

SPECIAL ARTICLE

The treatment of melanoma at Westminster Hospital in the 20th century

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Summary

At Saint Dunstan's Coffee House in 1715 four London men met to form "A charitable proposal for Relieving the Poor and Needy and Other Distressed Persons". The proposal marked the beginnings of Westminster Hospital in London. Following the admission of the first patient in 1720, Westminster Hospital and later Westminster Medical School dominated the medical scene of London for over two and a half centuries until its closure in 1993 and transfer to the new Chelsea and Westminster Hospital.

The Hospital and Medical school are credited with pioneering work in the fields of anaesthesia, immunology, bone marrow transplantation and the treatment of cancer.

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tiary referrals for cancer and under the leadership of Sir Stanford Cade and later of Gerald Westbury and Kenneth Newton the hospital pioneered the multidisciplinary management of malignant disease exemplified by the internationally-famous Wednesday afternoon clinics where the patients' best interests were discussed and served by a multitude of surgical and medical specialists.

This paper focuses on the treatment of melanoma at Westminster Hospital in the 20th Century,

placing in perspective the latest therapeutic developments based on the genetics of this cancer.

Key words: History, melanoma, treatment, Westminster Hospital

At Saint Dunstan's Coffee House in 1715 four London men met to form "A charitable proposal for Relieving the Poor and Needy and Other Distressed Persons". The proposal marked the beginnings of Westminster Hospital in London [1]. Following the admission of the first patient in 1720, Westminster Hospital and later Westminster Medical School dominated the medical scene of London for over two and a half centuries until its closure in 1993 and transfer to the new Chelsea and Westminster Hospital.

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Gerald Westbury and Kenneth Newton the hospital pioneered the multidisciplinary management of malignant disease exemplified by the internationally-famous Wednesday afternoon clinics where the patients' best interests were discussed and served by a multitude of surgical and medical specialists [2,3]. Not uncommonly the attending Doctors, often accompanied by distinguished experts from abroad, outnumbered the patients in these clinics.

René Laënnec (1781-1826) the inventor of the stethoscope, known as the French Hippocrates, is credited with the first description of melanoma in the modern era [4,5] although this credit may be shared with his teacher Guillaume Dupuytren (1777-1835) [6].

Sampson Handley attributed the first description of melanoma in England to William Norris,

a country practitioner at Stourbridge. Norris published in 1820, 14 years after Laënnec first described melanotic growths, the autopsy findings of a case of disseminated melanoma [7].

It is not known when the first patient with melanoma attended the Westminster Hospital during its long history.

Walter George Spencer a distinguished Surgeon of Westminster Hospital and a classical scholar delivered in 1923 the Bradshaw lecture at the Royal College of Surgeons of England with the title MELANOSIS (MELANIN: MELANOMA: MELANOTIC CANCER) [8].

In his opening remarks Spencer said that *“The subject of this lecture, Melanosis, in some of its aspects has engaged the attention of former lecturers and of contributors to the (Hunterian) Museum of the College”*.

Spencer gave a full account of melanogenesis and the biochemical pathways for the formation of melanin in extraordinary detail; he referred to what today we might call the “melanocytic system”, described diffuse melanosis cutis and melanuria and recorded the case of leptomenigeal carcinomatosis in a 36-year old female patient with widely disseminated melanoma [8].

Spencer concluded that *“the general bearing of recent observations suggests the hope that further chemical research may arrive at a means of controlling the disease by therapeutic measures”*.

A quarter of a century later another enlightened Westminster Surgeon, Sir Stanford Cade, was witnessing William Spencer’s prophesy with the onset of the chemotherapy era in the treatment of cancer [9].

Sir Stanford delivered in 1960 the 78th Bradshaw lecture at the same college and the topic was again melanoma [10].

Stanford Cade graduated in Medicine from Westminster Medical School in 1917 and was elected a Fellow of the Royal College of Surgeons of England in 1923, becoming years later its Vice-President [2].

His surgical training was influenced by three surgeons on the Westminster staff - Walter Spencer (already mentioned), Arthur Evans (who performed the first recorded oesophagectomy for cancer), and Ernest Rock Carling [2].

Although a surgeon, Cade developed a multi-disciplinary approach to the treatment of cancer and explored and utilised all available treatment modalities in his time [9]. He obtained the first supply of radium from the Radium Institute in Paris in 1924. Five years later he published his

Radium Treatment of Cancer [2].

In his Dorothy Platt Memorial Lecture given at King’s College Hospital on February 28, 1956 and published in the British Medical Journal [11], Cade presented a series of 132 patients with melanoma seen at Westminster Hospital over a period of 27 years. He argued that *prophylactic block dissection in the absence of enlarged lymph nodes is always indicated when it can be done in continuity with the excision of the primary growth*. He mentioned the radio-resistance of melanoma and observed that nitrogen mustard and Haddow’s compound C.B. 1348 (chlorambucil) were of temporary value in the treatment of metastatic disease.

In his Bradshaw lecture in 1960 Cade began: *Four years ago, from a review of 132 patients seen at Westminster Hospital, I pointed out that the initial or first treatment was of vital importance, and I made a strong plea that no patient should be submitted to minor excisions, biopsies followed by delay before treatment is undertaken, or other interference, as these result in a negligible chance of survival. Since then my series of cases has increased by nearly a hundred patients, and still it is a common experience to meet patients in whose treatment every canon of our surgical creed and every surgical principle in the treatment of cancer is lightheartedly broken. Pigmented lesions continue to be excised both in doctors’ surgeries and in out-patient departments of hospitals under local anaesthesia, inadequately, and not infrequently the specimen is thrown away and with it the slender chance of the patient’s survival* [10]. This dramatic plea for the correct surgical management of the primary lesion of cutaneous melanoma remains even more valid today with the developments in pathological micro-staging and the identifiable genetic mutations of the disease that can now influence treatment.

The emphasis of Cade’s approach was in the correct surgical management of the primary lesion with adequate excision. Inevitably little attention was paid to the biology of this cancer and its subsequent course, because the prognostic significance of the level of invasion of the primary lesion as described by Clark [12] and the thickness of the tumour described by Breslow [13] had not been determined at this time. Yet, Cade observed that *Prognosis depends in most cases on the size of the tumour; the larger the tumour the worse the prognosis. There are exceptions to this, when small and apparently insignificant lesions give rise to widespread metastases*.

He believed that pregnancy did not adversely affect the course of the disease and stated: *there is*

no indication for termination of pregnancy in malignant melanoma, but neither is pregnancy a justification to alter the radicalism of the treatment indicated in a similar non-pregnant patient [10].

Regarding the management of regional lymph nodes he wrote: *In the absence of clinically detectable lymph nodes, a so-called "prophylactic" block dissection is indicated only if the site of the primary melanoma submitted to wide local excision permits the regional lymph node block dissection to be done in continuity. Where an inguinal lymph node dissection is indicated it should include the lymph nodes on the external, internal and common iliac vessels. A block dissection of inguinal lymph nodes limited to the upper part of the thigh is not merely inadequate but quite useless and should not be practised* [10].

Fearful of the scourge of in transit metastases from melanoma he wrote: *it is true that the so-called "elective" block dissection, that is in the absence of clinically detectable enlarged lymph nodes, in discontinuity does yield from time to time the unsuspected discovery of microscopic lymph node metastases. It would seem, therefore, that such an, "elective" or clinically "prophylactic" block dissection is justifiable even if it is in discontinuity, yet the final five-year survival of such cases at the Memorial Hospital (Pack, 1959) is only 20 per cent., and the possibility of spread by lymphatic permeation should be kept in mind. If a careful routine follow-up can be assured, the "elective" block dissection in discontinuity may reasonably be avoided* [10].

The horrors of fungating in transit metastases persisting for months or years made the amputation of extremities inevitable in his time yet often futile with the appearance, not uncommonly, of metastases on the stump weeks or months after this radical approach.

This experience made Cade to conclude that *Surgery, radiotherapy and chemotherapy have each an important part to play in the management of the patient with malignant melanoma. The decision as regards the choice of method and technique, or a combination of methods and the sequence of their use, depends foremost on the stage of the disease when the patient is seen* [10].

He made use of chemotherapy pre-operatively (what we would call today neo-adjuvant) peri-operatively and post-operatively (adjuvant) mainly with alkylating agents available at the time.

At the same time Gerald Westbury, and colleagues attempted high dose chemotherapy with mannitol mustine hydrochloride B.M.C. followed by autologous bone marrow reinfusion [14].

Gerald Westbury in collaboration with the

clinical measurement department headed by Dr Percy Cliffe introduced in 1960 at Westminster hyperthermic isolated limb perfusion with high dose intra-arterial melphalan for in transit metastases of the extremities This technique was further developed later by David Rosin at Saint Mary's Hospital and Meirion Thomas at Chelsea and Westminster and the Royal Marsden Hospitals [10, 15-18].

The formation of the Tumour Biology Group at Westminster headed by John Hobbs, Gerald Westbury and Kenneth Newton began to explore the new field of tumour immunotherapy in melanoma.

At the Lawson Leukapheresis Unit of this Group, plasma exchange, was part of the research programme in solid tumours; a laborious procedure that ultimately proved futile with no effect whatsoever on the course of these cancers [19].

Intralesional administration of vaccinia was attempted with topical regressions of epidermal melanoma metastases but with no impact on the natural history of the disease [20]. Percutaneous administration of BCG with or without irradiated allogeneic melanoma cells and in combination with the newly synthesized alkylating agent dacarbazine (DTIC) was studied in disseminated melanoma [21]. A number of agents with perceived immune-modulating properties such as Levamisol, Thymosin, and later Interferons were also investigated in the laboratory and in the clinic, in melanoma as well as in other cancers [22 - 27].

In 1975 I joined the Tumour Biology Group as Research Lecturer and Clinical Senior Registrar, in a post funded by a Cancer Research Campaign grant.

By this time the Westminster Hospital had a database of over 850 patients with melanoma - their demographic and some basic clinical data recorded on perforated cards (the precursor of computers) maintained by Ms Beryl Hedley-Prole and her secretarial team. The study of these patients' hospital records, retrieved from the bowels of the Hospital, provided me within a short time with a unique insight into the natural history of melanoma and a reference database that were to prove invaluable in future studies.

A turning point in the management of metastatic melanoma was the introduction in 1977 of Vindesine then a new drug belonging to the class of Vinca alkaloids.

The modest antitumour activity of the highly emetogenic Dacarbazine [21] introduced in the



Panel A

Panel B

Panel C

Panel D

Figure 1. Patient with subungual melanoma and satellite and in transit (not shown here) regional metastases referred to the Melanoma Unit at Westminster Hospital for treatment. Panels **A & B** (13.11.1990) before ablation with CO₂ LASER (provided by Mr J.M. Thomas' team) and after two years of chemotherapy (26.11.1992), based on Dacarbazine and Vinca alkaloids (Panels **C & D**).

treatment of melanoma in the early 1970's and the absence at that time of effective supportive treatments for antiemetic prophylaxis made it intolerable for the majority of patients who often abandoned treatment after one or two courses.

In contrast the tolerance by the patients of Vindesine and its comparable to Dacarbazine anti-tumour activity against melanoma permitted long and continuous treatment beyond two years with some sustained and prolonged remissions [28-30].

The formal establishment in 1981 of a Med-

ical Oncology Unit within the Cancer Services at Westminster Hospital was soon followed by a designated Melanoma Unit, the first of its kind in London and one of the first in the United Kingdom and probably in Europe.

One of the first priorities of the Melanoma Unit was to incorporate and optimise the emerging concepts of surgical staging of primary melanoma such as Clark's level of invasion and micro-measurement of tumour thickness according to Breslow's principles [12, 13]. This was achieved

with the collaboration of Professors Douglas MacKenzie and Kristin Henry of the Histopathology Department [31-34].

A standard protocol for histo-pathological reporting was agreed and with the advent of computers; data for all patients were stored into an electronic database which developed into one of the largest pools of information for melanoma of a single institution [34]. This database, privately funded, was served by the data managers Ms Marion Mountain and Ms Thayarathy Nadarajah.

Through the gallant efforts of the late Dr Catherine Griffiths a patient of the Melanoma Unit [35], with funds which she and her family raised, the Catherine Griffiths Cancer Research Laboratory was established in 1986 to study at the cellular level the optimal use of anticancer agents in parallel with their introduction in the clinic. Research conducted by Dr Andrew Photiou PhD and a team of undergraduate and graduate scientists investigated a number of compounds with anti-tumour activity [36,37] focusing primarily on drugs targeting tubulin, such as Vinca alkaloids and Taxanes [38].

The treatment philosophy of the Melanoma Unit rested on three principles:

- The length of treatment is a determining factor in the outcome
- No cancer is effectively treatable, let alone curable, with a single agent no matter how active this agent may be against a specific tumour
- Translation of existing knowledge into effective action.

The emergence, based on these principles, of systemic treatments and chemotherapy protocols of the Melanoma Unit at Westminster Hospital has been discussed at length elsewhere [39-44].

In addition to isolated limb perfusion mentioned above and optimised palliative radiotherapy with sophisticated megavoltage equipment

(Drs Kenneth A. Newton; Iain W.F. Hanham and Robert H. Philips) new avenues of loco-regional treatments were explored for suitable lesions with the use of CO₂ LASER.

LASER ablation in combination with systemic treatments proved valuable for small superficial metastases outside the field of a limb perfusion or in anatomical areas where perfusion was not possible. Patients referred from other centres (Figure 1) who had refused amputation for subungual melanoma were offered the option of tumour ablation of the primary site with CO₂ LASER [44,45].

The closure of Westminster Hospital in 1993 and the relocation of its Melanoma Unit within the Cancer Services at Charing Cross Hospital caused an inevitable disruption of its basic and clinical research programme in the new environment. Particularly problematic proved the relocation of the *Catherine Griffiths Cancer Research Laboratory*, work however continued with a re-orientation of research into the genetic aspects of melanoma [46,47].

Despite the development in the 1990's of specialist Melanoma Units in other teaching Hospitals in London and the provinces, the original Melanoma Unit of Westminster Hospital continued after its- relocation at Charing Cross, to attract tertiary referrals in ever greater numbers.

The dawn of the 21st century saw new and exciting developments in the field of genetics of melanoma that were beginning to transform radically the therapeutic horizon of this once untreatable cancer [48]. A justified surge of optimism is attracting new players in the field with the hope that the conquest of this dreadful disease will soon be complete.

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