CANCER AS A SEQUEL TO WAR WOUNDS

LEON GILLIS and STANLEY LEE, LONDON, ENGLAND

From Queen Mary's Hospital, Roehampton, and Westminster Hospital, London

The purpose of this paper is to draw attention to a late complication of war wounds which, though rare, is important and deserves recognition. Twenty-four cases are presented in which a squamous carcinoma has arisen at the site of the wound; they have been selected from a considerably larger number because they allow no reasonable doubt as to the relationship of the carcinoma to the wound. Four of the cases are described in greater detail in order to illustrate certain special points afterwards discussed.

Chronically irritated tissues have long been recognised as fertile soil for the development of squamous carcinoma. In 1835 Caesar Hawkins of St George's Hospital, London, writing of "wartlike tumours in cicatrices," noted their occurrence in scars of burns and of flogging, and, in one instance, in an old gunshot wound of the leg. Carcinoma has been reported as a late complication of thermal, chemical and X-ray burns, of healed lupus, of chronic varicose ulcers (Marjolin's ulcer), of chronic tuberculous and osteomyelitic sinuses and of anal fistulae. Among pensioners of the first world war we have found other instances complicating sacral bed-sores, trophic ulcers and callosities on anaesthetic feet, and the scars of frostbite and flash burns. These cases have been excluded from the present series, as have some examples of sarcoma that appear to have arisen in deeper tissues around scars or foreign bodies. Some of them, however, are appended for interest in Table II.

Clinical material—The clinical features of the twenty-four cases of the present series are set out in Table I, and selected cases are illustrated in Figures 1 to 14. It will be realised that the cases form a highly selected group: all are males, and all were of military age during the first world war. The reasons for the preponderance of lower limb wounds are discussed below.

TYPICAL CASE REPORTS

Case 5—At the age of twenty-four years the patient received a wound in the upper part of the right thigh with fracture of the femur and consequent osteomyelitis. The sinuses never healed and the scars were extensive and adherent to bone. In 1943 increasing fetor of the discharge was noted and radiography showed extensive disease of the femoral shaft. Granulations around a sinus that had discharged continuously for twenty-five years were examined and showed clear evidence of carcinoma. The surgeon in charge recorded his conviction that the growth would be of low malignancy, and aimed to preserve an adequate stump by a guillotine amputation leaving five inches of femur. The operation was followed by early local recurrence and enlargement of the inguinal glands; and the patient died within a year. The histological picture showed that the tumour was of high malignancy.

Comment—In this case it seems that the surgeon shared the common misconception that it is unnecessary to take very seriously carcinoma arising in scar tissue. This view finds considerable support in the literature; thus Harrison, writing as recently as 1938, stated: "We have not found in the literature any instances of a carcinoma secondary to osteomyelitis in which there were distant metastases. Biopsy of nearby enlarged nodes has shown only chronic lymphadenitis." Bereston and Ney (1941), however, collected from the literature seven cases with proved metastases and added two of their own. It is the experience of the present writers, as will be seen from several of the cases presented, that the tumours may become very malignant, developing rapidly, infiltrating extensively, and disseminating widely. They must be treated as urgently and radically as any other carcinoma.

Case 7—Patient wounded in the right leg in 1918 at the age of eighteen years. The tibia was extensively damaged, and in thirty years the resultant sinuses never healed completely. There

FIG. 1
Case 6—Sinus cancer. Chronic sinus of the left buttock with development of carcinoma twenty-nine years after gunshot wounds.

FIG. 2
Case 6—Low power section showing histological appearance. Squamous-cell carcinoma.

FIG. 3
Case 6—Radiograph showing erosion of the left ischio-pubic ramus.

FIG. 9

Case 10—Sinus cancer. Deep ulcer in the sacral area after arrest of a carcinoma which developed thirty years after gunshot wounds. (By courtesy of Sir Stanford Cade.)

FIG. 10

Case 10—Radiograph shows extensive erosion of the sacrum.

FIG. 4

FIG. 5

Case 8—Sinus cancer. Figure 4 shows a deep chronic ulcer crater with development of carcinoma thirty-three years after gunshot wounds. Figure 5—malignant enlargement of the inguinal glands.

FIG. 6

FIG. 7

FIG. 8

Case 9—Sinus cancer. Figure 6—Commencement of carcinoma in a discharging sinus twenty-nine years after gunshot wounds. The rapidity of growth can be judged from comparison with Figure 7, a photograph taken only ten weeks later. Radiograph (Fig. 8) shows osteitis of the upper end of the femur.

FIG. 11

Case 31—Carcinoma at the site of a deep ulcer crater of the foot in relation to the calcaneum. Skeletal traction by calcaneal pin twenty-one years previously led to infection and chronic sinus. (Specimen in the museum of the Royal College of Surgeons.)

FIG. 12

Case 31—Radiograph shows extensive erosion of calcaneum. Note the soft-tissue swelling.

were many sequestra and he had at least seven operations. In 1946 radiographs showed large cavities in upper and lower ends of tibia; sclerosis of surrounding bone and synostosis with fibula opposite each cavity; and periosteal new bone formation around middle third of fibula. At that time there was much discharge, and histological examination of curettings from the sinus showed squamous-cell carcinoma. Amputation was performed eleven inches below the greater trochanter. A year later he was readmitted with an enlarged inguinal gland, clinically inoperable. His general condition was poor and radiographs of the chest showed a collapsed right lower lobe with effusion. He died within three weeks of admission. *Autopsy* revealed carcinoma in the amputation stump and in the inguinal glands, as well as in the lungs, diaphragm and pleura.

Comment—This case presents certain notable features: the malignant change began within a sinus and was already well established before much surface change was evident; an increase in the amount and fetor of the discharge first called attention to the neoplasm; the tumour itself was very malignant and metastasized widely.

Case 9—Patient aged thirty-six years at the time of wounding in the left thigh by bomb fragments in 1918. Apparently no gross bone injury. He was in various hospitals for four years and underwent a number of operations for osteomyelitis of the femur. Sinuses persisted in spite of treatment and never healed completely. In 1945 the presence of a sequestrum was noted but it was not removed. In 1947 a biopsy specimen taken from suspicious looking tissue at the margin of a sinus showed squamous-cell carcinoma. The rapid progress of the disease can be seen from the photographs (Figs. 6 and 7). No curative treatment was attempted and the patient died early in 1948. *Autopsy* showed extensive osteomyelitis of the femur with a massive carcinoma, but no visceral metastases. Amyloid changes were found in liver and spleen.

Case 22—In 1918, when twenty-eight years of age, the patient received a bullet wound of the right side of the face. The horizontal ramus of the mandible was shattered and there was much loss of soft tissue. The reconstructive programme occupied three years, after which the wound was healed, and there was fibrous union of the mandible, though movement was limited by scar tissue (Figs. 13 and 14). He remained well until 1942 when a malignant ulcer appeared on the mucosal aspect of the cheek close to a skin inlay. He was treated with high-voltage X-rays but, although the growth was arrested, an ulcer persisted; and in 1950 the disease again became active. Radical resection with repair by pedicle flaps was undertaken and the patient is alive, though probably with disease.

Comment—This case differs from the preceding three in that bone infection had not persisted and there were no sinuses. The carcinoma presumably arose in unstable scar tissue, thus resembling those occurring in old burns or lupus scars. Comparable cases are numbers 27, 28 and 30 in Table II.

PRE-CANCEROUS CHANGES

In a few cases the wound has been seen in a state of hyperkeratosis that could be regarded as pre-cancerous. Clinical details of three such cases are given in Table III, and one case is illustrated in Figures 15 and 16. It may be claimed that in these cases treatment has prevented the onset of malignancy.

DISCUSSION

Sinus cancer—This term is chosen to designate the larger of the two groups into which our series may be subdivided, comprising sixteen cases. There is a history of an osteomyelitic sinus discharging for long periods, often throughout the latent interval. The tumour sometimes arises deep in the sinus and may reach a considerable size before becoming manifest on the surface. Obviously these cases are analogous to carcinomata arising in other types of sinuses and fistulae, and well recognised as a complication of chronic osteomyelitis of civilian origin (Hueper 1942, Niebauer 1946). They occur almost always in the lower limb, buttocks or sacral area; we ourselves have never seen an undoubted example in the upper limb, though a few have been recorded, one of them by Volkmann (quoted by Bereston and Ney 1941). This heavy preponderance of lower limb involvement is not merely a reflection of the distribution of war wounds in general nor of the bones affected by osteomyelitis. In 1929 an analysis of limb wounds still disabling enough to require pensions (Sandison 1929) showed them to be distributed almost equally between arm and leg; while osteomyelitis, in a series of 2,400 cases admitted to the Massachusetts General Hospital and recorded by Benedict

FIG. 13

FIG. 14

Case 22—Scar cancer. Figure 13—Treated carcinoma at the site of an old gunshot wound of the mandible sustained twenty-four years previously. The wound had remained healed for twenty-one years after plastic reconstruction. Figure 14—Radiographic appearance; large defect in the right mandibular ramus.

FIG. 15

FIG. 16

Case 32—Pre-cancerous changes in scar. Figure 15—Photograph showing adherent scar with pre-cancerous changes thirty years after gunshot wounds. Figure 16—Histological section shows marked proliferative activity of the epithelium.

TABLE I
 TWENTY-FOUR CASES OF CARCINOMA ARISING AT THE SITE OF WAR WOUNDS
 (All cases confirmed histologically)

Case number	Age at time of wounding (years)	Age at onset of carcinoma (years)	Interval (years)	Site	History, treatment and outcome
1	35	55	20	Left hip	Gunshot wound with fracture of upper end of femur. The wound never healed, and scarring was extensive and adherent. Whole upper end of femur separated as a huge sequestrum. Carcinoma diagnosed as a result of increasing offensive discharge. Disarticulation. Died eleven years later without recurrence. Histology—well-differentiated squamous-cell carcinoma
2	28	49	21	Sacrum	Shrapnel wound 1917, with lasting bladder dysfunction. Wound never healed. Carcinoma diagnosed 1938. Died same year, with cachexia and bilateral pyelonephritis. Histology—squamous-cell carcinoma with cell nests
3	38	60	22	Right leg	Gunshot wound 1917, with fracture of upper third of tibia. Wound never healed. Carcinoma diagnosed 1939. Above-knee amputation. Spread to inguinal glands and death within a year. Histology—squamous-cell carcinoma
4	33	55	22	Right knee	Gunshot wound fracturing femur and patella. Sinus never healed; many sequestra. Scar deeply depressed and adherent. Carcinoma diagnosed 1940. Above-knee amputation. Well to date. Histology—squamous-cell carcinoma
5	24	51	27	Right thigh	Gunshot wound fracturing femur; sinus never healed, and scar very adherent. Offensive granulations 1943; carcinoma diagnosed. Amputation leaving 5 inches of femur. Rapid local recurrence in stump and death within a year. Histology—squamous-cell carcinoma
6	24	53	29	Pelvis	Wounds of lumbar spine and pelvis, with incomplete paralysis. Osteitis of ischio-pubic ramus, with sinus in adductor region that never healed. Carcinoma diagnosed 1945, and treated by wide excision. Local and general spread; died within a year. Histology—squamous-cell carcinoma (Figs. 1 to 3)
7	18	46	28	Right leg	Gunshot wound 1918, fracturing tibia. Much sequestration, with permanent sinus. Carcinoma diagnosed 1946, treated by above-knee amputation. Died within a year with fungating inguinal glands and pulmonary metastases. Histology—squamous-cell carcinoma
8	30	63	33	Pelvis	Gunshot wound 1914, with destruction of right sacro-iliac joint. Sinuses never healed. Carcinoma diagnosed 1947 in area of multiple sinuses with much bony sepsis. Died of disease within a year. Histology—squamous-cell carcinoma (Figs. 4 and 5)
9	36	55	29	Left thigh	Wounded 1918 by bomb fragments. No gross fracture, but bone sepsis followed and sinus never healed. In 1947 biopsy of suspicious granulations showed squamous-cell carcinoma. Died of disease within a year (Figs. 6 to 8)
10	28	58	30	Sacrum	In 1915 wounded by shrapnel bullet which lodged close to sacrum. Returned to active service, but later developed sinus over sacrum; this healed after removal of bullet in 1924. In 1935 sinus reopened, and radiographs showed bone destruction. Squamous-cell carcinoma diagnosed; treated by diathermy and radium (Sir Stanford Cade). Well to date (Figs. 9 and 10)
11	26	50	24	Left leg	Multiple wounds 1915. Fracture left tibia, with sinus for several years, and extensive adherent scars. Carcinoma diagnosed 1939; treated by above-knee amputation. Died within six months with abdominal and pulmonary metastases. Histology—squamous-cell carcinoma

12	23	47	24	Left leg	Gunshot wound 1918, with severe injury upper part of tibia. Depressed adherent scar with sinus for some time. Carcinoma diagnosed 1942; treated by radium implant. Well to date. Histology—squamous-cell carcinoma
13	34	61	27	Left thigh	Gunshot wound in 1917, with fracture of mid-femur. Sequestration, with sinuses for long periods, and extensive scarring. Carcinoma diagnosed 1944; above-knee amputation. Metastatic nodes dissected out. Well to date. Histology—squamous-cell carcinoma in wound and nodes
14	35	62	27	Left leg	Gunshot wound in 1916, fracturing tibia. Bone plated. Depressed, adherent scar with sinuses discharging for long periods. Carcinoma diagnosed in 1943; treated by amputation. Histology—rather anaplastic squamous-cell carcinoma. Well to date
15	34	62	28	Right thigh	Femur shattered by machine-gun bullet 1914. He had twenty-seven operations, and sinuses never healed. Carcinoma appeared in 1948 and spread rapidly. He died within a year. Histology—very active squamous-cell carcinoma
16	28	59	31	Left leg	Gunshot wound 1918, fracturing tibia. Sinus healed after two years, but reopened in 1927. It again healed till 1949, when carcinoma appeared in the sinus. Above-knee amputation, well to date
17	23	44	21	Left leg	In 1917, multiple wounds, with fracture of left tibia. Healed after about two years, but with large adherent scar. Later a chronic ulcer appeared without osteitis, and in 1937 an above-knee amputation was done. Histology—squamous-cell carcinoma. Well to date
18	28	57	29	Face and mouth	Gunshot wound through both cheeks 1917, with loss of right upper alveolus and separation of maxillae. Multiple repair operations and eventual healing. In 1946 a mucosal carcinoma arose beside a skin inlay. Treated with radium but died within a year (Sir Stanford Cade). Histology squamous-cell carcinoma
19	20	49	29	Right knee	Gunshot wound 1917, fracturing lower end of femur. Remained healed till 1946, though scar was extensive and adherent. Then reported with extensive subcutaneous carcinoma, with bone involvement and a sinus. Above-knee amputation. Well to date. Histology—well differentiated squamous-cell carcinoma
20	23	47	24	Face	In 1915 bullet entered right maxilla and passed out at left ala nasi. Wound healed but he continued to have troublesome discharge from the nose. In 1937 an antral empyema was drained, and in 1940 an antral carcinoma was diagnosed, proving rapidly fatal
21	36	56	20	Face and mouth	Gunshot wound in 1916 with fracture of mandible. Wound healed, leaving some trismus. Sequestration followed, but it is not known for what period. In 1936 an alveolar carcinoma arose at the site of fracture. Histology—squamous-cell carcinoma. Treated with radium, but died of disease in 1940
22	28	52	24	Face and mouth	In 1918, gunshot wound fracturing right mandible, and with considerable soft tissue loss. Plastic reconstruction took three years, and he then remained well till 1942. A squamous-cell carcinoma then developed on buccal aspect of cheek close to a skin inlay. Treated with radium. Alive with disease 1950 (Figs. 13 and 14)
23	31	52	21	Chest	In 1915 a glancing bullet made a 5-inch furrow in the soft tissues of the anterior chest wall. The wound healed rapidly and gave no trouble till 1936. He then developed a squamous-cell carcinoma in one end of the scar, with bilateral axillary glands. Treated with surgery and radium, but died two years later.
24	47	65	18	Right thigh	In 1918, severe flesh wound, with much muscle loss. The resultant large adherent scar was tender and developed an indolent ulcer. After some years this ulcer showed malignant change, and was excised widely. Histology—chronic ulcer with squamous-cell carcinoma at margin, showing many mitotic figures. Died 1942 without recurrence

TABLE II
SQUAMOUS CARCINOMAS INDIRECTLY ATTRIBUTABLE TO WAR INJURIES

Case number	Age at time of wounding (years)	Age at onset of carcinoma (years)	Interval (years)	Site	History, treatment and outcome
25	21	45	24	Right leg, sole	In 1916, gunshot wound with comminution of upper end of tibia, resulting in permanent foot-drop and anaesthesia of sole. After four sequestrectomies his wound healed but he rapidly developed plantar callosities, particularly beneath bases of outer toes. In 1939 an ulcer formed at this site, and a year later malignant change occurred in this ulcer. Below-knee amputation performed. Well to date
26	31	63	32	Foot	Frostbite of both feet in 1917 necessitated amputation of left foot and right toes. He soon developed a chronic ulcer beneath the heel, through which part of the calcaneum sequestered. The ulcer persisted, and in 1939 malignant degeneration occurred. Below-knee amputation was combined with dissection of inguinal glands, many of which showed deposits of squamous-cell carcinoma. Well to date
27	25	47	22	Right leg	Involved in aircraft crash in 1917; suffered severe burns of both legs, and the right was skin-grafted. An extensive granulating area persisted as a callous ulcer, in which a carcinoma developed in 1939. Below-knee amputation. There is no recurrence, but the opposite leg is now giving trouble
28	36	61	25	Left hand	In 1917 sustained cordite flash-burns of face, arms and legs. The hands, especially the left, were almost completely useless because of cicatricial contraction, and the thin, adherent epithelium showed keloid changes. In 1942 a carcinomatous ulcer formed in scar tissue on the left fifth finger. Amputation through metacarpo-phalangeal joint little finger. Microscopy showed epithelioma extending down to atrophied and degenerated bone. The amputation remained soundly healed and patient is well
29	31	53	22	Lumbar spine, buttock	In 1917 a shrapnel ball damaged the fourth lumbar vertebra and the cauda equina. The wound healed, but a trophic ulcer developed in an anaesthetic area over the right ischium. This ulcer persisted despite various surgical endeavours, and by 1935 there were multiple sinuses over the buttocks and perineum. In 1939 carcinoma developed, from which he died within a year
30	35	58	23	Left leg	In 1915 he was run over by an army lorry, which crushed the popliteal region and caused gangrene of skin from the upper thigh to the ankle. Skin was grafted, but there was persistent ulceration in the calf area. Carcinoma developed in 1938, and after amputation he died of metastases
31	25	56	31	Left thigh, left heel	In 1918 he sustained a gunshot wound of thigh with comminuted fracture of the femur. A pin was inserted through the calcaneum for skeletal traction. A small callosity persisted at the site of the pin insertion, and required paring down periodically. The leg also suffered from circulatory disturbance and there was some varicose dermatitis of the lower leg. In 1947 the callosity began to discharge. Ulceration deepened and in 1949 there was a deep malignant ulcer penetrating the calcaneum. Below-knee amputation, with clearance of inguinal glands. Well to date. Histology—squamous-cell carcinoma (Figs. 11 and 12)

TABLE III
THREE CASES OF PRE-CANCEROUS CHANGES IN WAR WOUNDS

Case number	Age at time of wounding (years)	Age at onset of changes (years)	Interval (years)	Site	History, treatment and outcome
32	20	50	30	Left thigh	Sustained extensive flesh wound front of thigh, with much muscle loss. Initial healing took eleven months, and the scar, which was papery and adherent to the femur, broke down after seven years. This happened several times, and after 1943 it never healed. In 1946 the ulcerated area, which was that most firmly adherent, had firm raised edges, and there were rough patches of hyperkeratosis. Radiographs showed underlying periostitis. Biopsy—Hyperkeratosis and acanthosis. Immediately under the epidermis there was a non-specific inflammatory reaction. The scar was widely excised and grafted by means of a cross-leg flap. Well to date (Figs. 15 and 16)
33	23	47	24	Right arm	In 1918 he sustained a through-and-through bullet wound near the right elbow, with fracture of the ulna and destruction of the ulnar nerve. Wound healed after one year, the scar being depressed and adherent to bone. Keloid change followed and in 1942 the keloid began to show a warty excrescence. Biopsy showed hyperkeratosis. Treated by excision of scar. Died of coronary disease three years later, without recurrence
34	30	60	30	Right groin	Sustained gunshot wound of pelvis in 1918, with damage to ilium and sinus that healed after three years. In 1948 he reported with a rough warty lesion in the scar. Radiographs showed underlying bony outgrowth. Wide excision. Well to date. Histology—simple epithelial papilloma

(1931), involved lower and upper limbs in the ratio of about three or four to one (Table IV). But it is in the lower limb that massive wounds with severe bone damage are treated conservatively and give rise to the persistent sinuses liable to undergo malignant change; it is common experience that such conditions are very rare in other regions of the body.

TABLE IV
ANATOMICAL DISTRIBUTION OF WAR WOUNDS, OSTEOMYELITIS AND SINUS CARCINOMA

Site	Pensioned war wounds (Sandison 1929)	Osteomyelitis (Benedict 1931)	Sinus carcinoma	
			(Benedict 1931)	Present series
Upper limb	113,000	415	None	None
Lower limb	117,000	1,358	12	16, including those in pelvic area

Scar cancer—There were at least seven of these in our series. There may be no history of prolonged infection, and no symptoms during the latent interval. The lower limb is not predominantly affected (this is also true of a series of burn scar cancers published by Treves and Pack in 1930). The growth starts in an area of thin, poorly nourished and brittle epithelium based on more or less extensive fibrous tissue and often firmly adherent to bone. In several of our cases the lesion was in the mouth, twice clearly in relation to skin inlays. The group corresponds in all respects to tumours occurring in other scars, such as those of burns, lupus and radiation. It is important to realise that even in this group, with little or no actual ulceration during the latent period, long continued carcinogenic influences are at work. Carcinoma does not occur in sound, supple, "resting" scars such as those produced by abdominal surgery. The dangerous scar is one in which cell division has been continuously stimulated for years under worsening conditions of deficient circulation and mechanical restriction. Such factors, it is easy to conceive, may lead to accumulation of metabolites, or to local deficiencies, eventually resulting in abnormal mitosis.

Incidence—Carcinomatous change as a complication of wounds and scars is clearly uncommon. McAnally and Dockerty (1949) found in the records of the Mayo Clinic nine cases of carcinoma in 4,000 cases of osteomyelitis, three in 3,000 cases of anal fistula, and one in 1,500 cases of empyema. Benedict (1931) in his 2,400 cases of osteomyelitis found twelve complicated by carcinoma. Such figures, however, tend to obscure the true position. What is necessary is to determine not the incidence of carcinoma in *all* sinuses or scars, but in those that are twenty years old or more; on this basis the incidence of malignant change will certainly reach a much higher figure. No estimate has been found in the literature, and unfortunately our system of records does not enable us to make an assessment. It is not possible, for instance, to determine the number of men whose sinuses persisted for long periods, or to discover the total number of carcinomata that have arisen.

Latent interval—In the present series no carcinoma developed sooner than eighteen years after the injury; and cases are still occurring more than thirty years after the end of the war. There is no method at our disposal for determining whether a peak has been reached; but it seems a likely supposition that, if there is in a given wound a tendency to malignant change, that tendency will increase as the years pass, right up to the patient's death. There is no apparent relation between the latent interval and the age of the patient. A long interval is well recognised in other post-traumatic carcinomata: twenty to fifty years in cases of osteomyelitic sinuses, ten years or more in X-ray dermatitis, ten to forty years in varicose ulceration, and so on. Burn scars, however, occasionally undergo early malignant change, and Treves and Pack (1930) distinguished a group of middle-aged patients with what they

called "acute burn scar cancers," appearing within months or even weeks of the injury. They emphasized, however, that in patients of this age the possibility of some earlier, forgotten trauma to the affected area must be allowed. In such cases the burn is to be regarded as the precipitating, rather than the predisposing, cause.

CONCLUSIONS

A patient with a chronic discharging sinus or an extensive adherent scar is never safe from the risk of malignant change. Examples are still occurring more than thirty years after the end of the first world war. The possibility should be kept in mind by those concerned with the long-term treatment of wounds of this kind. Reasonable prophylactic measures would be: excision of adherent or unstable scars with, if necessary, their replacement by suitable pedicle flaps having a good blood supply; and earlier amputation if a osteomyelitic sinus persists for several years and does not yield to treatment. Supervision of doubtful cases should be frequent and should not be relaxed with the passage of the years. Warty changes or indolent ulceration of scars should be regarded with grave suspicion and investigated by biopsy. Any increase in pain or discharge in association with a sinus should receive prompt attention. Finally, if malignant change supervenes, treatment should be as speedy and as radical as with any other cancer. At least thirteen of our twenty-four patients have died of cancer.

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