World War, when he joined the Royal Air Force, and the supplies of radium were dispersed because of the dangers of air raids on London. Interestingly enough, after the war, a review of the late results of his cases showed that these were comparable to those obtained by radical surgery. However, of course, there was a significant gain in the quality of life of these patients [38].

Hormonotherapy and breast cancer

Breast cancer shares with prostatic tumours the strange phenomenon that, in many cases, the growth is sensitive to changes in the sex hormone environment. George Beatson (1848-1933) in Glasgow, Scotland, although he knew nothing about the hormonal effects, reported in 1896 a regression of advanced breast cancer in patients in whom he had removed the ovaries This has been replaced by "medicinal castration", giving anti-oestrogen drugs which biock the effects of sex steroid hormones [40]. Hugh Lett (1876-1964) of the London Hospital reviewed 99 patients treated this way; in spite of spectacular early response to oophorectomy in several patients, only one patient had a relatively long and complete response. The isolation of cortisone as replacement therapy allowed Charles Huggins (1901-1997) to perform bilateral removal of the adrenals (adrenalectomy) together with oophorectomy in 1952. The rationale of this procedure is that, after removal of the ovaries, the adrenal cortex is a source of oestrogens. Huggins received the Nobel Prize in 1966, one of only 9 surgeons ever to receive this award [41]. Later, in the same sense, removal of the pituitary gland was employed. In large series of cases, regression of disseminated breast cancer would be found in about a third of the cases following these procedures, some with quite dramatic responses. In recent years, however, the development of new hormonal agents and of cytotoxic anticancer drugs has made these major surgical procedures obsolete.

Today, examination for breast cancer is combined with X-ray mammography, magnetic resonance mam-

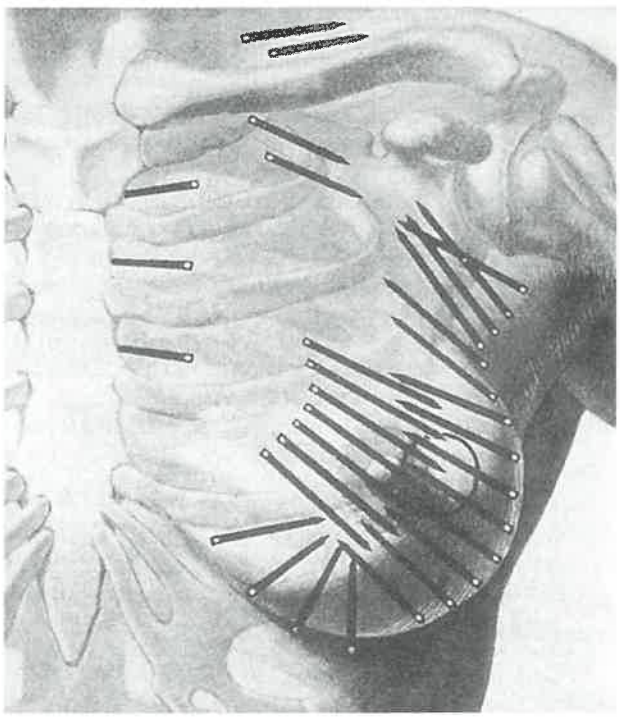


Figure 10. Geoffrey Keynes 'technique of radium implantation'.

mography, and breast ultrasonography, and microscopic study of tumours by fine needle aspiration cytology or surgical biopsy. If the disease is limited to the breast and the axillary lymph nodes it is considered as potentially curable, normally by removing them while leaving the muscle (modified radical mastectomy). Adjuvant hormonotherapy and/or chemotherapy are used when different adverse prognostic factors are present. These, and irradiation, can also help in advanced cases.

Breast cancer makes up a quarter of all cancer in women, and occurs at relatively young ages. Its stage and the histological type are decisive for the final outcome. The survival rate after 5 years is about 80% when cancer is confined to the breast, and 50% when it involves axillary nodes. Its earlier diagnosis with mammography contributes to improved survival and also to lesser surgical intervention; mammography can detect a very small tumour, requiring only its removal by segmental resection and radiotherapy to the rest of the breast. This conservative surgery is far less worrying to the patient. Moreover, postoperative reconstructions of the breast, including silicon prostheses, have become ever more common [1].

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