

Chapter 1. Eponymous Lectures

WOOLMER LECTURE

The Woolmer Lecture is dedicated to the contribution that Professor Ronald Woolmer made to the formation of a multidisciplinary approach to biomedical engineering.

Ronald Woolmer, an anaesthetist, was instrumental in convening a meeting at the Royal College of Surgeons, London, of colleagues interested in the many aspects of the evolving field of engineering applied to medicine. Approximately 40 people were present at this meeting which was held shortly after Ronald Woolmer and Alfred Nightingale (a medical physicist) attended the founding meeting of the International Federation of Medical Electronics in Paris during 1959. It was subsequently agreed that the group should hold regular meetings, and so the Biological Engineering Society (BES) was formed with Ronald Woolmer as the first President and Alfred Nightingale as Hon. Secretary. Unfortunately, Ronald Woolmer died about 2 years after the formation of the BES and it was subsequently agreed that a memorial lecture would be sponsored to recognise his tremendous foresight.

The Institute, as a successor organisation to the BES, is honoured that Professor A Unsworth will deliver the Woolmer lecture.

Hip Joint Replacement

Professor A Unsworth

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Survival data on artificial hip joints is based on designs which were current 25 years ago and shows that the best designs of that time gave 75% survival at 20 years. Since then there have been many developments in materials and designs all aimed at reducing wear. Wear is important because it is widely believed that joints fail due to loosening caused by the body's reaction to wear debris and there is evidence that there is a threshold level of debris (depending on the material) which causes failure.

Some of the developments include cross-linking the UHMWPE acetabular components, alternative sterilisation methods, the use of metal-on-metal joints, ceramic-on-ceramic and compliant surfaced joints designed to produce fluid-film lubrication and hence reduced wear. Measured laboratory wear rates are now between one-tenth and one-hundredth of those of the joints from the 1960's measured to have 20 years survival. This might imply a service life in current designs of between 200 and 2000 years. Are we in danger of over-engineering our joints?

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SPIERS PRIZE WINNER LECTURE

Near infrared Raman spectroscopy for the classification of epithelial pre-cancers and cancers

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Introduction The primary requirement for successful treatment of cancer is early detection. Current methods of detecting malignancies rely upon surveillance of at risk populations or on diagnostic investigations following presentation with suspicious symptoms. By the time symptoms are present tumours are usually of a significant size, and it is often too late to facilitate a full cure. The majority of malignancies originate in epithelial tissue, usually found lining the surfaces of organs. These epithelial cancers are called carcinomas. They are especially of interest because they develop over relatively long timescales on the surface or lining of an organ prior to invasion into deeper tissues. Endoscopic access can often be achieved, thus making the surveillance or screening of at risk populations possible. Furthermore the process of carcinogenesis in many epithelial tissues, although not fully understood, is known to frequently include a pre-malignant state. If this microscopic cellular change can be detected then early treatments, likely to be less damaging and more successful, can be performed.

The 'gold standard' for detection of malignancies and pre-malignancies is excisional biopsy followed by histopathological analysis. This technique relies upon sectioning tissue less than one cell thick (<10 microns), staining with haematoxylin and eosin (H & E), and viewing under a conventional light microscope. The analysis depends mainly on the subjective recognition of tissue morphology and architectural patterns. There are significant difficulties in obtaining an accurate diagnosis using the 'gold standard'. Firstly, the selection of biopsies for the detection of invisible microscopic surface lesions must rely upon a blind targeting protocol. This can lead to a high probability of missing abnormal tissue and large numbers of normal samples will be generated.

A study in the oesophagus following 16 patients undergoing surveillance for Barrett's oesophagus demonstrated that even a rigorous sampling protocol will be likely to miss abnormal lesions previously found in the organ. [i] Secondly, in the analysis of pre-cancerous lesions there are often high levels of discrepancy between pathologists, due to the subjective nature of histopathological analysis. Studies grading dysplasia in ulcerative colitis and colonic adenomas produced an overall agreement between any two pathologists ranging from 42% to 65%. [ii, iii] Similar studies demonstrated agreement of between 58% and 61% for oesophageal dysplasia [iv] and 54% for laryngeal dysplasia. [v] Furthermore the removal of tissue samples can have a damaging effect on the function of the organ, especially in sensitive organs like the larynx, where permanent loss of voice may result.

Histopathological examination of biopsy samples relies upon the subjective assessment of tissue architecture, which is likely to exhibit abnormal changes at a later stage than sub-cellular biochemical changes. Evidently, the development of a technique,

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enabling objective, non-invasive qualitative biochemical analysis of tissue would be of great value. The potential of Raman spectroscopy to distinguish between normal and malignant tissue has been demonstrated by a number of authors.

[vi, vii, viii, ix, x]

Objectives The goal of this study was to evaluate the potential for near-infrared (NIR) Raman spectroscopy, a highly specific optical analysis technique, to interrogate epithelial tissue biochemistry with the objective of distinguishing between normal and abnormal tissues.

The long term aim being to classify or discriminate between the pathological states of different epithelial tissues and thus demonstrate a future capability for in vitro classification and in vivo detection of early epithelial malignancies.

Six different epithelial tissues from the larynx, tonsil, oesophagus, stomach, bladder and prostate have been studied. Carcinomas develop in each organ from three distinctly different types of epithelial cells. This has enabled evaluation of Raman spectral analysis as a generic tool for detection and classification of disease in squamous, transitional and columnar epithelial cells.

Methods The samples were collected and snap frozen in liquid nitrogen following written consent from patients undergoing routine endoscopic investigations. Each sample was sectioned and histopathologically classified by a team of three consultant histopathologists. Rigorous histopathological protocols were followed with only homogeneous samples (non-mixed pathology) with a consensus of histopathology opinion being retained for analysis. Furthermore, the full spectrum of malignant disease found in each organ has been studied. This was to remove any bias likely to be

found in studies only comparing normal with cancerous tissue, i.e. the extreme pathologies.

A commercially available Raman microspectrometer has been optimised for biological tissue measurements (Renishaw System 1000) utilising a stable, high power, 830nm semiconductor laser as the excitation source.

Spectral diagnostic models for each organ have been constructed from large numbers of tissue spectra. Multivariate statistical analyses of the datasets were used to classify samples into pathology groups using supervised training from the consensus of histopathology.

Results Principal component fed linear discriminant models demonstrated excellent group separation, when tested by cross-validation. Larynx samples, with squamous epithelial tissue, were separated into three distinct groups with sensitivities ranging from 86 to 90% and specificities from 87 to 95%. Bladder specimens, containing transitional epithelial tissue, were separated into five distinct groups with sensitivities of between 78 and 98% and specificities of 96 to 99%. Oesophagus tissue can contain both squamous and columnar cell carcinomas. A three group model discriminated the columnar cell pathological groups with sensitivities of 84 to 97% and specificities of 93 to 99%; and an eight group model combining both columnar and squamous tissues in the oesophagus was able to discriminate pathologies with sensitivities of 73 to 100% and specificities of 92 to 100%.

Conclusion It is likely that any overlap between pathology group predictions will have been due to a combination of the difficulty in distinguishing between pre-cancerous states using the 'gold-standard' histopathology and the fact that there is believed to be a continuum of biochemical progression from the normal to the diseased state. Further work is required

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to develop NIR-Raman spectroscopy into a clinical instrument. However, the initial findings demonstrate the facility of the technique to provide a non-invasive, real-time diagnostic tool for the objective and repeatable detection and classification of early-cancerous changes in epithelial tissues.

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DURHAM LECTURE

The sun has got his hat on

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In the first half of the last century the sun was perceived as benign and sun exposure generally associated with good health. This view gradually changed over the past 50 years to the extent that sun exposure is now widely regarded as detrimental to health. Campaigns by public health and other agencies encourage us to avoid unnecessary sun exposure, whilst the cosmetics industry is now incorporating ultraviolet (UV) filters into topical products intended for daily use in the belief that year-round sun exposure in the UK needs to be controlled.

Provided the daily use of topical products containing UV filters does no harm and considering the potential health benefits, manufacturers and others may argue that these products are in a small but measurable way providing a positive impact. Indeed, there is some limited evidence from studies in sunny countries indicating that daily application of a high sun protection factor (SPF>15) sunscreen may prevent squamous cell cancer and contribute to the prevention of solar elastosis.

Active ingredients in sunscreens have favourable toxicological profiles and, in general, do not pose a concern for human health. However it is known that, although uncommon, ultraviolet absorbers in sunscreens are now the commonest cause of positive photopatch tests. Concern has been raised about systemic absorption of sunscreens after topical application, cellular toxicity, impact on vitamin D synthesis and estrogenic activity, although the

significance of these reports to human health consequences of sunscreen use remains circumspect.

Furthermore the majority of case-control studies on cutaneous malignant melanoma report significantly higher risks among sunscreen users. Although these studies could be taken to suggest an increase in the risk of melanoma due to sunscreen use, they are difficult to interpret because of problems of positive and negative confounding.

So whilst these concerns are insufficient to cease using sunscreens as part of a sun protection strategy, they do suggest that there is an optimal use of topically-applied UV filters beyond which the benefit of further use may be both unnecessary and unjustified. This presentation will explore where this point may be in the context of people living in countries not known for their sunny climate, such as the UK.

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