Aspirin Research And Reflections On The Welsh Contribution To 2010

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Abstract

Aspirin reduces the risk of cardiovascular events and there is emerging evidence that it may also help prevent cancer. An increased use of the medicine could therefore have important public health benefits. In this two part paper, a summary of the current literature on aspirin is presented in part 1 and the contribution of Wales to aspirin research discussed in part 2. To help ensure that the benefits that aspirin can afford are maximised, perhaps an international scientific meeting might be a helpful next step.

PART 1: GENERAL OPENING REMARKS

The United Kingdom, which has a population of about 60 million residents, is constituted by the countries of England, Northern Ireland, Scotland and Wales. Over the last decade, increasing political powers through a process of devolved Government in Northern Ireland, Scotland and Wales has led to country specific health policies being developed in the United Kingdom (1,2). In Wales for example, which has a population of nearly 3 million residents, there has been a drive to improve the cohesion between health and social care services (3) as well as a policy of free prescriptions (4) which is unique in the United Kingdom.

Wales has also been pro-active on a number of policy and research areas. The former includes introducing a Commission for Older People and implementing a 10 year National Service Framework (NSF) for Older People programme which sets out a comprehensive range of evidence-based health and social care standards (5). On the latter, Wales has made important contributions to the field of aspirin research.

Aspirin, which has a chemical name acetylsalicylic acid, is an easily obtainable and inexpensive medicine that is widely used to treat a number of conditions (6). The medicinal use of salicylates spans several centuries (7) and continues to this day, for example as part of medicines to treat conditions of the skin and gastrointestinal tract. In 1974, Professor Peter Elwood and colleagues reported the first randomised controlled trial on aspirin and the risk of a subsequent heart

attack in those with a history of an event (8). This trial was conducted by a team from the Medical Research Council (MRC) in Wales and at that time, the Director was Professor Archie Cochrane. The Cochrane Collaboration today, which is named in recognition of his legacy, is an international organisation dedicated to furthering the development of evidence-based medicine around the world (9).

OVERVIEW OF THE PUBLIC HEALTH POTENTIAL OF ASPIRIN

The International Antithrombotic Trialists' Collaboration has published meta-analyses of randomised controlled trials. These present powerful evidence supporting the effectiveness of 75-150 mg low-dose aspirin in reducing the risk of death, heart attack and ischaemic stroke in high-risk patients (10,11). High-risk patients include those with a history of cardiovascular events or with another condition associated with the increased risks associated with occlusive cardiovascular disease, such as angina pectoris.

In addition, there is also a growing evidence-base that perhaps aspirin may reduce the risk of developing cancer (12). As supported by meta-analysis data (13), the evidence appears most persuasive for a beneficial effect in reducing the risk of colorectal cancer, which is one of the most prevalent malignancies in adults. There are, however, uncertainties remaining on aspirin and colorectal cancer, including optimum dose, duration and frequency that might achieve risk reduction.

Cardiovascular events and cancer, which share some common risk factors such as smoking and increasing age, are two major causes of disease, disability and death in the population (14). The potential of the increased use of aspirin in the population to improve public health has been recognised by a number of commentators. For example, Professor Charles Hennekens (15), who directed the United States Physicians Health Study, has suggested that 'Worldwide, aspirin used more widely and appropriately would avoid many deaths'. An increased role for aspirin disease prevention in developing countries has also been suggested (16).

However, the exploitation of the public health potential of aspirin is limited by undesirable effects, most notably stomach irritation and bleeding which can occasionally be serious (17). Efforts to mitigate the undesirable effects of aspirin include the co-administration of medicines that reduce stomach acid production (18) and the eradication of Helicobacter Pylori (19), a bacterial cause of stomach ulcer. Enteric coating of aspirin may also provide the least irritant formulation of the medicine (20) although this approach may have significant disadvantages, such as poor absorption (21).

As well as undesirable effects, the public health potential of aspirin should not be seen as a either a competitor or an alternative to other population measures that address disease determinants. As suggested by epidemiological evidence (22,23), benefits arise from smoking cessation, exercise promotion, reduced alcohol intake and diets with high content levels of fish, fruits and vegetables. Aspirin could complement these measures and for example, health education messages produced by the Agency for Healthcare Research & Quality in the United States (24) highlight the role of the medicine within the wider context of all disease control, including lifestyle, cancer screening, cardiovascular disease risk management and immunisation uptake. Each of these can play a role in reducing disease in the population.

Such a holistic approach (24) might avoid, at least in part, possible risk compensation in which some individuals might neglect to address lifestyle determinants of health because they believe that aspirin use will compensate for the risks associated with smoking, inactivity, harmful or hazardous drinking of alcohol or a poor diet with low intake of fish, fruits and vegetables. However, the increased use of aspirin might add to concerns that health is progressively becoming medicalised, with older people in particular being inappropriately turned into patients (25).

Three sections now follow. The first of these explores the contribution of aspirin to the prevention of cardiovascular events. A second related section explores the use of aspirin in the metabolic syndrome. The third section then considers aspirin and cancer.

I) CONTRIBUTION OF ASPIRIN TO THE PREVENTION OF CARDIOVASCULAR EVENTS

There has been a considerable amount of interest and debate over predicting the risk of cardiovascular events (26). Prediction is important in order to offer individuals appropriate interventions, which might be lifestyle advice, pharmacological measures or a combination of the two approaches. However, all prediction frameworks have strengths and limitations (27), highlighting the importance of clinical judgement.

Because increasing age is a powerful predictor of cardiovascular event risk, there is an interest in pharmacological interventions being offered to individuals as they become older. For example, the 'polypill' is a proposal to combine a number of medicines, including a statin to reduce cholesterol and blood pressure lowering drugs with low-dose aspirin into a single tablet (28,29). Although there is evidence from computer models that this could be highly effective and safe in individuals 55 years of age (29), there remain questions about the cost-effectiveness of this approach (30).

By contrast, cost-effectiveness studies appear to support the wider use of aspirin (31,32). There are, however, a number of issues with aspirin in the prevention of cardiovascular events. One of these is that some individuals may be resistant to the cardiovascular benefits of aspirin (33). More research is needed on aspirin resistance, which might be related, at least in part to non-compliance (34) and this in turn is further associated with increased risks of experiencing a cardiovascular event (35).

Another issue is that there remain uncertainties about the benefit versus risk balance of aspirin taking in some individuals, for example those with type 2 diabetes mellitus (36). Several questions arise: Who should be taking aspirin? Who decides? Who is actually taking aspirin in the community? What impact is this having? Each of these questions deserves further consideration and research.

There are also further lines of research in respect of the mechanisms of aspirin and perhaps the medicine alone exerts 'polypill' effects. These might be important at the early stages of the cardiovascular disease process and perhaps aspirin might be useful in the management of the metabolic syndrome (37). The implications of aspirin being able to exert benefits in the metabolic syndrome are far reaching for the field of preventive medicine and could lead to an expanded use of the medicine in the population.

II) MIGHT ASPIRIN BE A 'POLYPILL' AGAINST THE METABOLIC SYNDROME?

Some aspects of the metabolic syndrome are presented in Box 1 (38-54). One of the pathophysiological markers of metabolic syndrome is that individuals appear to have increased activity of pro-thrombotic markers, such as platelets. To some extent, this might account for resistance to the cardiovascular benefits of aspirin (55). Low-dose aspirin might not therefore be sufficient to exert anti-platelet effects in those individuals with the metabolic syndrome (56, 57).

Experimental models of the metabolic syndrome have used aspirin doses of 10mg/kg (58) but in humans this would equate to about 5-10 times the usual dose used for cardiovascular event prophylaxis. Such a dose might confer an increased risk of undesirable effects, although uncertainties remain about the interaction between aspirin dose, age and Helicobacter pylori infection in the aetiology of gastrointestinal ulcers (59).

Perhaps aspirin might be helpful in the metabolic syndrome as a complement to other interventions, such as lifestyle modification. There is evidence from studies in humans that low-dose aspirin taken at bedtime might lower blood pressure by effects on homeostatic mechanisms that become active during the night (60). Aspirin might therefore reduce the risk of hypertension developing. Given that there also appears to be a relationship between hypertension and an increased risk of type 2 diabetes mellitus (61), this effect could be far reaching.

There is also experimental evidence that aspirin might reduce cholesterol levels (62). This potential benefit might be mediated by the salicylate metabolite gentisic acid, which appears to have anti-oxidant properties (63). This metabolite can be measured in human plasma (64) and may also have beneficial effects by reducing the oxidation of low density lipoprotein (LDL) by glucose-derived radicals. In the aetiology of atherosclerosis, the pathological process associated with fatty plaques forming blood vessels, this oxidation appears to be important (65). An anti-oxidant effect of aspirin in this context might therefore be salutary.

In some circumstances, however, the contemporary benefit versus risk evidence on aspirin prophylaxis is imprecise, for example in patients with type 2 diabetes mellitus (66). In these circumstances, astute individual clinical judgments might also be required (67). In the case of the metabolic syndrome, however, where many individuals may be unaware of their predisposition to cardiovascular events, issues of the benefit risk balance of aspirin remain to be fully clarified so policy recommendations on the use of the medicine for this indication are currently lacking. Further research is therefore warranted.

Box 1: Some aspects of the metabolic syndrome

Often manifesting phenotypically as increased subcutaneous and intra-abdominal fat, the metabolic syndrome has been described as a cluster of cardiovascular risk factors, including raised blood pressure and excessive amounts of circulating glucose and cholesterol levels (38,39). There are, however, unresolved issues about the definition of the metabolic syndrome (40). Indeed, whilst the metabolic syndrome has been described in many different populations around the world (41), including North America (42) and Asian Indians (43), the definition of the metabolic syndrome might vary according to ethnic group, for example in African American populations (44). Furthermore, the metabolic syndrome may also occur in children and adolescents, which might raise the need for there to be age-specific definitions (45,46). The problems of defining the metabolic syndrome compromise epidemiological studies and their comparability. It has been suggested that oxidative stress might be one of the pathophysiological processes that underpins the relationship between a cluster of risk factors for cardiovascular events (47). Regarding management, the European Society of Hypertension has recognized the importance of treating high blood pressure in the metabolic syndrome (48). Non-pharmacological approaches to management include weight reduction, suggested to be the most important intervention especially if it is achieved to a large extent by physical activity (49). Of additional relevance to weight reduction is the increased risk of cancer which appears associated with obesity and type 2 diabetes mellitus (50). One issue is to understand some of the factors that appear to be underpinning the metabolic syndrome. The 'nutrition transition' in which global population diets are becoming more calorific, coupled to reducing food prices and reduced activity, appears to be important (51). This might explain, at least in part, the increasing prevalence of nutrition related non-communicable diseases (52). So

addressing the metabolic syndrome, however it is defined, may require political solutions and the role of aspirin might only offer some pharmacological mitigation against the increased cardiovascular event risk. Possibly, new markets for aspirin use might arise in developing countries given the increasing prevalence of nutrition related non-communicable diseases. There are ethical issues with this possibility (53) as well as other priority issues, such as the development of sanitation systems, rather than the focus on the management of chronic long-term conditions.

III) COULD ASPIRIN CONTRIBUTE TO CANCER CONTROL PROGRAMMES?

Chemoprevention describes the potential of pharmaceutically manufactured or naturally produced chemicals to intervene and block the complex processes of cancer formation, so called multistage carcinogenesis (68). In the case of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), this might be via a range of mechanisms such as inducing programmed cell-death and reducing inflammatory reactions that over time may increase the risk of cancer. Other agents with cancer chemopreventive potential have also been described, such as retinoids (69), curcumin (70) and ginseng (71).

Other medicines may also have cancer chemopreventive effects (72). For example, celecoxib, a new generation NSAID with less toxicity to the gastrointestinal tract, exerts chemopreventive benefits against colorectal cancer (73). Contrasting to aspirin, new generation NSAIDs increases cardiovascular event risk making them questionable candidates for cancer risk reduction in the general population (74).

The cancer chemopreventive potential of aspirin is being further tested through randomised controlled trials. Such trials, however, are evaluating this potential in high-risk individuals, such as those with precancerous lesions, so the results will is not readily generalisable to the general public. Yet, the general public are already receiving media reports of varying accuracy on aspirin and cancer, which might possibly lead to usage.

Inaction therefore does not seem a reasonable option. So what happens next? As a general principle, it would seem reasonable for the role of aspirin to contribute to existing cancer control programmes. In addition, the cardiovascular benefits of aspirin are also a relevant consideration. So what happens next?

There is also another dimension to the possible role of aspirin in cancer prevention. Salicylate, which is the principle metabolite of aspirin, is consumed by humans through fruits and vegetables. Salicylate deficiency might be a risk factor for cancer (75,76) and perhaps aspirin exerts benefit, at least in part, by counteracting this (77). There is also evidence that humans might synthesise salicylate (78) and further research is required to confirm this finding and clarify the possible pathophysiological roles it has. Perhaps salicylate might also be re-classified as vitamin S? (79).

PART 2: WELSH CONTRIBUTIONS TO CONTEMPORARY ASPIRIN RESEARCH

Wales is the first and only country to date that has established a specific group that has attempted to influence policy to convert the public health potential of aspirin into a reality and organisational aspects are presented elsewhere (80). The Welsh Aspirin Group was formed during the summer months of 2003 as a network of health service professionals and academics with an interest in the public health potential of aspirin. The original aims and membership of the Welsh Aspirin Group are given in Appendix 1.

There were a number of antecedent events that were important in the formation of the Welsh Aspirin Group. This included prior interest of the Chairman and Secretary in the public health potential of aspirin (81,82). Another driver, given that most of the work was unfunded and for some on a voluntary basis, was social responsibility (83). This may be considered a responsibility for scientists to actively promote the public health implications of their work.

Possibly the experience of the Welsh Aspirin Group might also bring a new dimension to the concept of social responsibility. It has been suggested that the greatest advances come not from incremental improvements in efficiency but from new and better approaches (84). Is this suggestion entirely reasonable? Aspirin cannot be considered a new approach yet the appropriate wider use of this well known medicine, which is over 100 years old (85), could contribute much benefit to public health. Social responsibility, therefore, might include maximising the benefit of existing resources.

At least in part, the modus operandi of the Welsh Aspirin Group might be considered to be action research given that work was focussed on activities and products. Action research is practiced under a variety of names (86) and has been applied in many settings (87). Action research may include a process of reflection on a problem, taking action leading to evaluation and learning from the process. On reflection, the original 6 aims offer a basis for evaluation (Table 1) (88-96) and there is evidence that most of the aims were convincingly fulfilled whilst the final aim of influencing policy and practice was perhaps partially achieved. Box 2 discusses resistance to policy change (97).

DISCUSSION

Although the Welsh Aspirin Group was disbanded in 2008, aspirin research is still continuing in Wales, for example the potential contribution that the medicine might make to colorectal cancer screening programmes (98). In addition, the concept of aspirin taking on age-grounds has been extended to suggest that individuals aged about 40 years might take the medicine given that this may modify disease processes predisposing to cardiovascular events and cancer (99). Underpinning all of this is continued dialogue with the Welsh Assembly Government about the public health potential of aspirin although there remain significant challenges to policy development, such as ethical considerations which include benefit versus risk balance (100,101). The use of aspirin in the acute management of myocardial infarction is another potential indication for the medicine which requires further research (102).

Figure 1

Table 1 : Aims and Achievements of the Welsh Aspirin Group

Aim	Achievements
To collect, critique and organise literature	review papers and focussed on the existing and emerging uses of aspirin (88) as well as the role of aspirin in older people (89).
To debate and discuss aspirin research and policy	A debate paper on the use of aspirin on age grounds was published in the British Medical Journal (90). This presented evidence that the risk of cardiovascular events at the age of 50 years justifies aspirin use being considered. A non-medical model was suggested in which individuals are encouraged to make informed choices about whether to use aspirin. In addition, a conference to debate the public health potential of aspirin was convened in Wales (91).
To stimulate and co-ordinate research projects of aspirin use	A number of research initiatives were progressed. One of these was a survey of aspirin taking in individuals at highrisk of a cardiovascular event (92). About 1,500 individuals were included in this survey and an under-use of the medicine by about 50% was indentified. In addition, a number of mathematical models were constructed on various aspects of aspirin use. One of these was a health impact assessment on increased aspirin use in Wales which suggested a potential all-cause mortality reduction from the medicine as high as 10% (93).
To disseminate information on aspirin and publish papers	In addition to published papers and the conference, a consultation document on 'Converting the public health potential of aspirin into a reality' was widely disseminated across Wales in October 2007. This consultation was sent to all health organisations in the country, academic institutions and community groups. Although a low response rate of approximately 5%, those received were valuable and interesting.
To correspond with interested bodies from outside Wales	Attendees at the conference came from other constituent countries of the United Kingdom. In addition, an extensive review of the literature on aspirin and cancer, published in the Lancet (94), was conducted in collaboration with colleagues from Wales, Northern Ireland and Scotland.
To influence aspirin health policy and practice in Wales	A response was submitted to the consultation on the NSF for Older People and aspirin was included in the stroke standard, possibly also because of other feedback. Furthermore, two policy proposals were published, namely the promotion of aspirin to high-risk patients (95) and a population based health education campaign (96). Several meetings with the Welsh Chief Medical Officer and Public Health Chairman also held.

Box 2: Resistance to Policy Change

It has been suggested that the failure to fulfill 6 factors can result in resistance to policy change (97). These factors offer a framework to consider the limited influence that the Welsh Aspirin Group had on policy and practice. Perhaps it may be acknowledged that some of the aims of the Welsh Aspirin Group might have been ambitious. i) The importance and value of having multi-disciplinary teams This factor was satisfied with the formation of the Welsh Aspirin Group ii) The need to have a broad evidence to draw upon This was satisfied, at least in part, as evidenced by the publications iii) The need for policy implementation to be locally sensitive The two policy proposals were firmly grounded in the Welsh context iv) The benefit of stakeholder involvement Perhaps the consultation was a missed opportunity to engage stakeholders v) The circular relationship between research and policy The survey might have been used to influence

aspirin taking in non-users vi) Support by the national Government Discussions and correspondence continue with Welsh Assembly Government It appears that although the Welsh Aspirin Group had followed a process that may be considered consistent with policy development, crucial elements were not achieved. Had the consultation process been expanded, for example introducing a follow up to increase the response rate and also consulting directing with primary care physicians, or had the survey included an intervention of encouraging non-aspirin users to comply with their prescribed regimen then more policy influence might have been achieved. Subsequent to this, recommendations have been made for further areas of aspirin research which have implications for policy. This is available at:

http://www.ecancermedicalscience.com/news-insider-news.a sp?itemId=503 Last accessed December 1 st 2010

Another of the initiatives in Wales was a Citizen's Jury (103). This is a pseudo-legal framework in which 16 community members receive evidence and offer informed comment. Table 2 below shows one of the key judgements made by the 16 member Citizen's Jury and this is consistent with a recommendation made independently by the Welsh Aspirin Group (Box 3).

Figure 2

Table 2 : Welsh Citizen's Jury Judgement On Whether Public Money Should Be Spent To ADVISE Healthy People Over The Age of 40 To Take Aspirin

Yes	14
No	2
Don't know	0

In other countries, policy makers are developing guidelines on aspirin use. For example, the United States Preventive Service Task Force guidelines (104) encourage low-dose aspirin use in men 45-79 and women 55-79 to prevent first heart attack and ischaemic stroke respectively, when the benefits outweigh the risks. This raises the issue of judgement on benefits and risks which varies (105). There is also evidence that compliance with aspirin taking is related to intelligence (106). It might therefore be the case that the more intelligent members of the population, who tend to adopt the healthier lifestyles and have other advantages associated with affluence, might benefit most from aspirin resulting in an increase in health inequalities. Other factors impact on health, such as environmental factors and social cohesion. Each plays a role and if a given community has

particular social problems, aspirin might be a low policy priority. Views on priorities from a community might be termed 'popular epidemiology'.

Box 3: Possible comparison between Wales and England

In this study, it is assumed that the evidence of benefit over costs is made sufficiently to obviate the need for randomised trials. Intensive and repeated publicity about the benefits and costs of low-dose aspirin prophylaxis will be given throughout Wales, using every medium available. Comparisons of trends will be made with predictions, and with possibly other countries. Advantages: Relatively inexpensive and simple Avoids the disadvantages of the randomised trial Puts onus of decision on the individual Disadvantages: No randomisation, no matched control, no blinded comparisons Changes in the numbers of patients with dementia* would probably be impossible to detect Source: Morgan G. Elwood P. Extract of an options** paper presented to the Welsh Aspirin Group meeting on June 22 nd 2004 *Refers to vascular dementia ** Other options considered were 'do nothing' and a large cluster randomised trial comparing areas of Wales, rejected due to practicalities and costs

The political aspects of public health are also a consideration (107). The intimate link between politics and public health, perhaps underpinned in part by social medicine, suggests that Government policies that tangibly help all members of the community are often received sympathetically by the electorate. This raises a possible scenario in which aspirin use could be particularly encouraged in deprived communities with high levels of cardiovascular disease and premature death. Such communities have the potential to be helped by increased aspirin use and the resultant reduced demand on health and social care services would release valuable resources for benefit to the wider population.

Policy developments in public health, such as smoking cessation, appear to increasingly use financial incentives to encourage uptake (108). One of the difficulties, however, is that the general public faces a barrage of health messages about health through the media (109) (Box 4).

There is interest in the wider use in other medicines. For example, anti-platelet medicines such as clopidogrel might have similar efficacy to aspirin for reducing cardiovascular event risk (110) but might be more expensive and therefore less cost-effective for this indication. In addition, the increased use of statins has been suggested (111) yet the

policy implications of this proposal, as well as possible impact, remain unclear. Aspirin research also continues and numerous studies or trials are ongoing in relation cancer and treatment (112), adjunct therapy in mental health (113), pregnancy (114) for which it is recommended in the UK for hypertension management in pre-eclampsia and also macular degeneration (115). Many countries have contributed to aspirin research and Wales has been particularly active on the public health potential and on influencing policy. An international scientific meeting might be a helpful next step. Given the potential of aspirin to make a contribution to healthy ageing, perhaps this could be undertaken on October 1 st, which is international day for older people.

Box 4: Are media Editors key health advocates?

A headline in a widely read British newspaper suggested that aspirin may be 'bad' for you. This headline appeared premature given that it was prompted by a conference paper and furthermore it could also be argued that other news items might have been more appropriate for front page coverage. A number of issues arise, for example media headlines can be too simplistic. To suggest that aspirin may be bad might be interpreted as a dichotomy of effects, namely that aspirin is either good or bad. This ignores the many effects that aspirin has, beneficial and undesirable. Furthermore, there are ethical complexities on the balance between beneficence and non-malificence which varies between individuals and their risk factors. Given previous media coverage on the evidence suggesting that aspirin might lower the risk of cancer, another concern is that the general public are being offered mixed messages. In the case of aspirin, this is particularly unhelpful given that the medicine is easily available, inexpensive and widely use for a range of indications including prophylaxis against vascular disease. Media coverage has the potential to influence individual decisions on whether or not to use aspirin. So is it ethical for health services, particularly public health, to stand back and do nothing?? On the specific point of aspirin, a health education campaign on the benefits and undesirable effects of aspirin could be implemented in order to allow informed decisions on aspirin prophylaxis to be made. Such a health education campaign could set out the evidence on aspirin and vascular disease, the emerging evidence on cancer with caveats and the risks of harms such as bleeding, within a broader context of lifestyle advice. This approach, a combination of a medical model and a social intervention, might be an effective combination of a pro-active health service and empowered population. More generally, would

training media Editors in appraising evidence be helpful? Such training, if adopted, might lead to fewer publications of unhelpful and potentially misleading headlines. Implicit within this is the responsibility that comes with mass communication. So the example of aspirin appears to lead to a more important question. Should health services recognise the key role played by media Editors and seek to engage with them at local, national and international levels as key health advocates? A mature and respectful relationship between health services and media Editors has the potential to ensure a balanced impact on public health. Yet health is a difficult concept to define. It therefore follows that public health is also difficult to define. So how can media Editors contribute to the public health agenda when there are unresolved issues of definition? This entire situation may be termed 'lay epidemiology' and further research might also be conducted on the amount of health related information that services provide to the general public, the uptake and impact of this.

Appendix 1: Welsh Aspirin Group Aims and Membership

- to collect, critique and organise aspirin literature
- to debate and discuss aspirin research and policy
- to stimulate and co-ordinate research projects of aspirin use
- to disseminate information on aspirin and publish papers
- to correspond with interested bodies from outside Wales
- to influence aspirin health policy and practice in Wales

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UWS = University of Wales Swansea

NPHS = National Public Health Service

Box 5 offers perspectives on Welsh non-government organisations (NGOs)

Box 5 : Perspectives on Welsh non-government organisations (NGOs)

NGOs vary in their size, constitution, aims, policy interest and operational style. Furthermore, classifying nongovernment organisations into categories is complex as some combine service provision and pressure group activity. Furthermore, pressure groups are diverse and the insider and outsider status has been used to define the relationship that they have with Government (116,117). This framework, however, is not entirely satisfactory given that insider and outsider status is not always clearly demarcated (118). Using the 'realist review' method, driven by the question 'What works for whom in what circumstances and in what respects?', six case reports on Welsh non-government organisations were prepared using information in the public domain. A number of themes appear to have emerged, including the different ways that non-government organisations use to engage with and influence Ministers and officials, such as using policy developments and events for raising awareness. The underpinning thread binding the different approaches used is the ability of non-government organisations to develop and maintain constructive relationships with Ministers and officials. It follows that an important determinant of influencing policy appears to be the behaviour of the members of non-government organisations. Positive engagement and professional behaviour helps constructive relationships with antagonism counterproductive. The case reports on non-government organisations in Wales can be set in context of the literature. For example, research from Western Australia (119) supports a pressure group model in which organisations are

divided into four types of insider status (core, specialist, peripheral and failed) and two types of outsider status (by ideology or goal, or by choice). This model also recognises the complexities of relationships between pressure groups, decision makers and policy processes. The Welsh case reports are consistent with this model given the previously highlighted importance of relationship building. The Welsh Aspirin Group cultivated insider status. Relationship building also appears to be a key determinant of how nongovernment organisations gain increased insider status. It has been stated that 'adopting an insider strategy amounts to a conscious choice by group leaders to establish stable and harmonious relations with Government' (120). Furthermore, there has been an increasing trend for single issue pressure groups to be formed and their operational methods include using the media and websites (121). This can be problematic, for example patients with serious illnesses campaigning for drugs to be available can generate emotive media coverage (121). This may be important in shaping relationships. Productive research avenues might include a systematic description of non-government organisations in Wales, more case studies on pressure groups and their policy influence and also research on the organisational characteristics of non-government organisations, including their management structures, modus operandi and the factors that influence whether or not they are sustainable and the role of emotional intelligence in relationship building.

ENDNOTE

In 2009, the Welsh Aspirin Group experience was included in a study about interests of groups and their activities.

http://www4.rgu.ac.uk/files/Interest%20Group%20Organisations%20DH1.doc

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ABOUT THE AUTHOR

Dr Morgan has had an interest in aspirin for nearly 20 years. This initial interest explored the potential of aspirin in the treatment of cancer and shifted in emphasis to the preventive potential of the medicine. This further expanded to the public health potential of aspirin and the formation of the Welsh Aspirin Group in 2003. Papers in press include a health economic comparison of aspirin with breast cancer screening and a discussion on the unfulfilled public health potential of the medicine. Dr Morgan has published on other matters, including reflective practice, renal service provision, 'popular epidemiology', problems of defining

health and vitamins. His other interests include dignity in care and healthy ageing.

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