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PUSHING THE FRONTIERS OF RADIOBIOLOGY: A SPECIAL FEATURE IN MEMORY OF SIR OLIVER SCOTT AND PROFESSOR JACK FOWLER: COMMENTARY

An appreciation of the science and philanthropy of Sir Oliver Scott, founder of the Gray Cancer Institute

BARRY D MICHAEL, PhD

Formerly of the Cancer Research UK Gray Cancer Institute, Mount Vernon Hospital, Northwood, UK

Address correspondence to: Dr Barry D Michael

E-mail: barry.mchl@gmail.com

ABSTRACT

This Commentary focuses on the landmark paper about hypoxia in radiotherapy by Gray, Scott et al published in 1953. By then, it was known that hypoxic regions in tumours could make them resistant to radiation treatment and that this was a possible cause of failure. The paper proposed that oxygen breathing could substantially decrease this resistance without incurring significant additional damage to normal tissues, thus reducing the likelihood of recurrence. Although the paper's supporting data were in some respects incomplete, the case it made was convincing and it prompted pilot clinical trials that combined radiotherapy with oxygen breathing, including under elevated pressure. Research into tumour hypoxia and strategies to overcome its adverse effects soon expanded and entered full clinical trials. Meta-analysis of their results showed improved outcomes in accord with the original proposals of Gray, Scott et al. A secondary result of their 1953 work was the founding at Mount Vernon Hospital of what later became Cancer Research UK's Gray Cancer Institute. This project was initiated by Oliver Scott and construction of the new laboratories was funded by a donation that he provided

INTRODUCTION

The achievements and philanthropy of Sir Oliver Scott, MD, FRCR, who died on 4th November 2016, have been commemorated in the scientific literature^{1,2} and in the press. He had read natural sciences at King's College, Cambridge, then medicine at St Thomas' Hospital, London. He worked for a time with JS Mitchell at Addenbrooke's Hospital, Cambridge on a project to see whether synthetic vitamin K could be used to sensitise tumours to radiotherapy. During national service as a surgeon-lieutenant in the Royal Naval Volunteer Reserve, Oliver gained experience of oxygen physiology and high-pressure oxygen administration for submariners. He developed the concept that high-pressure oxygen might be combined with radiotherapy to sensitise hypoxic regions of tumours to radiotherapy. This was intended to overcome their radioresistance which was suspected to be a cause of recurrence. He discussed the idea with experts in cancer treatment, but it was only Dr LH Gray, who was Deputy Director of the MRC Radiotherapeutic Research Unit at Hammersmith and its Director of Research, who understood and appreciated the concept. Oliver worked with Hal Gray and his

colleagues at Hammersmith and this led to their landmark publication in 1953.

TUMOUR HYPOXIA: LAB TO CLINIC

Although the paper of Gray, Scott et al³ has proved to be pivotal to the field of hypoxia and cancer therapy, Oliver Scott, being modest by nature, would have been unlikely to make such a strong claim. However, in a historical review (OCA Scott, private communication, 1993 Annual Report of The Cancer Research Campaign Gray Laboratory) he did venture that, "If citation is a fair measure of success, it [their 1953 paper] must be judged to have done rather well." This was because by then, some 40 years after publication, "... it was *still* [his italics] quoted 20 times [per year] in the world literature." He discussed the several factors that appear to have worked for, or against, the paper's eventual place in the literature and these can be summarised as follows:

(a) By 1953, the topic was certainly not new.^{4,5} From 1904, various reports had shown that blood flow and/or oxygen status could affect the radiation response of normal tissues. By the 1930s, it had been found that blood supply

and availability of molecular oxygen influenced the radiation response of cells in a tumour.⁶ JC Mottram had applied this finding to tar warts in mice and found that the survival of tumour cells increased with their distance from the blood supply.⁷ He attributed this resistance to hypoxia.

(b) Gray and Scott had not been the first to propose the administration of oxygen during radiotherapy. JW Hollcroft had previously shown that oxygen breathed at one atmosphere pressure enhanced the radiation responsiveness of transplanted tumours in mice.⁸ At about the same time and unknown to Gray's group, W Dittrich had been studying tumours in mice and found that breathing two atmospheres of oxygen enhanced the response.⁹

(c) The measurement of the relationship between oxygen concentration and cellular radiosensitivity ("K-curve") had been key to Gray and Scott's prediction of a therapeutic gain. Although earlier studies using plant and insect systems had indicated a plateau at high concentrations, this was the first successful study with mammalian cells and confirmed that they showed a plateau. Up to this point, Gray and Scott's proposal for oxygen breathing during radiotherapy had not been generally accepted. The determination of the shape of the mammalian cell K-curve enabled a more convincing case to be made: oxygen breathing would increase cell kill in tumour regions that were poorly supplied with oxygen, but would not do so in well-oxygenated normal tissues because their response was already at a maximum on the plateau.

(d) The paper's case for a therapeutic gain was also supported by its account of Oliver's experiments on tumours and normal tissues in mice. These compared responses breathing air with those while breathing oxygen at one or three atmospheres pressure. There were many difficulties, including an outbreak of disease in the mouse colony. Following certain other adverse events described below, too little time remained to optimise tumour size, oxygen pressure and radiation dose to allow sufficient data to be obtained for proper statistical analysis. Due to these limitations, the mouse data were preliminary. However, the effects observed on tumour regression, when compared with those on skin and hair, were consistent with a therapeutic gain from breathing oxygen.

Pilot clinical studies with oxygen breathing during radiotherapy were performed at one atmosphere on skin tumours (four cases) by KA Hultborn and A Forssberg¹⁰ and at three atmospheres on breast and lung tumours (eight cases) by I Churchill-Davidson et al.¹¹ These studies followed soon after the publication of Gray, Scott et al³ and both groups had focused on the paper in their rationales. Both studies concluded that the results of their studies warranted further work.

UNFORESEEN EVENTS

The adverse events occurring as a background to the experimental work on hypoxia at Hammersmith were to have wider consequences. There had been seemingly irreconcilable differences between Gray and the Unit's Director over a rearrangement of the overall programme. In particular, Gray was deeply

concerned that, without consulting him, it had been decided to start neutron radiotherapy before conducting the radiobiology experiments that had been planned to establish safe dosage for patients.

The MRC set up a committee to resolve matters. Although the committee recognised Gray's concerns, he was forced to resign. In addition, a reconsideration of the structure of the Unit was recommended. This took place on the day after Gray had received the Silvanus Thompson Memorial medal of the British Institute of Radiology, of which he was a past President. He was banned from the Hammersmith site for 6 months, apart from access over one weekend to remove his papers. In protest over the outcome, three of Gray's colleagues resigned immediately, including Oliver Scott and Jack Boag. The biographies of Gray written by M Yamasaki et al¹² and S Wynchank¹³ describe these events.

Gray was dismissed in May 1953, before all of the experimental work for Gray, Scott et al³ was complete. The authors decided that they should publish what they had achieved so far. It was intended to be an interim report that would also support Gray and his reputation. The paper was submitted to the British Journal of Radiology and accepted for publication in September 1953.

OUTCOMES

As is evident from the reports in this Special Issue, the decision to proceed with publication of the interim report was vindicated by the research that it stimulated (e.g., chemical radiosensitisers¹⁴) and by the results of clinical trials of the various strategies that were developed to overcome hypoxic radioresistance of tumours. Meta-analysis of the clinical trial results⁴ confirmed the original prediction by Gray, Scott et al³ of a therapeutic gain. [Figure 1](#) updates the remarkable citation history of their paper and shows a progressive rise to about 50 citations per year, reflecting the ongoing level of activity in the field.

In the 1993 historical review referred to above, Oliver describes a secondary effect of the production of the 1953 paper. Persuaded of Hal Gray's genius, he felt justified to found a new laboratory for Gray and his colleagues to continue their work under Gray's Directorship. The British Empire Cancer Campaign (BECC, later Cancer Research Campaign (CRC) which merged with the Imperial Cancer Research Fund to become Cancer Research UK (CRUK) in 2002) agreed to build and own its first laboratory. This was made possible by a substantial donation to the BECC; while the donor wished to remain anonymous, this was in fact the first of what was to become significant and generous philanthropic support for radiobiology from Oliver and the Trust named after his father and formed in 1951. Not only was the generosity of Oliver and his family pivotal in founding what was to become the Gray Laboratory, there were later further, very substantial donations from the Sir Samuel Scott of Yews Trust to support both laboratory and clinical research at Mount Vernon, as well as regular contributions to radiobiology conferences and to support individual researchers over many years. The Trust continues to be a generous donor to diverse medical research charities. The Chairman of BECC, the physician Lord Horder, had agreed in

Figure 1. Citation history of Gray, Scott et al.³ Data from Web of Science Core Collection (solid line). A trendline (dashed) is included.

principle to support a new laboratory during a short interview with Oliver. This required a change in the BECC constitution. The laboratory was built close to Mount Vernon Hospital and its cancer centre, where Gray's work as a research physicist from 1933 to 1946 had been supported by the BECC. It was completed in 1956 and officially opened in 1957. After Gray's death in 1965, Oliver was appointed Director, but had to resign in 1969 for health reasons. He was succeeded by Jack Fowler, followed by

Juliana Denekamp. In 2001, under the Chairmanship of Stanley Dische, the Gray Laboratory was renamed the Gray Cancer Institute to reflect its growth. An internal review found that to secure the Institute's future it should move to an environment with a supportive research base. In 2004, Gillies McKenna was appointed its Honorary Director and in 2008 the Institute relocated within the CRUK/MRC Oxford Institute for Radiation Oncology that he directs.

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