computed tomography demonstrated extensive small airway plugging with a ''tree-in-bud'' pattern associated with early lower lobe bronchiectasis (fig. 1). A clinical diagnosis of DPB was made and he commenced 500 mg of erythromycin twice daily. Over the course of the following 6 months, he experienced a dramatic improvement; his productive cough and rhinnorhoea resolved completely, exercise tolerance returned to normal, and lung field infiltrates on plain chest radiograph resolved while his FEV1 and FVC improved to supra-predicted values (fig. 2). During this period, his ICS/LABA therapy was not altered. Over the following period the erythromycin dose was reduced to 250 mg twice daily, but within a few weeks he had experienced a recurrence of symptoms and a small, but persistent, drop in FEV1. This improved on increasing the erythromycin dose to 500 mg twice daily, which he remains on at the present time. Although the patient did not undergo surgical lung biopsy, the clinico-radiological presentation and response to macrolide therapy is highly consistent with a diagnosis of DPB.

This case highlights the importance of considering this rare illness in patients of non-Asian origin who present with difficult airways disease. Without appropriate macrolide therapy, the patient faces the prospect of a disease characterised by inexorable decline and early death; however, with appropriate therapy the patient can expect a far better prognosis and quality of life.

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STATEMENT OF INTEREST

None declared.

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Cannabis and lung cancer

To the Editors:

The elegant and eminent study by ALDINGTON *et al.* [1] of the Cannabis and Respiratory Disease Research group is to be welcomed at a time when, as the authors rightly point out, there are many suggestive case studies and clinical series on lung cancer, and indeed other tumours, occurring particularly at younger ages in past and present smokers of cannabis. The authors' careful methodology and succinct summary of much of the relevant literature in relation to this subject is a relevant and timely addition to the literature, particularly in the context of increased interest in this subject in both lay and professional circles.

The point made by ALDINGTON *et al.* [1] in relation to the lack of research into the molecular underpinnings of cannabis-related oncogenesis is particularly relevant at a period in research history when the molecular bases of disease have received unprecedented attention. It is to be expected that their elucidation might lead to better understanding of the mechanisms of common disorders including cancer and, in time, improved therapeutics. Interestingly, cannabis use also featured in our case review of malignant and pre-malignant disorders of the cervix uteri in an addicted population [2].

From the vast published literature on cannabis, several main pathways emerge as being most relevant to oncogenesis in addition to the obvious factors related to carcinogen content and smoking technique. Cancer is defined as a disorder of uncontrolled cell growth, and mechanisms of DNA toxicity and dysregulated DNA replication are its genetic hallmarks. Damage to DNA, therefore, as might occur with free oxygen- and nitrogen-centred radicals, is relevant to molecular pathogenesis. Indeed, normal signalling of the endogenous cannabinoid ligand, anandamide, *via* the oxidative damage of guanine to 6-oxoguanine and its routine restoration by base excision repair has been described in cultured cells [3]. Free radical generation both at receptor binding (S.T. Carney, North Carolina Central University, Durham, NC, USA; personal communication) and by mitochondrial uncoupling [4] has been demonstrated.

Cannabis is widely acknowledged to stimulate the mitogen activated protein kinase (MAPK) pathway, which is a major stimulant of developmental and malignant cell growth. MAPK dysregulation has been identified clinically in tuberous sclerosis, neurofibromatosis and acute myelomonocytic leukaemia (AMML), and greatly increased incidences of AMML have been identified in paediatric populations after *in utero* maternal exposure to cannabis [5]. There are reports in sub-acutely ''stoned'' animals (a use pattern reminiscent of that seen in many patients) that heavy cannabis use is associated with severe telomeric (end-chromosomal) damage in male germ cells [6]. The burgeoning literature on telomeres demonstrates that this field is intimately involved in pathways of both ageing and tumourigenesis. Key DNA repair enzymes topoisomerase II [7] and Rad51 have been shown to be inhibited by cannabinoids. Germ line chromosomal abnormalities in addition to MAPK stimulation constitute putative pathways of inheritable oncogenesis.

Reports that cannabis is associated with severe dental disease [8], osteoporosis [9] and mental illness [10], together with unpublished studies from our clinic showing accelerated vascular ageing in heavy cannabis smokers, suggest that cannabis may be modifying the ageing process itself. Ageing is of course the leading risk factor for most nonpaediatric tumours. It is well known that there is extensive cross-talk including heterodimerisation at the cell membrane between the cannabinoid type 1 receptor and other guanosine triphosphate-coupled receptors including adrenergic receptors which are well known to be involved in ageing processes. Cannabinoids are also known to induce cell cycle arrest, senescence and apoptotic cell programmes. Senescence is increasingly associated with oncogenic induction [11]. Cannabis has well-recognised immunosuppressive properties [12] that are likely to be of relevance to tumour surveillance activities of the immune system, both in the pre-clinical stages and in the metastatic spread of advanced disease.

Sleep disturbances are clinically prominent and highly problematic in cannabis-dependent patients and imply significant disruption to the cellular circadian genetic clock mechanisms [13]. Circadian disruption has been linked to acceleration of the ageing process in mammals [14]. Finally, it is not widely appreciated that histone deacetylases, central regulators of the epigenetic code, have been shown to be major regulators of ageing [15] (including neurogenesis [16]), psychopathology [17], addiction [16] and cancer [18].

In summary, while cannabinoids, and especially smoked inhaled cannabis, are strongly implicated in oncogenesis by several molecular pathways, there are multiple leads that might prove useful for mechanistic exploration and perhaps, one day, therapeutic exploitation of the cannabinoid system.

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STATEMENT OF INTEREST

None declared.

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