

A man before his time: Russell's insights into nicotine, smoking, treatment and curbing the smoking problem

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ABSTRACT

Background and aims This narrative review aimed to provide a brief overview of five key research 'classics' produced by the innovative and radical thought leader, Professor Michael Anthony Hamilton Russell (1932–2009), drawing upon his other work wherever feasible. **Methods** Narrative review. From more than 250 publications, we selected papers we considered seminal texts, published in 1971, 1976, 1978, 1979 and 1991. **Results** Russell was among the first researchers to explain that smoking was a dependence disorder caused by the drug nicotine decades before this was recognized formally. He therefore saw quickly the importance of delivering nicotine in a less harmful format as a way of controlling nicotine withdrawal when stopping smoking, first studying nicotine gum. In addition to pharmacotherapies, Russell's research also explored the role of behavioural support, particularly the role of general practitioners (GPs), alone as well as supported by specialist clinics; this research underpinned initiatives in England to reimburse doctors for giving advice to smokers, and to provide a national network of smoking cessation services. Research on nicotine uptake from other delivery systems and routes led Russell to theorize that the speed and dose of delivery impacted upon the effectiveness of a product to act as a substitute for smoking. He commented on the addictiveness of the high nicotine boli delivered in quick succession when smoking cigarettes and argued that alternative recreational nicotine delivery systems would need to be promoted actively to smokers in order for them to compete with cigarettes, a forerunner for contemporary debates on electronic cigarettes. **Conclusions** The legacy of Russell's landmark research is seen in present-day nicotine science, policy and discourse.

Keywords Brief advice, dependence, M.A.H. Russell, nicotine, smoking, tobacco.

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Professor Michael Anthony Hamilton Russell (1932–2009) was an innovative and radical thought leader who provoked and inspired many researchers to dedicate their careers to tobacco control research in the United Kingdom. Russell studied medicine at the University of Oxford and then undertook his clinical training at Guy's Hospital in London. Russell began his smoking research a half-century ago in 1967, while training to be a psychiatrist at the Maudsley Hospital in London, first carrying out a pilot trial on electric aversion therapy and then securing a Medical Research Council project grant, with the help of Griffith Edwards, to conduct a full trial. In July 1969, Russell joined the then Addiction Research Unit, Institute of Psychiatry in London as a research worker, thinking it would only be for a few years, but he remained

there (and its successor, the National Addiction Centre) until the end of his career.

Russell published his first paper, which was on electric aversion treatment for smoking, in 1970 in the *British Medical Journal* [1]. He then became a prolific writer, publishing more than 250 manuscripts across the range of tobacco control and nicotine research, until 1998, when he was forced to retire with early Alzheimer's disease. Russell's work spanned four decades and covered such diverse topics as motives for smoking, the relationship between price and consumption, measurement of smoke intake for active and passive smoking, nicotine dependence, pharmacological and behavioural treatments for stopping smoking and safer cigarettes. In most of these areas, Russell was the 'first in the field'. Here, we have selected five

publications to discuss in detail, drawing upon details of other examples of his published research where feasible within the constraints of this short paper.

The first of Russell's papers that we have chosen to discuss was entitled: 'Cigarette smoking: natural history of a dependence disorder' published in 1971 [2]. The importance, insights and thoroughness of this paper at such an early career stage was phenomenal, and a forerunner of much of what was to follow. In this paper, Russell set out the case for regarding cigarette smoking as a dependence disorder that was not only psychological, but also physiological, with nicotine as the drug of dependence. He achieved this more clearly than anyone had done previously, and the paper should therefore have been a gamechanger. He explained that, over recent centuries, 'no population has dispensed with one form of tobacco use without replacing it by another' and 'once experienced, nicotine use has continued in populations as it does in individuals'. It is in this paper that we find his famous quotation: 'if it were not for the nicotine in tobacco smoke people would be little more inclined to smoke cigarettes than they are to blow bubbles or light sparklers'. At that time, this paper did not cause a sea-change in thinking world-wide, but a few researchers began to follow him and build upon his work (e.g. [3]). It took several more decades before the importance of the role of nicotine in tobacco dependence was to be recognized formally [4,5].

In recognizing the importance of nicotine Russell was sensitive to its potential as a therapeutic aid, the focus of the second paper we have chosen to cover. This was entitled: 'Effect of nicotine chewing gum on smoking behavior and as an aid to cigarette withdrawal', published in 1976, and was a double-blind placebo-controlled cross-over trial of 2-mg nicotine gum [6]. Russell first heard of nicotine chewing gum in 1971 at the 2nd World Conference on Smoking and Health (2018 sees the 17th World Conference on Tobacco and Health in Cape Town, the city where Russell was born). The paper aimed to test the therapeutic value of nicotine gum in dependent smokers and its impact upon smoking behaviour, including the effect on nicotine and carbon monoxide intake. This elegantly designed trial included 43 smokers who were given either active or placebo gum, first when they were smoking, and then secondly when trying to stop. This study also incorporated methods developed under Russell's stewardship to measure nicotine levels in blood and urine (e.g. [7]), along with carboxyhaemoglobin (COHb) to validate abstinence. In smoking cessation trials today, it is a requirement to validate self-reported abstinence with biochemical measures. This requirement and other outcome criteria for smoking cessation trials were set out by a group of academics as the 'Russell Standard' in honour of Russell [8]. Russell also utilized these measures to assess, for the first

time, smoke intake in passive [9] as well as active smokers, and also those using different doses of nicotine gum [10].

The cross-over trial was important for several reasons: (i) data from measures of blood nicotine and COHb levels illustrated the importance of separately assessing smoke and nicotine intake; (ii) the paper led to subsequent correspondence on appropriate cut-off levels for COHb [11]; (iii) a discussion of the placebo effect was included; (iv) Russell subsequently acknowledged early errors in the trial, wherein they 'thought that if we simply gave it to smokers it would "cure" them' and 'we also gave it for too short a period (only six weeks in our first trial) and terminated its use too abruptly' [12], and insufficient dosage was also highlighted as a key factor in the low success rates, all of which are errors repeated frequently and discussed subsequently [13,14]; and (v) the 1 year follow-up results were promising, and led to the first randomized double-blind placebo-controlled trial of nicotine gum [15]. At about this time, Russell was developing his theory about how the different nicotine delivery systems affected their ability to act as a substitute for smoking, and he next suggested the nasal route [16], which led eventually to the development and evaluation of a nasal nicotine spray. Today there are eight different licensed nicotine replacement therapy (NRT) delivery systems and more than 150 randomized controlled trials, many of which spawned from Russell's early research in this area [17].

Having identified the capacity of nicotine replacement therapies to help smokers to stop smoking, Russell then turned his attention to behavioural interventions from health professionals, particularly general practitioners (GPs). In the third paper we have chosen to discuss, 'Effect of general practitioners' advice against smoking', published in 1979 [18], Russell aimed to test the impact of simple firm advice (brief advice) to stop smoking given routinely by GPs. In this, the first evaluation of such advice, 2138 smokers attending 28 GP surgeries in London were randomized (in 4 weeks) and allocated to one of four groups: (i) a control group who did not receive an assessment or intervention; (ii) a control group who received only an assessment (to control for questionnaire effects); (iii) an intervention group who were advised by their GP to stop smoking; and (iv) an intervention group who were advised by their GP to stop smoking, given a leaflet and told they would be followed-up. The four-page leaflet contained information about 'how you can give up smoking', issued by the Department of Health and Social Security. The advice to stop smoking was described as 'simple but firm', and given in the doctors' own style for 1–2 minutes during a routine consultation. It is important to remind readers that nicotine replacement was not available on prescription at the time the study was conducted, and although Russell established his own stop smoking clinic, such clinics were rare at this time.

Patients provided follow-up data after 1 ($n = 1884$, 88%) and 12 months ($n = 1567$, 73%). The proportions who made a quit attempt during the first month were (i) 10.2%, (ii) 9.2%, (iii) 11.2% and (iv) 17% in the four groups, respectively. The proportions who stopped smoking during the first month and were still not smoking 12 months later were 0.3, 1.6, 3.3 and 5.1%, respectively. Quit rates were significantly higher in the advice groups because more people tried to quit. They concluded that brief advice motivated more people to try to quit, rather than increasing the success rate of those who tried. Russell recommended that GPs adopt this simple intervention to trigger a quit attempt in every smoker they saw. Twenty years later, in England, the 1989 White Paper *Smoking Kills* [19] recommended that: 'All health professionals working in hospital or community settings should provide simple advice to give up smoking on as routine a basis as possible'.

During the past 40 years, as pharmacology and behavioural support for smoking cessation became available, the content of brief advice has evolved slightly. In some countries such as the United States, it developed into a longer 'brief intervention' known as the five 'As' (ask, advise, assess, assist and arrange). Despite widespread acceptance that assisting smokers to quit is an essential part of a GP's role, brief interventions were implemented poorly [20,21] and health professionals were distracted by assessing if smokers were motivated to make a quit attempt. One of the more recent influential studies in this area is a systematic review and meta-analysis to assess the effects of brief physician advice to stop smoking and offer of assistance on attempts to stop and quit success [22]. They concluded that physicians may be more effective in promoting attempts to stop smoking by offering assistance to all smokers, instead of advising smokers to quit and offering assistance only to those who express an interest in doing so. In the United Kingdom, tobacco treatment experts have accordingly renamed brief advice as 'very brief advice' (VBA: ask, advise and act). The routine provision of VBA is recommended in several National Institute of Clinical and Public Health Excellence (NICE) guidelines (e.g. [23]) and, for several years, primary care services in England receive payments for recording cessation advice. Hospital services (acute and mental health) are being incentivized financially to provide VBA to all in-patient smokers. Arguably, none of this would have happened in the absence of Russell's paper.

Russell developed his research on GP interventions by showing that augmenting brief advice with the offer of nicotine chewing gum doubled success rates [24]. He also tested GP brief advice, supported by the local smokers' clinic [25]. In this study, Russell found that brief intervention supported by the clinic increased the success rate to 13% of smokers at 1 year, compared with 8% usual

care, and the use of nicotine gum in the supported brief advice group was associated with higher success rates (27%). It was some years later, the White Paper in England, *Smoking Kills* [19], established the first of what would become a national network of smoking cessation clinics which can be traced back initially to Russell's paper.

In 1978, Russell & Feyerabend published a highly cited paper, 'Cigarette smoking: a dependence on high nicotine boli', the fourth paper we present [26] (which was the subject of a presentation Russell gave to a symposium on drug disposition). This paper aimed to describe how the pharmacokinetic characteristics of ingested nicotine explained why people used different forms of tobacco and why cigarette smoking was so highly addictive compared to other forms of taking the drug. The paper was wide-ranging and covered historical issues around different forms of tobacco use, as well as nicotine metabolism, pH, method of ingestion, fatal doses, half-life and absorption. He included his own experiments with smokers, users of 2- and 4-mg gum, one individual smoker's ingestion of high levels of nicotine and one experiment which included himself ([26], Fig. 6 footnote). He concluded that, for smokers, it was the puff-by-puff high-nicotine bolus, which reached the brain within seconds of inhalation, that made cigarette smoking so addictive. This paper would help many researchers and policymakers understand nicotine more clearly and the importance of the speed of nicotine delivery in addictiveness. In a subsequent paper, Russell [27] argued that there were three types of smokers: non-inhalers, peak-seekers (~ one cigarette per hour gives a blood nicotine profile of repeated high blood nicotine peaks), who smoke predominantly for positive pleasure, and trough-maintainers (~ one cigarette every 30 minutes), motivated by the need to maintain a high blood nicotine level to avoid unpleasant withdrawal effects. This concept of different types of smokers is informing our understanding of different types of vapers and their use of e-cigarettes with varying levels of nicotine and flavours today (e.g. [28]).

Russell's earlier research had demonstrated that smoke intake was determined largely by smokers' individual pattern of puffing and inhaling rather than cigarette consumption, cigarette type or tar and nicotine yield (e.g. [29]). This led to Russell reflecting upon safer cigarettes [30]. He advocated for a change in the 1970s low-tar low-nicotine policy to a low-tar medium-nicotine policy in another seminal paper, in which he coined the phrase: 'People smoke for nicotine but they die from the tar' [31]. While governments eventually dropped their low-tar strategies, efforts to alter cigarettes to make them less dangerous are ongoing. These include a very recent announcement by the US Food and Drug Administration, which places nicotine central to tobacco regulation, but also a consultation on reducing nicotine content in

cigarettes to very low levels [32], which would be inconsistent with Russell's views.

The last of Russell's papers we discuss, 'The future of nicotine replacement' [33], identified a solution to the smoking epidemic, which was a significant step forward from his earlier expositions on safer smoking and cigarettes. In this paper, Russell acknowledged the timeliness of thinking about how to precipitate a rapid demise of tobacco smoking, commenting that this would depend upon how soon rational policies were adapted; such policies, he said, needed to be predicated on the fact that it was nicotine that people could not easily do without, not tobacco. This paper is one cited frequently today in our presentations, writing and teaching, because it is still highly relevant. Russell had enormous foresight, and just about every sentence in this paper is critically important and as pertinent today as it was 25 years ago when it was first published. In it, Russell reiterated the centrality of nicotine to the persistence of the smoking problem and went on to recognize the significance of NRT to solving this: 'It is not so much their efficacy as temporary replacement to aid cessation, but their potential use for long-term self-administration which merits the most serious consideration'. This paper was again a gamechanger, being the first, we believe, to discuss recreational nicotine use as a solution: 'that our main concern is to reduce tobacco-related diseases and that moral objections to the recreational and even addictive use of a drug can be discounted provided it is not physically, psychologically or socially harmful to the user or to others'. Russell went on to describe how the tobacco industry had failed to clean up the delivery of nicotine, but that isolated attempts to do so had been thwarted: 'To cap it all, when a tobacco company in the United States spends 300 million dollars to develop a sophisticated, virtually tar-free, and far less harmful cigarette (R. J. Reynolds Premier Cigarette, 1988) its sale is blocked by bureaucratic technicalities abetted by misguided pressure from health experts'. This pattern is sadly being repeated today in response to tobacco industry manufacture of heat-not-burn or electronic cigarettes (e-cigarettes). Of key importance was Russell's premise: 'nicotine addiction is not harmful', a fact that is still a minority view among tobacco control and public health researchers and practitioners 25 years on. He argued, therefore, for competitive nicotine products to be promoted: 'The case advanced is that selected nicotine replacement products be made as palatable and acceptable as possible and actively promoted on the open market to enable them to compete with tobacco products'. This has been achieved for some nicotine replacement therapy (NRT) products, partially in countries such as the United Kingdom. However, this debate has resurfaced with e-cigarettes and currently, despite the fact that they are less harmful forms of nicotine delivery, 27 countries ban the sale of all types

of e-cigarettes [34]. Russell concluded: 'few countries have so far achieved a sustained decline in smoking prevalence in excess of 1% per year. It is difficult to see how active promotion of nicotine replacement will do anything but help to accelerate this process. On the contrary, can we afford to quibble and delay...'

In conclusion, we hope we have outlined how Russell was one of the key thinkers and leaders in the nicotine/tobacco field, and have emphasized his vast legacy. His pioneering research improved the quality of life of smokers and saved the lives of many more. However, had Russell's work been taken seriously earlier, his impact upon mortality and morbidity could have been even greater. It is possible that Russell's ideas were simply too ahead of their time to be accepted, and while scientists today cite his research, this is not done uniformly. In addition, it is a sad indictment of our community that his work is still not recognized adequately by all those working in tobacco control, some of whom still fail to recognize the centrality of nicotine in tobacco use and the implications of this. We believe that Russell's publications should be essential reading for all early career researchers and advocates in the addictions field, and invite readers to ensure that his contributions are acknowledged appropriately in the future.

Declaration of interests

A.M. was a research worker in Professor Russell's smoking research group from 1985 to 1990. D.R. has no competing interests.

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