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THE INCOMPUTABLE FACTOR IN CANCER PROGNOSIS*

BY

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The subject I have chosen for this address is one of which I believe that Mitchell Banks might have expressed approval, since the special contribution to surgery for which posterity now justly acclaims him dealt with cancer and he repeatedly insisted on the necessity for appropriate surgery for this malady. To myself Mitchell Banks has long been a legendary figure of unusual interest, since in the exact moment of his arrival on the surgical stage and in the date of his first appeal, an appeal to be oft reiterated, for more radical surgery in cancer, especially in relation to mammary cancer, he stands intermediate between two Middlesex Hospital surgeons of former years. Charles Hewitt Moore (1821-70) became lecturer in anatomy and junior surgeon to the Middlesex Hospital at the phenomenally early age of 26. In 1867 Moore drew attention to the utter inadequacy of the operations that were being performed at that time for malignant disease. This epochal communication of Moore had the effect of determining Christopher Heath (1871, 1898), of University College Hospital, to remove the axillary glands when enlarged in breast cancer, but it was Banks (1878) who emphasized the importance and need of clearing the axilla, whether the glands were palpable or not.

Hard on the heels of Banks followed Alfred Pearce Gould (1882, 1892, 1910), whose private assistant I was for the nine years that preceded the outbreak of the 1914-18 war, who since 1880 had in his surgical practice embraced the tenets laid down by Banks in 1878 and who had reaffirmed them before the Medical Society of London in 1882. "A. P. G." throughout a long life of surgical teaching never failed, as I remember, to ascribe to Banks the credit of the extended operation for mammary cancer, including the systematic removal of the axillary glands in every case.

The stupidity and rank hostility of contemporaries, especially those in London, did not deter Banks from continuing on the course that he was convinced to be correct: but it required surgical propaganda, with all the glamour that inevitably arises from a transatlantic source, to convert those who had hitherto deliberately and obstinately closed their ears and eyes to the results of British endeavour. Gould, Heath, Jacobson, and Morris paid their tribute where tribute was really due.

William Mitchell Banks, born November 1, 1842, in the Scottish capital, and the son of a Writer to the Signet, received his education at the Edinburgh Academy

and Edinburgh University. His M.D. thesis in 1864 on the Wolffian bodies remained for many years the recognized authority on this subject. Banks's researches in the field of embryology are the more remarkable since they were conducted a number of years before a reasonable microtome for serial sections was first described by His (1870).

He was fortunate in coming under the influence of great anatomists such as Goodsir and Turner in Edinburgh, and he was a demonstrator in the anatomical department of Allen Thomson in Glasgow in 1865 at a time when Lister was busy with his early researches in antiseptic surgery. Mitchell Banks had therefore an unrivalled anatomical background, which almost inevitably secured for him in turn the posts of demonstrator, lecturer, and finally professor of anatomy in the original Liverpool Infirmary School, which was to change its style and name in the years to come: it was only in 1894, when the Derby chair of anatomy was instituted in the University, that Banks resigned the professorship, and A. Melville Paterson succeeded him; he was made emeritus professor of anatomy. These were the days, as in my own case, when the avenue to the surgical staff of a hospital lay through the dissecting-room.

I have spoken of Banks's anatomical teachers, but in his address to the students of Yorkshire College, Leeds, in 1892 (Banks, 1893) he reveals his own humanity in the special tribute which he pays to Warburton Begbie, physician to the Edinburgh Infirmary in Banks's period there. He writes of Begbie thus: "I have always thought of him in my own mind as the Gentle Doctor and have always striven in the hospital ward, and in the clinical theatre, to imitate his example"; and again, "When he entered a ward, a new light seemed to shine in the faces of the sick. The very way in which he would put his hand on a patient's shoulder seemed to give the invalid comfort and strength."

Banks had the privilege in Edinburgh of being dresser and house-surgeon to James Syme, whom he speaks of as "the Napoleon of Surgery."

Sir Henry Morris, who sat next to Banks for several years in the Council Room of the Royal College of Surgeons of England, refers to him as an impressive and easy speaker, with a persuasive and pleasing manner, adding that there were three subjects on which Banks was very emphatic: (1) that Members of the College should not have votes for the Council; (2) that the number of physiologists in the Royal Society was unfairly in excess of the number of anatomists and of surgeons; and (3) that academic robes and ceremonial add to the dignity and impressiveness of official

*This is a slightly abridged version of the Mitchell Banks Lecture delivered at the University of Liverpool on October 29, 1958.

functions. He was responsible for the gown of the Fellows of the Royal College of Surgeons.*

The history of Mitchell Banks's achievement in the sphere of medical education, administration, and organization is scarcely germane to the subject of my lecture, but his worth was recognized by his election to the Council of the Royal College of Surgeons, and also as a representative on the General Medical Council. Mitchell Banks had interests outside surgery: he possessed expert knowledge of art, music, architecture, and archaeology; in one of his addresses he speaks of rowing in his younger years; Harrison refers to boxing in his memorial address; he also enjoyed mountain-climbing.

An Elusive Element

I have ventured to entitle this address "The Incomputable Factor in Cancer Prognosis" and desire to emphasize that elusive element, the unpredictable resistance of the individual to cancer invasion. *Tempora mutantur*. Time was when the competitive spirit in surgeons exhausted itself in vainglorious boastings of the removal of tumours remarkable for their pounds avoirdupois or huge cubic capacity: however, the day of colossal tumours in this country at least is past and gone. Surgical megalomania is now more happily satisfied by the recordings of unexpected, even unprecedented years of survival of patients after operation, radiotherapy, or hormonal or other form of treatment for malignant disease.

It is a matter of common knowledge that the prognosis in any case of cancer depends on certain factors: (a) perhaps most importantly, the histological grading of the tumour by an expert pathologist; (b) the stage of the new growth, especially the infiltration of surrounding parts, including neighbouring veins; (c) the invasion of lymphatic nodes; (d) the presence of metastases; (e) the appropriate method of treatment; and (f) the patient's own resisting power to cancerous invasion.

The importance of this last-named factor seems to be emphasized the more in view of the recent remarkable discoveries of Warren Cole and his co-workers (Cole *et al.*, 1958; Roberts *et al.*, 1958) concerning early invasion of the blood stream by cancer cells, and by the reflection that, despite these ominous findings, post-operative survival may often be indeed quite protracted.†

The proverbial *varium et mutabile* often ungraciously applied to the feminine counterpart of *homo sapiens* is not inapplicable to the behaviour of a cancerous growth. There are many modes of behaviour in a malignant tumour: it may proceed relentlessly to its ending; it may run a hurricane course; it may linger on for many

years and may not even be the final cause of death of the patient, its protracted course betokening its low malignity, the vigorous resisting power of the patient, or the interplay of these two factors.

On the other hand a tumour which is growing strongly may have the metabolic balance turned against it by some metabolic alteration of the parent organism and may cease growing for a variable time and even become smaller, only to assume its proliferative activity again at a later period. Some of us have observed new growths disappearing completely, so that the patient is apparently cured. This phenomenon has been observed in secondary as well as in primary growths.

Latent Carcinoma

The "latent carcinomata" appear also to attest this *vis medicatrix naturae*, and those unknown forces which can keep cancer cells dormant in the vicinity of the excised primary tumour or in the lymph nodes or distant anatomical regions for a mammoth number of years before their resurgence point to a great auxiliary defensive power resident in the host in some cases.

In the matter of latent carcinoma of the prostate, to which Franks (1954, 1956a, 1956b) especially has drawn attention, these tumours possess all the morphological structure of carcinoma and some biological characteristics, including infiltration of capsule, blood vessels, and lymphatics and, exceptionally, infection of lymphatic nodes. Nevertheless these tumours have not occasioned the patients any serious harm and were certainly not the cause of their death. Raeburn and Spencer (1953) found latent carcinomata in the lungs, while Nicholson (1923), Newcomb (1936), Trinkle (1936), and Willis (1953) have described latent carcinoma of the kidney.

Unsuspected carcinoma in surgically removed goitres, often invading blood vessels, has of course frequently been reported, and it is well known that carcinoma of the thyroid may remain latent and only reveal itself by the development of metastases in bone, lung, or liver.

Small cortical nodules may be found in the adrenal; such may recur locally after removal or may metastasize. Even in the gastro-intestinal tract latent carcinomata have been demonstrated.

In some cases, especially in the prostate, the cause of latency may be hormonal environment; this suggestion is a laudable effort to explain "the resisting power of the host" in the light of recent researches.

Hadfield (1954) pointed out that when the interval between the excision of some primary malignant tumour and the appearance of secondaries exceeds say, 2, and reaches 4, 14, or 40 years, it is difficult to believe that cellular proliferation in the residual tumour has been continuous, and it seems almost impossible to escape the conclusion that the cells of the dormant growth have been in a state of temporary mitotic arrest. Such a conclusion becomes all the more irresistible when we observe sometimes the marked resurgence of clinical activity in these long-dormant growths after years of latency. When we can only faintly adumbrate the causal agencies determining the growth, regression, and even the disappearance of tumours, still less do we know the environmental factors required to induce mitotic arrest for from 3 to 30 years.

Dormant cancer cells are prone to lurk (a) in or near the site of the original operation; (b) in regional lymph nodes; (c) in deeply placed organs. Such foci must have been implanted before or during the excision

*A special gown for Fellows was authorized by the Council on May 12, 1898, after a motion to that effect by Mr. Mitchell Banks. The design of the gown, very much as it is now, was authorized at the subsequent meeting of the Council. Banks had retired from the Council before a gown for Members was authorized at the end of 1899. The Hunterian Professor's gown, which had been in use for some time, appears to have been the model for the Fellows' gown.

†According to Warren Cole and his associates cancer cells can be demonstrated in the circulating blood in a considerable percentage of cancer patients, even at a relatively early stage of the malady. In Warren Cole's and in Engell's (1955) series a positive finding was found even in the peripheral blood in upwards of 10% of "curable" patients. Clumps of cells are more likely to be found in blood taken from a vein draining the tumour area, and there is often an increase in the number of cancer cells in the circulating blood during the manipulations incident to the removal of the tumour, and in certain cases examined the cancer cells disappear from the circulating blood within a few minutes of the removal of the primary tumour. These results have been confirmed in D. H. Patey's unit at Middlesex Hospital.

of the primary neoplasm. In at least 50% of cases of malignant disease recurring after latent periods varying from 5 to 30 years the reactivated metastases are found in the haemopoietic bone marrow. Clifton and his co-workers (1952) especially have emphasized this proclivity of the bone marrow to invasion by cancer cells which may lie dormant for a long time; they state that in 33% of cases of carcinoma of the prostate cancer cells were demonstrated in the sternal bone marrow and in the ilium, and that in 9% there was widespread skeletal dissemination of growth with no diagnostic evidence other than that provided by the marrow biopsy. The haemopoietic system, the hypophysis, and the adrenal appear to be especially vulnerable to this early invasion.

Kettle (1912) drew attention to the existence of microscopic foci of metastatic carcinoma in the normal-sized spleen, and suggested that such growths lying in the territory drained by the portal vein might be the source of hepatic metastases when the primary growth lay outside the portal vein drainage area.

Carcinoma of the Breast

The protracted period during which mitotic activity may be arrested and to which Hadfield (1954) referred is well exemplified in some cases of cancer of the breast. One of my own patients who had been operated on by me for carcinoma of the breast 36 years before was alleged to have died of an "abdominal recurrence"; however, no histological evidence was forthcoming, and the verdict of this exceptionally late recurrence must remain "not proven."

On the other hand, one of Bryant's (1902) cases of cancer of the breast did recur in a woman of 82, 32 years after her initial operation, while another of his patients, aged 77, developed a recurrence over the sternum 31 years after the first operation for mammary cancer. She was alive five years later—that is, 36 years after the original operation.

Still another case reported by Bryant concerned a woman of 63 who developed a recurrence in the scar 25 years after the removal of a mammary tumour. She was alive five years later—that is, 30 years after the original operation.

In a case of recurrent carcinoma of the breast recorded by Steward (1925) with praiseworthy accuracy the patient had had her left breast removed by Butlin 31 years previously, and when seen by Steward was 81 years of age. A few months before Steward was consulted her general practitioner had discovered three small hard nodules beneath the skin in the immediate vicinity of the operation scar: these had slowly enlarged. Steward found them to be each half an inch (1.3 cm.) in diameter, each one separated from the other two by about one and a half inches (3.8 cm.): they were not attached to the skin, or apparently to the deeper structures. During the previous two months there had been some enlargement of the veins on the front of the chest, and there was some degree of breathlessness.

Whether the disease recurred at four separate spots at the same moment or whether the subcutaneous nodules were efflorescences from a mediastinal recurrence is immaterial, but the fact remains that cancer cells had lain dormant for 31 years.

Verneuil (1888) dealt with a recurrence in a woman 30 years after her first operation for a mammary tumour; and I myself saw in consultation an abdominal

tumour subsequently reported as a "spheroidal-celled carcinoma of mammary type"; the breast had been removed by the late Sir Cuthbert Wallace 30 years before.

Bowlby's (1925) case of recurrence 24 years after the surgical removal of a mammary tumour by Sir Thomas Smith showed itself as a small lump two inches (5 cm.) below the middle of the right clavicle; there was also a hard gland above the clavicle. Examination under anaesthesia revealed that the recurrent malady had already spread more widely, and the patient died within a year with visceral dissemination and infected cervical glands.

About a quarter of a century ago I saw within a very brief space of time three cases of recurrence in the scar of a previous radical mastectomy performed by sundry other surgeons, respectively, 21, 22, and 23 years previously, and only recently (October, 1958) I was informed of a small recurrence in the scar of a radical mastectomy performed by me 21 years ago.

It becomes difficult to ignore the pronouncement of Mitchell Banks in his Lettsomian Lectures of 1900 that no matter how early the case of cancer or how thorough the treatment no patient is free from the possibility of recurrence until death ensues from some other cause.

Causal Factors in Recurrence

In the preceding paragraphs I have been especially referring to recurrence in breast cancer, and in some cases no causal factor save possibly advancing age can be impugned as standing in any relationship to the recrudescence of the malady, but in others recurrence does appear to have been preceded by intercurrent disease or by surgical operation for some independent condition.

In one of my patients a recurrence in the scar of a previous radical mastectomy developed 17 years later—a few weeks after a very severe attack of acute pyelonephritis for which I had seen the patient, the previous operation area at that time being completely sound. The reactivated malady ran a hurricane course, and in a month or two the patient was dead.

In another case of my own an attack of "shingles" seemed to determine recurrence of the malady 12 years after the initial surgery; in still another case recurrence in the scar followed quickly on a haemorrhoidectomy performed 16 years after the breast operation.

Thrice I have seen recurrence follow an operation for an independent condition—for example, gall-stones—and once after a herniotomy performed under local anaesthesia for an irreducible inguinal hernia.

In these cases cancer resistance or cancer immunity long maintained appears to have been broken down by happenings unconnected with the original malady.

Certain tables set forth in previous communications (Gordon-Taylor, 1938, 1948) of mine dealing with prognosis in mammary cancer emphasize the not inconsiderable percentage of patients that may be expected to survive 10 years according to the stage of the disease (and the histological grading) when the patient comes under treatment. It would have been fascinating to ascertain the ultimate fate of upwards of 150 patients with cancer of the breast who in 1938 had survived 10 years since their operation, but the destruction by enemy air activity in 1941 of case records and tables of cases carefully worked out has effectively

precluded this; nevertheless certain cases of long survival remain indelibly impressed on the palimpsests of memory.

In particular, I would mention the case of a woman, now an octogenarian, operated on 47 years ago, in whom at the time of the operation there were already one or two infected glands in the axilla. Ever since the time of her operation she has been cursed by oedema of her arm when she performs much in the way of exercise; but there has been no recurrence of her malady.

Another patient, operated on in July, 1914, for a carcinoma of the breast without involvement of the axillary glands, has remained free from recurrence more than 44 years. Still another patient who had a preliminary biopsy and a radical operation a few days later on account of the sinister histological report survived 36 years and unfortunately met with a fatal road accident. Another is alive and free from recurrence 35 years after a radical operation.

Two patients with carcinoma of the breast came under my care in 1925 and in 1931 respectively, in whom at operation the axilla was found to be literally stuffed with infected glands. The earlier case I have lost sight of since the outbreak of the 1939-45 war, but she certainly survived 14 years. The later case I frequently saw; this patient was a few days short of 90 when she recently died suddenly free from recurrence, nearly 28 years after what seemed an ill-omened start.

Cancer of the Tongue

Cade and Lee (1957), in their excellent contribution on cancer of the tongue, refer to reactivation of the disease after many years of apparent "cure"; they quote cases recurring at 5, 6, 8, 10, and even 16 years after treatment, and mention Juliette Baud as having observed a recurrence as long as 21 years after previous successful radiotherapy.

A patient was admitted to the Middlesex Hospital under my care about 30 years ago with severe haemorrhage from a huge carcinomatous ulcer of the tongue, for which Holmes Sellors, at that time my registrar, ligatured the external carotid artery. Four days later a total glossectomy was performed, the alveolar portion of the lower jaw on the affected side being removed with the tongue. The man was seen periodically for 21 years, when he presented himself with a growth of the palate, which was inoperable. In view of the very extensive character of the growth 21 years before, and the deep infiltration of the palatine neoplasm I was inclined to regard this as a late recurrence rather than a separate primary growth.

A man was admitted under my care in 1923 with a huge carcinoma of the tongue involving the lower jaw. A total glossectomy along with removal of half the jaw was followed by freedom from recurrence for 24 years, the man dying from natural causes.

A man was operated on at his home in the wilds of the country: hemiglossectomy was performed by diathermy excision in 1926, followed by an elective block-dissection of the neck. The patient remained well for 15 years, dying in 1941 aged 78 from prostatic breakdown for which he obstinately refused to submit to surgery.

Perhaps the longest survival of a patient with cancer of the tongue is that reported by Manson (1922), of Warrington, who published a case of cancer of the

tongue excised in 1888. The patient remained well until 1922, when he developed a carcinoma of the cardia, 34 years after the surgical removal of the lingual epithelioma.

Cancer of Cheek and Lip

Cancer of Cheek.—A distinguished patient had a considerable carcinoma of the buccal aspect of the cheek, which was first treated by telurium, but recurrence took place; radium needles were then inserted. This appeared to "flare" the growth; a wide excision of the cheek was performed, including a portion of the alveolar process of the maxilla and of the mandible. The whole defect was left open, and the gap subsequently repaired by a plastic by Professor T. P. Kilner. More than 22 years later the patient died from causes unconnected with the original malady.

Basal-celled Carcinoma of Lower Lip involving Mandible.—G.L., in 1925, had a local excision of an ulcer and minor plastic repair. A recurrence which took place 10 months later was treated by diathermy; in 1928 the ulcer, which had recurred and was now attached to the bone, was submitted to radium treatment. In July, 1929, the malignant ulcer was treated by further radium. In March, 1930, further recurrence necessitated the removal of the whole of the lower lip, much of the mandible, and part of the left cheek and left upper lip. By July, 1932, plastic repair by Sir Harold Gillies of soft tissues for lip and chin was complete, and in November, 1933, a bone graft from the ilium was inserted. In 1958 the patient was sound and well nearly 29 years after the radical operation.

Carcinoma of Lower Lip involving Mandible.—Miss H.P. in 1917 received some x-ray treatment abroad for excess of hair on her chin and face. In 1920 she was given snow treatment and in 1921 diathermy, by which time an ulcer was present on the chin. In 1937 she underwent the removal of some portion of her lip and bone and many plastic operations in Berlin, where the condition had not been considered malignant. In 1939 the stark malignancy of the condition demanded a wide excision of the whole area, including almost all the mandible. The degree of mutilation necessitated a temporary gastrostomy for feeding purposes. By the end of 1940 soft-tissue plastics by Sir Harold Gillies had proceeded far enough to allow the patient to swallow and the gastrostomy to close. Many bone grafts failed, but ultimately, in March, 1948, there was produced a solid bony arch, which could support her tongue and enabled her to wear a denture.* She died from an independent condition 11 years after operation.

Carcinoma of Hypopharynx and Oesophagus

Hypopharynx.—Several early cases of cancer of the hypopharynx treated by lateral pharyngotomy have survived upwards of five years before recurrence took place. One case, the sister-in-law of a distinguished general, survived 24 years without recurrence, and died only a year or two ago.

Oesophagus.—Only one case of mine of cancer of the thoracic oesophagus survived five years: this man died, without recurrence, from perforation of a peptic ulcer at the junction of the presterinal skin-lined tube with his stomach. On the other hand, one case of cancer of the

*The above two cases were shown at the Clinical Section of the Royal Society of Medicine with four others on November 12, 1948, by Sir Harold Gillies (1949), to illustrate team surgery in cancer.

cervical oesophagus where a segment of the gullet was replaced by a cutaneous plastic survived 20 years.

Fibrosarcoma of Stomach, Spleen, and Splenic Flexure of Colon

At an operation performed in December, 1927, under paravertebral anaesthesia, supplemented by "splanchnic block," a fibrosarcoma of the stomach implicating the spleen and splenic flexure of the colon was removed. Five or six years later the patient became pregnant: the pregnancy was deliberately terminated by a hysterotomy, yet the patient developed a recurrence in the original upper abdominal scar. The recurrence was dealt with radically and the patient remained well for a number of years. Recurrences in the abdominal scar took place at intervals. Since 1952 I have lost sight of her, but she had survived my first operation 25 years.

Carcinoma of Body of Pancreas

A middle-aged man was operated on in July, 1927, for a cancer of the body of the pancreas; the tumour was about the size of the closed fist; it was removed, only a portion of the head of the pancreas in the concavity of the duodenum remaining. A length of splenic artery and splenic vein were removed with the tumour: the spleen was not ablated. The tumour was reported as a columnar-celled carcinoma: a lymphatic gland attached to the mass was not infected. The patient remained in excellent health for 11 years, when his general health began to deteriorate and a recurrence took place in the scar and was found on exploration to extend down to the vicinity of the previous area of ablation.

Carcinoma of Large Intestine

Cancer of the right-sided colon; carcinoma of caecum and ascending colon, implicating the abdominal wall: resection. Five years later, primary carcinoma of stomach: resection. Death one year later.—A married woman aged 45 had been under treatment at a private institution which exploited a fruit diet as a panacea for all ills. Unfortunately an extensive carcinoma of the right-sided colon was found to be present, which implicated the lateral abdominal wall; a portion of the abdominal parietes was included in the resection. Five years later the patient developed a carcinoma of the stomach, which was removed. Death followed from recurrence of the gastric cancer just over a year later, but there was no return of the cancer of the large bowel despite its initial extent.

Carcinoma of the hepatic flexure, involving lateral abdominal wall and liver.—A man aged 48 underwent in February, 1930, an excision of the right-sided colon, which had implicated the abdominal wall and the right lobe of the liver. About one-fifth of the liver was removed, including the gall-bladder. The patient died seven years later, doubtless from recurrence.

Primary carcinoma multiplex. Carcinoma of the right-sided colon involving the stomach: colectomy and partial gastrectomy. Nine years later, carcinoma of sigmoid involving bladder: resection. Three years later, Wertheim's hysterectomy for carcinoma of the cervix. Finally carcinoma of the bronchus, 19 years after her first operation.—A stout Jewess, aged 45, was operated on in the beginning of 1930. A new growth of a short right-sided colon was found to involve the pyloric end of the stomach. At the first operation, which

was determined by symptoms of intestinal obstruction, the mass was completely excluded, the appropriate anastomoses being effected between the proximal segment of the stomach and jejunum and between the ileum and the transverse colon. A few days later the mass was excised: a pathological fistula had traversed the growth from caecum to transverse colon. Almost 10 years later the patient then returned under my care with a carcinoma of the sigmoid. The tumour was removed by the Paul-Mikulicz procedure, the invasion of the fundus of the bladder necessitating removal of the upper part of this organ along with the colonic neoplasm. Some four years later Mr. Victor Bonney performed a Wertheim hysterectomy for a carcinoma of the cervix. Finally, in 1947 she reappeared with an obviously malignant gland in the left supraclavicular fossa, which proved to be secondary to a bronchial carcinoma, and the latter malady brought this story of recurrent cancer to its close.

A major aged 64 was operated on for a carcinoma of the caecum implicating a coil of small intestine remote from the ileo-caecal junction. Resection of right-sided colon and separate enterectomy of ileum were carried out. The patient remained well for nearly six years, and then developed a metastasis in the liver from which he died.

Cancer of left-sided colon and rectum. A 34-year survival after resection of a sigmoid growth.—A carcinoma of the colon occurred in a woman aged 56, for whom I performed a resection in 1924, very dissatisfied at the time with the limited amount of bowel below the tumour that I could take away in order to restore its continuity by an end-to-end anastomosis. The patient survived operation for almost 34 years, and died of causes unconnected with the primary malady.

There have been other survivals of long duration in cases with cancer of the left colon.

Carcinoma of sigmoid implicating the left tube and ovary. Resection: patient alive and well 27½ years later.—A married woman aged 56 was operated on for large-bowel obstruction on April 4, 1931. A sigmoid growth implicating the left ovary and tube was treated by a Paul-Mikulicz type of resection. The patient remained well nearly 28 years later.

Carcinoma of sigmoid implicating the abdominal wall, and left tube and ovary.—A married woman aged 60 was operated on for acute intestinal obstruction; a blind caecostomy was performed. Subsequently a malignant mass appeared, which comprised pelvic colon and left tube. The patient survived 20 years.

A 19-year survival after resection of a sigmoid growth.—A naval officer was operated on in October, 1939, for a sigmoid growth which produced acute intestinal obstruction. An exteriorization-resection method was employed. The patient remains in excellent health, more than 19 years later.

Carcinoma of the pelvic colon implicating abdominal wall, uterus, and left adnexa.—A married woman aged 55 was operated on in 1927 for acute intestinal obstruction. Laparotomy revealed a cancer of the pelvic colon: the abdominal incision was closed and a caecostomy performed. Subsequently the colonic growth was removed with a portion of the abdominal wall, the body of the uterus, and the left tube and ovary. The patient remained well till 1939—12 years—but has been lost sight of.

Carcinoma of pelvic colon, involving the abdominal wall, two coils of small intestine, and fundus of urinary bladder.—This patient survived 10 years, but has been lost sight of since the war.

A man aged 60, from whom a large abdominal mass was removed, involving the pelvic colon and many segments of small bowel. The abdominal muscles were quite considerably involved, and there was a large infected lymphatic gland. The man was alive and well eight years later.

Carcinoma of Rectum

Sister M., aged 48, a nun from a London convent, was referred to me at the end of 1929 for a huge ulcerating carcinoma of the rectal ampulla which had involved a considerable extent of the posterior vaginal wall and had perforated the posterior vaginal fornix. The vulva and perineum were constantly bathed in an offensive sanguineous and purulent discharge which leaked from the bowel and the genital passage: any attempt to remove the mass had to be preceded by some drainage of the colon.

A left inguinal colostomy was performed, and at the time of this operation it was possible to assure oneself of the absence of any metastases in the liver or of any involvement of the omentum or pelvic peritoneum. Advantage was taken of the general anaesthesia to determine the local operability of the huge growth and to decide to what extent the genital tract need be sacrificed.

The condition of rectum, vagina, and perineum rapidly improved as a result of the deflection of the faecal stream, and irrigation of the bowel and vagina soon rendered possible the extirpation envisaged. An abdomino-perineal excision of the rectum with removal of the uterus and vagina was performed, along with a small portion of the bladder: the patient made a good recovery.

All went well for six years, when a recurrence took place in the inguinal glands of the left groin. This was ulcerated and past removal by the time the patient made known her condition, and she died from haemorrhage from a large artery. There was no evidence of any abdominal or pelvic recurrence.

Carcinoma of rectum infiltrating the prostate and vesiculae seminales: abdomino-perineal excision with prostatic-vesiculectomy.—A somewhat remarkable case is the following: A man aged 35 had a huge carcinoma of the rectum, infiltrating prostate and vesiculae seminales. The latter were removed along with the rectum, and the membranous urethra was attached to the neck of the bladder over a catheter. For some weeks urinary leakage ensued from the perineal wound. Providence sometimes kindly interferes on the surgeon's side: the perineal wound finally healed, but, alas, the patient was incontinent, and for 33 years has controlled urination by means of a soft rubber catheter tied round the root of his penis. A fair amount of the time since his operation has been spent in Her Majesty's gaols, but when I met him a year or two ago he assured me that he was "going straight." It is difficult to withhold admiration from a man with a colostomy and a "garrotted" root of the penis who can indulge in games of chance and hazard with the police force. Thirty-two years have passed since his operation.

Carcinoma of rectum: abdomino-perineal excision: survival of 33 years.—A spinster aged 35 had a large

ulcerating carcinoma of the rectum, almost surrounding the ampullary portion of the rectum. Abdomino-perineal excision. Patient well 33 years later.

Canon H. was operated on for a carcinoma of the rectum in 1931: a perineo-abdominal excision was performed. He required a transurethral resection of his prostate before 1939, and underwent a successful partial gastrectomy for a bleeding ulcer during the last war. He died from old age a few weeks ago, but there had been no recurrence of his cancer in the 27 years that had elapsed.

Metastases in the Liver

The high fertility of hepatic tissue as a soil for tumour-cell proliferation has often been commented on. This fertility determines (a) a high incidence of "takes" for the initial neoplastic emboli entering the liver, and (b) an increased rate of proliferation of the cells of the established deposit.

Nevertheless, Lloyd-Davies's (1957) case of excision of the right lobe of the liver for a metastasis survived three and a half years.

The incomputable factor in cancer prognosis enabled almost 10% of palliative operations in Lockhart-Mummery's (1958, personal communication) recent collective series to survive five years, one even 10 years. The average survival was 1.7 years.

Carcinoma of the Kidney

In the case of renal carcinoma early metastases are more frequent in high-grade malignant growths. The histological grade of the tumour seems to be the most important single factor in the prognosis; nevertheless in Sir Eric Riches's series certain cases with anaplastic growths and without irradiation were known to have survived 15, 13, and 8 years after operation.

On the other hand, Riches (1958) in his series found metastases present at the time of nephrectomy in 9% of cases, and in only one, situated in the chest wall, was it possible to perform a separate excision: however, this patient was alive five years later.

Per contra, metastases may not appear until six, eight, or ten years later, as in cases reported by Clairmont, Albrecht, and Fischer, and by Broster (1923, 1930): in Broster's patient fracture of the femur from a secondary growth took place nine years after nephrectomy.

Still more remarkable was a case of my own where I had performed a nephrectomy for a hypernephroma 23 years before the man came under Reginald Murley's care with a secondary hypernephroma at the lateral end of his clavicle. Despite x-ray therapy and later surgery, the secondary tumour which had lain dormant so long now ran a relatively rapid course, and the man died within a year with multiple deposits in the lungs.

Wilms Tumour

The prognosis for a unilateral Wilms tumour is still doleful, although more recent reports, especially from the Children's Hospital, Boston, U.S.A., suggest more grounds for optimism. The prognosis for bilateral Wilms tumour is indeed devastating, although Ladd had a survival of 15 years in a patient treated by right nephrectomy with pre- and post-operative radiotherapy followed by intensive radiotherapy to the opposite kidney.

P. P. Rickham (1957), of Liverpool, reported a case of bilateral Wilms tumour treated by nephrectomy and

excision of the tumour on the opposite side followed by radiotherapy: the child was still alive five years later.

Sir Eric Riches's wonderful case, where he removed a Wilms tumour in a girl of 2½ years, has now, 24 years later, two children of her own. She had no x-ray therapy at the time of her surgery.

Osteoblastic Sarcoma and Sarcoma of Tendon-insertions

I have written so often about the "hindquarter" operation that I hesitate to make even the briefest reference to the procedure or to the patients for whom it is required. Some of the good results are doubtless due to the grading of the malignant tumour, but others seem to involve the patient's own resisting power to malignancy.

A woman seven months pregnant had an osteoblastic sarcoma of the upper end of the femur. The pregnancy was terminated and a hindquarter amputation performed. She is free from recurrence 14 years later.

A girl aged 18 had a huge tumour of the upper end of the left thigh: there was a pathological fracture of the femur at the level of the great trochanter. A hindquarter amputation was performed in the Sydney Hospital in June, 1947: the tumour was a sarcoma originating in the insertion of the gluteal muscles. The patient is alive and free from recurrence more than 11 years later.

Melanoma

The behaviour of no other tumour is so unpredictable as that of a melanoma: only rarely is a frankly malignant growth cured by excision, and it has been said of malignant melanoma that it is "virtually a death warrant." It is, however, germane to my thesis of cancer resistance that occasionally even a melanoma which has metastasized undergoes spontaneous retrogression.

James McClure (1936) records the case of a malignant melanoma in the vicinity of the eyebrow of a colleague, in whom there was already an infected lymph node in the neck. About a year after operation followed by radium treatment a recurrence appeared in the neck: this was excised and the patient survived operation without further recurrence and died 32 years after the initial surgical removal (*Brit. med. J.*, 1954).

Still more wonderful are Hogarth Pringle's (1937) two cases. In the man of 30 years there was a melanoma of the medial aspect of the left thigh, and the inguinal and lower external iliac lymphatic nodes were already invaded: he was operated on by the technique associated with Hogarth Pringle's name and remained free from recurrence 30 years later.

Even more remarkable was the girl of 17 with a melanoma of the flexure of the left elbow and with axillary gland involvement. She was alive 38 years later, having survived the anxieties of several pregnancies.

In comparison with these long survivals one of my own seems of little moment. The Seigneur of one of the districts in the Channel Islands had a melanoma of the skin of the cheek and a number of infected cervical nodes. The lesion of the cheek was widely excised and grafted: a block dissection of the neck was performed on the same side. Contrary to all expectations the man lived 20 years and died of an intercurrent malady.

A woman had a melanoma of the right buttock excised by the late Professor Grey Turner. Five years later some abdominal discomfort led to the diagnosis of appendicitis and a laparotomy revealed the presence of melanotic lymphatic nodes along the course of the external iliac vessels. The abdomen was closed and a hopeless prognosis was given. Further consultation suggested a hindquarter amputation, since it was felt that by this procedure there was a better chance of extirpating the lymph channels from the site of the original tumour in the buttock through the sciatic notch to the iliac glands. The patient has now passed six and a half years without recurrence of the melanoma.

An extraordinary case was reported by A. C. Allen (1949). A woman was first seen in 1942 with a melanoma of the right forearm, which was excised: a year later a melanomatous mass in the scar was removed. Nearly a year later, during the seventh month of a pregnancy, there was wide dissemination of secondaries. By the third month after parturition all the nodules had disappeared, except in the right groin. She was entirely well 12 years later.

Regression may take place unexpectedly in the most malignant of tumours as in the case reported by Sumner (1953). The patient was a woman of 30 who had a malignant melanoma with secondaries in the skin, breast, and inguinal lymph nodes. Some of the larger tumours were removed as a purely palliative procedure. Seven and a half years after the original tumour was first seen she was alive and well.

Intraocular Melanoma

In the case of intraocular melanomata a number of examples of long delay before metastases make their appearance have been recorded. The interval between enucleation of the eye and the appearance of metastases in the case recorded by Webb-Johnson and MacLeod (1924) was 18 years: Cairns (1922) saw orbital recurrence and a large metastasis in the scapula 18 years after enucleation of the eye: Mori (1913) encountered widespread metastases 15 years after the eye operation: Dawson (1922) and Elsberg (1928) each met with cases metastasizing at 14 years, and Wilbur and Hartman (1931) reported cases with intervals of 13, 10, and 10 years after removal of the eye. One of the longest intervals was in a case of Essex Wynter (personal knowledge) — 30 years — but the delayed interval metastasis of 32 years in Wilder's (1900) case is probably the longest recorded.

In one case of my own an unsuspected metastasis of absolutely minute size was removed from a breast, mainly to relieve the anxiety of the patient, who had been fearful of a primary mammary tumour. An eye had been removed six years before: the mammary tumour was discovered to be a melanotic metastasis by the histologist outside the operating theatre and proved to be the harbinger of abdominal metastases in the course of the next few months. I have also encountered a hepatic metastasis 12 years after eye-enucleation for melanoma.

Many more than 20 years must have elapsed before generalized dissemination closed the life of a Scottish gynaecologist who had lost an eye for an intraocular melanoma. The liver is the site *par excellence* for the recurrence in these patients with long-delayed metastases.

What fans the smouldering cinders to flame?

Conclusion

The incomputable factor in cancer prognosis! I make no boastful claim for surgical responsibility for those "successes" which I have ventured to place before you: many causal factors are concerned, not least the innate resisting power of the individual patient to cancer invasion. Sir James Barrie tells us somewhere that God gave us memory "that we might have roses in December." Those patients to whom I have referred are some of my "roses in December." I have wanted to share my roses with you. They are my sources of encouragement in the cancer fight: they are an earnest of the coming of "the rose-fingered dawn," when for the cure of cancer gross mechanical destruction and cruel mutilation of tissues shall perhaps no longer be required, nor the scorching methods and machinery of Hephaestus, the blacksmith god, or of Prometheus, who stole fire from heaven.

I will conclude with this message of confidence that was employed by Sir Alfred Pearce Gould in the closing sentence of his Bradshaw Lecture in 1910, and in the *ipsissima verba* of my old master: "We are apt to envy the astronomers who know so well the movements of the spheres, that they foretell the happenings of the universe with a precision that is the despair of workers in other branches of natural science. But with all their knowledge of these laws they cannot hasten on the day, or affect in one small circumstance the movement of a planet, or alter the destiny of a single grain of meteoric dust. But when the biologist shall know the laws that govern cell-growth, with a knowledge akin in its sweep and accuracy to that of the astronomer, he will have power, and that power will enable him to prevent, to control, and to cure cancer."

Research has taught us that that power is not so far distant from our grasp to-day.

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TREATMENT OF HYPERTENSION WITH PENTOLINUM AND MECAMYLAMINE

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Ganglion-blocking agents are now recognized as being the treatment of choice for the more severe forms of hypertension. The ideal ganglion-blocking agent has yet to be found, and in the meantime there is a temptation to turn too readily to each new preparation as it appears, without properly evaluating its predecessors.

At the present time, therefore, when new ganglion-blocking agents are continually being put at our disposal, two of which are currently being used in this department, it seemed worth while to consider what measure of long-term control could be obtained by means of pentolinum and mecamlamine, both of which have now been widely used. The present paper is based on our experience of these drugs in the treatment of 78 patients with severe hypertension between April, 1954, and May, 1958.

Selection of Patients

Of the 78 patients in the present series, 47 were judged to have malignant hypertension from the level of the diastolic blood pressure and the presence of papilloedema. The remaining 31 all had severe benign hypertension with diastolic pressures over 120 mm. Hg and lesser grades of retinopathy. Several of these patients were probably in a pre-malignant phase in view of the progressive retinopathy. We wish to emphasize that we have not included patients with mild benign hypertension and a diastolic pressure below 120 mm. Hg in this series. All patients with these criteria were treated with ganglion-blocking agents unless some contraindication to treatment was present. A raised blood urea, recent cardiac or cerebral thrombosis, and severe cerebral arteriosclerosis were all considered to be partial but not absolute contraindications. Each patient was judged on his or her