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高級工商管理 EMBA研修班

主辦

北京大學創辦於1898年，初名京師大學堂，是中國第一所國立綜合性大學。北大是一所以文理基礎教學和研究為主的綜合性大學，校友和教師有400多位兩院院士，中國人文社科界有影響的人士相當多也出自北大。

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Asia Health Care Journal

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Featured topic: Dementia and related health care issues

Factors modulating the onset of *Alzheimer's disease* – Genetics and Environment

Dr. Ma Suk Ling
The Chinese University of Hong Kong

Challenges in Disaster Medical Response

Dr. Susan Briggs
Harvard Medical School

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A Word from the Editor in Chief

Prof. Jack Wong, Editor in Chief
Director, Regulatory Affairs, Johnson & Johnson Medical
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Email: speedxquality@yahoo.com

Welcome to our 2nd issue of Asia Health Care Journal. It is a platform that links diverse health care related expertise together, and is supported by ARPA (Asia Regulatory Professional Association) and the Hong Kong Health Care Federation.

At the moment, we are developing our Editorial Committee. A number of government officials in the Ministry of Health, certification bodies and academic and industry experts have shown great interest to support. I will keep the readers updated about the progress in the next issue. Do contact us if you are interest to contribute.

Currently, we are pleased to have Dr. Saleh S. Al-Tayyar, the Chairman of the Asia Harmonization Working Party (AHWP) to be the president of ARPA. AHWP is the significant and renowned non-profit organization that seeks to study and recommend ways to harmonize medical device regulations in Asian and other regions.

In this issue, we have a variety of topics that share the findings and experiences from the latest medical and healthcare fields. Given the issue of aging population and rising demand for Dementia research effort, we focus on the topic of Dementia in this issue. Hope you enjoy reading. ■

Prof. Jack Wong
Asia Regulatory Professional Association

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Encouraging news from Alzheimer's disease research field – a response to Professor Gu's article on the treatment of Alzheimer's disease

Professor Gu has given us a very comprehensive review of the current treatment of Alzheimer's Disease. With the advancement of scientific investigation and technology, a range of medical and behavioural treatments have been proven to be effective. Nevertheless, these treatments were still criticized to be domain-specific, that is, Alzheimer Disease patients often need to undertake different types of treatments, both pharmaceutical and behavioural.

Aging population is a global pressing issue, and a lot of elderly disorders such as Alzheimer's disease and other dementia-related disorders are experiencing an inevitable rise. Sadly, not all dementia-related disorders are as treatable as Alzheimer's disease. Moreover, even though member-enhancing drugs appear to be effective on memory function in some patients, they do not appear to influence the course of dementias. Other medical treatments are limited by its adverse side effects.

It is nevertheless encouraging to see that much research attention and resources around the world has been devoted to the causes and treatment of Alzheimer's disease. It is anticipated that the concerted research efforts will lead to some breakthroughs, which hopefully will allow us to acquire deeper understanding of Alzheimer's disease.

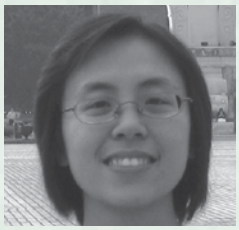
- Si Ying, Hong Kong

rTMS shed lights on Autism treatment? A response to Dr. Yi's article entitled "rTMS Treatment for Autism"

It is very encouraging to see that repetitive Transcranial Magnetic Stimulation (rTMS) appears to be an effective means to treat Autism Spectral Disorder (ASD). To date, the causes and nature of ASD remains largely unclear. ASD therefore appears to be an incurable disorder plaguing approximately one to two children in every thousand worldwide. Although some children with mild symptoms are able to find coping strategies that help restore their social life, others with more serious symptoms may find it difficult to cope with the disorder.

The case studies reported by Dr. Yi lent support to the effectiveness of rTMS. However, the representativeness of case studies remains to be highly limited, and we must rely on larger scale studies to shed light on the effects of rTMS. Furthermore, application of electromagnetic treatments to young children is controversial, as the brain structure is still developing. Any side effects that are weak to adults may exert a prolonged effect on children. We are thus hoping that further investigation into this technology will shed light onto ASD treatments.

- S. Yu, Sydney, Australia



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Dr. Ma Suk-Ling is currently Research Assistant Professor at the Department of Psychiatry, the Chinese University of Hong Kong. Dr. Ma received her B.Sc degree in Biochemistry, M.Phil. and Ph.D. degree in Medical Sciences from the Chinese University of Hong Kong. Later she received a M.Sc. degree in Bioinformatics from the University of Manchester. She received her postdoctoral training from Harvard University. Dr. Ma has a major interest in genetics of Alzheimer's disease and the development of molecular and bioinformatic methodologies and their applications to early detection of AD and the prediction of conversion from mild cognitive impairment (MCI) to AD.

Factors Modulating the Onset of Alzheimer's Disease – Genetics and Environment

Abstract

Alzheimer's disease (AD) is a major health issue in the aging population and it is the most prevalent form of dementia. Evidences suggested the involvement of genetic and environmental factors for the risk of AD. On the other hand, age-at-onset (AAO) determines the prevalence of AD and a small delay of AAO of AD is predicted to reduce prevalence of AD by one-fourth by 2050. In this review, the genetic and environmental factors modulating AAO of AD will be discussed. It is hoping that the understanding on the factors modulating AAO of AD will be beneficial to the development of lifestyle recommendations and treatments in the future.

Introduction

Alzheimer's disease (AD) is the most common form of dementia, currently affecting over 33 million people worldwide. With the advancement in medicine, life expectancy is increased and it is expected the number of AD patients will be doubled by 2050. The pathological hallmarks of AD included the deposition of amyloid plaques and formation of neurofibrillary tangles in the brain. Only less than 5% of AD diagnosed are familial AD with mutations in genes associated with amyloid precursor protein (APP), presenilins 1 (PSEN1) and presenilins 2 (PSEN2) [1]. Sporadic AD accounted for the majority of AD and is modulated by both environmental and genetic factors. Over the past decades, many genetic association studies and epidemiology studies were performed to identify the risk factors related to the predisposition of AD [2].

Since the first report of AD in 1906, a lot of studies were done on AD and there have been many scientific breakthroughs in the understanding of the pathology and mechanisms in AD in the past decades. AD is a complex neurodegenerative disease and the etiology is multifactorial involving genetics and environment. Some of the risk factors of AD include age, barriers of risk-predisposition genotypes, family history, head trauma, female gender and vascular factors [3]. Predisposition to disease is only one mode of modulation in disease risks and severity. Age-at-onset (AAO) is also an important factor in modulating the prevalence of a disease. The prevalence of AD increases with age and doubles every 5 years after the age of 65 [4]. Identifying the factors which modulate the AAO of AD will be important for the development of therapies or life style recommendation to delay the onset of the disease beyond lifespan. Studies suggested that intervention delaying the average AAO of AD by only 2 years will reduce the expected prevalence of AD by 23% by 2050 [5]. In this review, the genetic and environmental factors modulating the AAO of AD will be discussed.

Significance of research in AAO of AD

Currently, most studies in AD are focused on the investigation of the underlying mechanisms/pathways in AD, so as to understand the disease and to facilitate the development of pharmacological/non-pharmacological treatments to cure the disease. However, until now, there is still no treatment that can completely cure the disease and only medicine that relieves some of the symptoms was identified. On the other hand, identifying factors modulating and delaying the onset of AD will extend the years of disease-free before developing AD. In addition, delaying the onset age of AD will also delay the progress of disease from mild to severe stage, which will reduce the suffering of the patient and burden to the caregivers. While most studies focused on the identification of risk factors for the predisposition of AD, the understanding of the factors contributing to AAO in AD is clearly lagging behind.

Genetics and AAO of AD

Genetics is an important factor in modulating the risk and onset of AD. Over the past decades, apolipoprotein E (ApoE) is the widely studied and accepted genetic risk factor for AD. Studies suggested that ε4 allele increased the risk of AD in a dose-dependent manner while bearing ε2 allele is protective for the disease [6-8]. ApoE does not only modulate the risk of AD, it also contributes up to 10% of the effects on AAO of AD [9], suggesting there are additional loci modulating AAO in AD. Since ApoE affects both the risk and AAO of AD, it complicated the observation of ApoE on AAO. Several studies observed the effect of ApoE genotype on AD risk also showed a significant difference in AAO among those groups [10-12]. A recent study suggested that bearing ApoE ε4 allele lowered the AAO of AD and increased the risk of getting AD [13, 14]. Therefore, the role of ApoE in the risk and AAO of AD is unclear.

A number of genome-wide association studies (GWASs) and linkage studies attempted to identify the loci or genes associated with AAO in AD and a strong signal appeared in chromosome 19 (ApoE is located on the same chromosome)[15-17]. It is unclear wheather the association of loci at chromosome 19 and AAO in AD is due to the effect of ApoE or wheather there are other genes contributing to this trait, as the ApoE has a strong impact on both disease risk and onset. Other than chromosome 19, Hollman et al. identified the association between chromosome 21 and AAO of AD [16]. The association of chromosome 6 and 10 with AAO of AD was reported by other investigators [17]. Kamboh et al. recently performed GWAS on AAO of AD and showed significant association with ApoE, as it was observed in other studies, and revealed additional loci on chromosome 4q31.3 [18]. The study included samples from 3 independent centres, 1440 AD patients from the University of Pittsburgh Alzheimer's Disease Research Center (ADRC), 844 AD patients from Mayo AD GWAS project and 188 AD patients from Alzheimer's Disease Neuroimaging Initiative (ADNI). Other than ApoE, the authors also identified the association bewteen TOMM40 and AAO. A study showed that individuals with long poly-T repeats at TOMM40 were associated with AAO 7 years earlier when compared to subjects with shorter poly-T. This was previously reported in subjects with ApoE ε3 allele [19] and was replicated by other investigators [20-22] but not all [23, 24]. Given the close proximity between TOMM40 and ApoE and the strong linkage disequilibrium (LD) between these two

genes, the controversial results on the association between TOMM40 and AAO observed in different studies might be due to the difference of ApoE genotypes of the AD patients examined.

A copy-number (CN) variation located on chromosome 14q11.2 and the signal came from the olfactory receptor gene cluster in the region. Shaw et al. showed a dosage-dependent association of the CN copy number with the AAO of AD [25]. An increase in one copy of CN of olfactory receptor gene increased 1.12-fold relative risk for an earlier onset of AD, and the effect on AAO was stronger with the presence of ApoE ε4 allele. The finding on the association between CN variation of olfactory receptor and AAO of AD was supported by the increased incidence of cognitive impairment in normal subjects with increased CN of olfactory receptor at 5-year follow-up [26]. The finding suggested that genes associating with earlier AAO of AD also increased the severity or risk of AD.

Other than ApoE-related genes, the GWAS by Kamboh et al. revealed a strong association between DCHS2, a gene located on chromosome 4q31.3, and AAO of AD [18]. Since this gene is outside of the ApoE region, its association with AAO was significant regardless of the ApoE genotype of the subjects. Some other loci associated with AAO of AD revealed by GWASs included chromosome 1, 6, 7, 9, 10 and 15 [15, 16, 27]. The genes identified were overlapped in some of the GWASs but not all and the discrepancies might be due to the genotype of ApoE and the effect of ApoE on the gene in LD. Independent association studies were performed by other investigators to identify genes in these regions responsible for the AAO of AD. Some of the genes, including glutathione S-transferase omega-1 (GSTO-1) [28, 29] and calcium homeostasis modulator 1 gene (CALHM1) on chromosome 10 [30, 31], angiotensin-converting enzyme (ACE) on chromosome 17 [32], estrogen receptor 1 (ESR1) on chromosome 6 [33] and peptidyl prolyl cis/trans isomerase (Pin1) on chromosome 19 [34], were associated with AAO of AD. Although these loci were first identified through linkage analysis or GWASs and further investigated by case-control association studies, not all the results were confirmed by other groups [35]. Biological mechanism or functional studies are required to provide further evidence to support the findings from the association studies. Two of the examples (GSTO-1 and Pin1) will be discussed in this review.

Glutathione S-transferase (GSTs) is a superfamily known to have enzymatic activities of thioltransferases and dehydroascorbate reductases that is important in promoting antioxidant activity and cell defense mechanisms [36]. GSTO-1 is a member of GSTs and is involved in the regulation of inflammatory process, calcium channels control [37] and interaction with serine protease inhibitor [38]. The association of GSTO-1 with AAO of AD was first identified in a linkage analysis and the polymorphisms responsible for the trait were further identified through association study by the same group [17, 28, 29]. However, the result was not replicated by other groups [35, 39, 40]. The controversial findings may be due to the bias on population selection or diagnostic criteria employed in different studies. On the other hand, expression studies or functional studies gave further evidence to support the findings on association studies and avoided the bias on subject inclusion. Allen et al. confirmed the association between GSTO-1 and AAO of AD but found no association between the reported GSTO-1 SNPs and expression level of GSTO-1 in the brain. However, the authors identified GSTO-1 as an important player of the glutathione metabolism pathway, supporting the functional role of GSTO-1 in the pathogenesis of AD [41].

Pin1 is a prolyl isomerase and it catalyzes the conversion of cis to trans conformation specifically at certain phosphorylated Ser/Thr-Pro motifs [42-45]. Biochemical studies suggested its functional role in the pathogenesis of AD and association studies reported the relationship between polymorphisms of Pin1 and the risk of AD [46-48]. However, the association between Pin1 polymorphisms and the risk of AD was not confirmed in studies with populations other than the first study (Italians) [49, 50]. Our group replicated the study but we did not identify any significant association between Pin1 polymorphisms and the risk of AD. Instead, we showed that the Pin1 SNP, rs2287839 was strongly associated with a 3-year delay on average in AAO of AD. In addition, we identified the functional role of this polymorphism in modulating the binding of the transcription factor AP4. The allele that accounted for delayed AAO of AD prevented the binding of AP4 to Pin1 promoter. The inhibitory function of AP4 was therefore disabled, resulting in an increased expression of Pin1 which is protective for AD pathogenesis [34]. Our result added to the previous biochemical studies and provided further support to the importance of Pin1 in modulating AAO of AD.

Environmental factors and AAO of AD

A number of environmental factors are associated with the risk and onset of AD. Genetic factors may affect the susceptibility and downstream consequences of the environmental factors exposed to a subject. Provided that the genetic background is the same among subjects, a number of environmental factors may modulate the risk and onset of AD.

Inflammation – anti-inflammatory drugs

The association between inflammation and the risk of AD was supported by genetic and epidemiology studies. The hypothesis on inflammation and the pathology of AD suggested that amyloid β deposition and formation of neurofibrillary tangles increased the inflammatory response in the brain, and this formed a viscous cycle that speeds up the pathology of AD [51]. Non-steroidal anti-inflammatory drugs (NSAIDs) is the commonest type of anti-inflammatory drugs that inhibit the activity of cyclooxygenase (COX), a major player involved in inflammation. Finding from a number of studies, including our group's, suggested that increased COX-2 was associated with increased risk of AD [52-54]. Epidemiology studies showed a lower risk for people using NSAIDs in developing AD [55, 56]. The Rotterdam study included almost 7000 subjects aged over 55 and reported that the risk of AD subjects who were prescribed for NSAIDs for over 24 months was reduced by 80%. However, such reduced risk of AD were not found in subjects with shorter prescription period [57]. The largest case-control study investigating the association between NSAIDs and the risk of AD, which involved 691 AD patients and 973 unaffected family members, reported a reduced risk for patients taking NSAIDs for over 6 months (odds ratio = 0.64, 95% CI: 0.38-1.05) [58]. In addition, cross-sectional retrospective study supported the finding of reduced AD risk for subjects using NSAIDs [59]. Cognitive decline as an outcome measure was investigated in the Nurses Health Study, one of the largest survey which involved over 16100 females aged 70-81 years old. The result suggested a protective effect on cognitive decline for subjects using NSAIDs and aspirin, with relative risk of 0.79 and 0.75 respectively [60].

Protective effect for AD was supported by epidemiology studies. However, no significant improvement was observed among subjects who had established AD [61] or were presented with preclinical pathology [57]. These observations agreed with the inflammatory hypothesis for AD that continuous inflammation and the pathology in AD formed a viscous cycle, therefore NSAIDs prescription is not beneficial to pre-existing AD pathology and the condition is not reversed by NSAIDs. The results from epidemiology studies suggested a protective effect of NSAIDs which may be useful for delaying the onset of AD.

Cognitive reserve

The concept of cognitive reserve suggested that education, intelligence and life styles act against the damage or pathology in the brain and reserve its normal functioning [62]. Bilingualism is suggested as a protective factor for AD and it was associated with delayed onset of AD. Several studies reported languages improved the performance in cognition and attention [63, 64]. Education is regarded as a protective factor for the development of AD but a study reported a mean AAO of 71.4 among monolingual subjects who received higher education, lower than the bilingual group who had comparatively lower level of education that had a mean AAO of 75.5 [65].

This observation suggested bilingualism might be a strong protective factor in delaying the AAO of AD. A follow-up study by the same group that recruited another set of subjects showed a persistent delayed onset of AD for a bilingual group, 5.1-year difference when compared to the monolingual group [66]. Another study reported the beneficial effect of bilingualism was only observed in subjects with lower education level, which is different from the result as reported by Craik et al. [67]. However, both studies suggested bilingualism delayed the onset of AD and this might be associated with the preservation of cognitive reserve to act against the AD pathology in the brain.

Diet

Life styles such as diet and dietary habits were associated with the risk of AD, based on the hypothesis on the relationship between oxidation and the risk of AD. General evidence supported the relationship between improved nutrients and cognition [68]. Studies suggested chronic accumulation of reactive oxygen species caused damage to the brain and increased the risk of AD. Nurses Health study reported a protective effect of high vegetable consumption against cognitive decline [69]. Therefore, fruits and vegetables containing antioxidant is expected to delay the onset of AD. A randomized controlled trial suggested that vitamin B slowed the rate of atrophy as commonly observed in mild cognitive impairment, predicting its beneficial effect on delaying AAO of AD [70]. At present, there is no clear evidence on how and whether diet can delay the onset of AD but there is clear evidence that diet high in anti-oxidant offered a protective effect on the risk of AD.

Conclusion

AD is a complex neurodegenerative disease and accumulating data suggested the contribution of genetics to the pathogenesis. On the other hand, environmental factors such as age, education and life styles played an important role in modulating the outcome of the disease. It is believed that AAO of AD is closely associated with the progression of AD from mild cognitive impairment or normal cognition and is the balance between risk factors and protective factors towards the pathology of AD. There are not many studies investigating the interaction effect of genetic and environmental factors on AAO of AD. However, studies on the predisposition of AD risk showed genetics played an important role in the effect of environmental exposure. ApoE ε4 is a well-known risk factor for AD, however, it showed a decreased risk in subjects using NSAIDs, consuming daily coffee and wine, and doing regular physical activity [71]. The finding supported the gene/environment interaction in AD. Likewise, it is possible such gene/environment interaction modulated AAO of AD, as the factor modulating the risk of AD may also affect the AAO and severity of the disease.

Studies suggested that delaying the onset of AD by 2 years will reduce the expected prevalence of the disease by 23% by 2050 [5]. In this review, the genetic and environmental aspects on modulating the AAO of AD were discussed, especially the environmental factors, which are modifiable. It is hoping that the continuous research in these areas will provide new knowledge on risk/preventive factors and pathological mechanisms, which will be useful in the development of treatment and recommendation of life style habits to prevent or delay the onset of AD, which is an important issue for a sustainable society in the aging population. ■

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Losses and Gains: a Meaning-Based Framework of Working with Caregivers of Persons with Dementia

Abstract

Caregivers may often experience stress and a feeling of being burdened in providing care to family members who suffer from dementia. One particular emotional burden is that of losses and grief, when they observe the changes in their family members following dementia. Yet, caregivers may also experience gains, different positive aspects of caregiving. Thus, in working with caregivers of persons with dementia, we may consider both their losses and gains. In this paper, a meaning-based framework is proposed to conceptualize dementia caregiving as a process of experiencing losses and gains. In this framework, the adjustment to caregiving is suggested as depending on the search for meaning in caregiving. Two ways of facilitating caregivers' search for the meaning in caregiving are proposed: making sense of the losses in caregiving and finding positive aspects in caregiving. Practice implications that focus on these two ways are discussed.

Introduction

Providing care to family members with dementia is often considered a stressful task, especially when they show various behavioral problems (Gaugler, Wall, Kane, Menk, Sarsour, Johnston, Beusching, & Newcomer, 2010). The majority of previous research studies also focus on the burden of caregiving, such as the negative impact on the physical and psychological well-being of family caregivers of persons with dementia (Au, Lai, Lau, Pan, Lam, Thompson, & Gallagher-Thompson, 2009; Chang, Chiou, & Chen, 2010; Pinquart & Sörensen, 2003; Vitaliano, Zhang, & Scanlan, 2003).

One specific topic that is closely related to the emotional burden is the grief experienced by these caregivers as a result of different losses (Holley & Mast, 2009). For example, as the dementia progresses, caregivers are well aware of the changes in their family members, and they may experience loss of meaningful relationships and changing communication patterns with care recipients, as well as loss of freedom and future plans (Farran , Keane-Hagerty , Salloway ,& Kupferer, 1991). Very often when we mention grief, we may associate it with bereavement and the post-death period. The grief of caregivers in the process of caregiving is often overlooked, but it may have a great influence on whether they can cope with the stressors of caregiving (Noyes, Hill, Hicken, Luptak, Rupper, Dailey, & Bair, 2010). In the Chinese context, surprisingly, few research studies have explored the grief of Chinese caregivers of persons with dementia in both pre-death and post-death periods. Yet, grief of caregivers of persons with dementia appears to be a culturally universal phenomenon. Considering its clinical significance, it is important for helping professionals to help caregivers face the loss and grief in dementia caregiving. Also, the clinical experience of working with caregivers of persons with dementia may reveal that caregiving is not merely a process of experiencing losses but also experiencing gains. In the recent literature, more and more attention has also been paid to the positive aspects of caregiving (Cohen, Colantonio, & Vernich, 2002; Liew, Luo, Ng, Chionh, & Goh, 2010; Pinquart & Sorensensen, 2004). In a national study of caregivers in Canada, it was found that up to 73% could identify at least one positive aspect of caregiving (Cohen, et al., 2002). Caregivers may experience different positive aspects; for example, Carbonneau, Caron, and Desrosiers (2010) proposed three domains of positive aspects of caregiving: a) quality of caregiver and care receiver daily relationship, b) caregivers' feelings of accomplishment, and c) meanings of caregivers' role in daily life. Positive aspects of caregiving are only briefly explored in the Chinese context. For example, Lai (2010) investigated positive aspects of caregiving among Chinese people in Canada and conceptualized this as a kind of appraisal, which includes a) perceived gains, b) perceived economic costs, and c) perceived value of providing care. Filial piety was found to be a key protective factor that may enhance the positive effect of caregiving appraisal on caregiving burden. Again, experiencing the positive aspects of caregiving appears to be a culturally universal phenomenon. Apart from focusing on the grief of caregivers, it seems to be equally important for helping professionals to explore caregivers' positive experience in caregiving, so as to understand what may help them (Kramer, 1997).

Caregivers actually experience both losses and gains in providing care to their family members with dementia (Ott, Sanders, & Kelber, 2007). In order to better work with these caregivers, helping professionals may need to focus on both their losses and their gains. The literature seems to lack discussion on the intervention model, a model that may highlight the importance of both the losses and the gains of caregivers. Thus, in this paper, I would like to propose a framework that aims to conceptualize and incorporate the losses and gains of caregiving and shed light on the intervention for caregivers for persons with dementia.

Proposing a meaning-based framework

As mentioned above, caregivers may experience both losses and gains in caregiving. Thus, in this proposed framework, caregiving is conceptualized as a life event that includes caregivers' experience of losses and gains. With reference to Chan, Epstein, Reese, and Chan (2009), this framework highlights the coexistence of negative and positive aspects of caregiving (losses and gains) (as shown in Figure 1). This idea is represented by the Chinese concepts of yin (negativity) and yang (positivity). It reflects the dynamics and interplay between the experience of losses and gains in caregiving. That means the overall caregiving experience is changing, and at a certain point, caregivers may experience more losses than gains; at other times, they may experience more gains than losses.

To conceptualize the caregiving process in the context of experiencing losses and gains, this framework suggests that the adjustment to caregiving may depend on whether caregivers can search for the meaning in experiencing losses and gains. The literature also indicates that searching for meaning in caregiving is crucial for the well-being of caregivers of persons with dementia (Farran , et al., 1991; Farran, Miller, Kaufman, Donner, & Fogg, 1999; Noonan & Tennstedt, 1997). With reference to Davis, Nolen-

Hoeksema, and Larson (1998), in this framework, meaning searching is conceptualized to include two components: making sense and finding benefit. To integrate the concept of meaning searching in the context of experiencing losses and gains in caregivers, this proposed framework targets two key components (see Figure 1): a) making sense of the losses in caregiving and b) finding positive aspects in caregiving.

Making sense of losses and finding gains are conceptualized to be interactive (as indicted by the two-way arrows in the figure). For example, making sense of the losses in caregiving may have an impact on finding positive aspects in caregiving. The reverse is also true. Similar ideas have also been expressed in the literature of bereaved caregivers, e.g. indicating that positive memories of caregiving may help caregivers to search for meaning in the grieving process when the care recipients die (Boerner, Horowitz, & Schulz, 2004; Davis, et al., 1998; Frankl, 1984). All of meaning searching in caregiving represents a simultaneous process of making sense of the losses and finding positive aspects of caregiving.

Figure 1. Search for meaning in caregiving in the context of experiencing losses and gains.

Implications for practice

This framework suggests that helping professionals may facilitate caregivers' adjustment to dementia caregiving mainly through two ways: making sense of the losses in caregiving and finding positive aspects in caregiving.

Making sense of the losses in caregiving

As mentioned above, the grief of caregivers in the process of caregiving is often overlooked. Doka (2002) used the term "disenfranchised grief" to illustrate the situation in which a person may be deprived of the right to grieve. Caregivers of persons with dementia may also experience disenfranchised grief when others do not understand their grief when the care recipients are still alive. They may find it hard to express their grief and losses, when others associate grief only with death. Thus, the first step for helping professionals to help caregivers to make sense of the loss may involve active listening and normalizing caregivers' feelings of grief. Caregivers have the right to express their grief, and grieving is part of the process of making sense of the losses.

In bereavement counselling, one of the intervention focuses is to help bereaved persons to develop a healthy continuing bond with the deceased family members (Field, 2006; Neimeyer, Baldwin, & Gillies, 2006). Similarly, in working with caregivers' grief during caregiving, it may be important for helping professionals to help the caregivers maintain the continuing bonds with the family members who suffer from dementia. Caregivers may often focus on the losses and changes of the family members after they suffer from dementia, e.g. their personality changes. This may bring a deep sense of grief when they think the family members they knew well have gone and their bonds are broken. Yet, helping professionals may acknowledge the caregivers' sense of changes and grief; they may also help caregivers to make sense of the losses by focusing on "things unchanged". In Logotherapy, Frankl (1983) suggested a way of facing the losses by realizing the eternal nature of time. He stated that something that happened remains eternal, as no one can take away the past. In exploring the grief of Chinese older adults following the death of a spouse, Chan and Chan (2011) also stated the importance of time perception in the adjustment to bereavement. In the context of dementia caregiving, helping professionals may help caregivers to realize that dementia cannot take away the past that has been built together between the caregivers and care recipients. For instance, helping professionals may say, "Yes, it's really difficult for you to experience so many changes in your husband since he's been suffering from dementia. However, is there anything that you think remains unchanged between you two?" This kind of dialogue may help bringing out the message that not everything has been lost, and something is unchanged, e.g. he is still your beloved husband although he suffers from dementia. In this way, caregivers may better rebuild the continuing bonds with the care recipients and make sense of the losses.

Finding positive aspects in caregiving

Helping professionals may often undermine the positive aspects of caregiving, especially when they work with caregivers who are more deprived and stressed. Yet, facilitating caregivers' search for the meaning in caregiving by identifying the positive aspects of caregiving may be important in the intervention. In fact, the experience of positive aspects of caregiving may reveal crucial information to helping professionals, e.g. the reasons the caregivers may sustain the stressful caregiving role.

In actual practice, helping professionals may find it hard to explore the positive aspects of caregiving among caregivers, particularly in the Chinese context. Chinese people may not be very expressive in disclosing their feelings. For example, Ho, Chan, and Ho (2004) indicated that Chinese people with cancer tend to control their emotions. Even when caregivers are willing to share their feelings, helping professionals may realize they tend to share their negative emotions and stressful caregiving experiences. In the bereavement literature, Walter (1999) proposed the term "policing grief" which describes the culture's constraints on how we should grieve. If we apply this concept to understand the situation of Chinese caregivers of persons with dementia, we may better understand why caregivers may not be ready to share the positive aspects of caregiving. Our current societal beliefs have somehow defined caregiving as a stressful and negative task, and Chinese caregivers may think it is not appropriate for them to express the positive aspects of caregiving.

However, this is exactly the first step that helping professionals can take in exploring the positive aspects of caregiving, i.e. helping caregivers realize that positive aspects of caregiving can still be experienced although caregiving is a stressful task. In this way, helping professionals may normalize caregivers' expression of positive experience in caregiving and assist them to search for the meaning in caregiving.

Next, helping professionals may adopt the technique of Socratic Dialogue as mentioned in Logotherapy (Frankl, 2004), to help them explore an alternative perspective, including the positive aspects of caregiving. For example, when caregivers are mostly occupied by negative emotions and experiences, helping professionals may ask a surprising Socratic question: "Yes, it's such a hard task, and you suffer too. But may I ask you a question that you may find a bit strange? If taking care of him is so stressful, why do you continue to do so?" Caregivers may reply immediately, "I don't have a choice. I have to do so." If the helping relationship is mature enough, helping professionals may further explore it: "Do you really have no choice? A person may leave the family and quit the caregiving task, but you don't. Do you think there is a reason for you to continue in the caregiving role?" In this way, helping professionals may have a chance to explore the posi-

tive meaning underlying the stressful caregiving role. Helping professionals need to be aware that they should not force the caregivers to search for the positive aspects of caregiving. Instead, they may perform the role of facilitator and encourage the caregivers to appreciate the small hopes and beauties in caregiving.

Conclusion

Taking care of persons with dementia is a great challenge for many family caregivers. It is true that it may be a stressful task, and caregivers may also experience losses and grief when observing the changes in their family members who suffer from dementia. Yet, the proposed framework in this paper may also remind us that caregiving may not only involve losses but also gains. This is consistent with helping professionals' experience: We encountered very stressful and depressive caregivers; we also encountered ones who are so grateful that they have a chance to take care of their family members. Helping professionals should not forget that many caregivers possess their own strengths and personal resources (Chan, 2009), and they are able to cope with the caregiving challenges.

In the proposed framework in this paper, caregiving is conceptualized as a life event that includes caregivers' experience of losses and gains. The key to adjustment may depend on the meaning-searching process, which includes making sense of the losses in caregiving and finding positive aspects. It is hoped that this conceptual framework will provide some insights to helping professionals when working with caregivers of persons with dementia. Future research studies are required to further examine the proposed ideas empirically. ■

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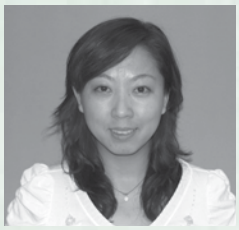

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Practice Person-centered Care for Demented Older Adults In Hong Kong Residential Care Facilities: A Qualitative Exploration

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Abstract:
Introduction: Along with the rapid pace of an aging society in Hong Kong, the demand for dementia care becomes an increasing pressure in long-term care services industry. A scientific care approach is urgently needed to ensure quality of care. Person-centered care (PCC) has been proved as "most desirable" for demented older adults. However, how PCC has been understood and practiced in Hong Kong is unknown. This study aims to examine practices of PCC for demented older adults in residential care facilities in Hong Kong.

Method: Qualitative method, in particular in-depth interviews was applied to this study. Brooker's four major elements of PCC were used to guide developing interview guidelines. 11 superintendents of residential care facilities in Hong Kong were interviewed on their perceptions of PCC towards demented older adults in their service settings, their daily practices relating to Brooker's four major elements of PCC, and barriers of applying PCC.

Findings: Findings showed that interviewees have a diversified understanding of PCC, which failed to reach a consensus of PCC conceptualization. A variety of practices, including conventional practices and innovative ones have been identified, which shows a strong identification towards PCC. Interviewees reflected a range of good practice relating to Brooker's four major elements of PCC. It includes 1) valuing demented older adults and their caregivers as a stepping stone of practicing PCC; 2) individualized care as a mechanism of practicing PCC; 3) continuous assessment as a pathway to practicing PCC; and 4) nurturing environment as a facilitator in practicing PCC. Lack of knowledge and skill competence, and increasing work stress and environmental constraints have been seen as the major barriers towards PPC.

Implications: This situation calls for further policy intervention on setting up consensus and standards of PCC; systematic training; scientific evaluation on quality of care; and evidence-based research on the PCC.

Keywords:
Person-centered care; demented older adults; residential care facilities, Hong Kong

Introduction

Along with a rapid growth of the aging population, the number of demented older adults in Hong Kong has increased by 18,000 per year and reached 110,000 in 2010 (JCCPA & HKCSS, 2010). This number is estimated to increase to 280,000 by 2036 (HKCSS, 2011). Residential care has become one of the most pressing issues among all of the services for demented older adults in social and health systems, not merely because of the accelerating demand, but also due to the complex and increasing needs of demented people along the changes in the kinds of diseases, which outranged the capacity of many families to provide quality care. Just like in other developed countries, policy strategies are highly expected to meet these challenges by adopting a scientific and efficient care approach to ensure good quality of care (QoC) for demented older adults. A recent report,

which is a five–year strategic plan on dementia care published by the Hong Kong Council of Social Service (HKCSS) in 2011, advocated improving quality of care as a future policy goal. It would be important and timely to examine a possible framework that could lead to improved quality of care for demented older adults systematically.

Along the process of seeking better QoC for demented older adults, previous literature showed that person-centered care (PCC) is one of the most desirable approaches (Price, 2006). PCC was developed in response to the needs for resident-oriented healthcare service, and was established on a rich understanding of residents' circumstances and needs (Price, 2006). Studies showed that applying PCC interventions by formal caregivers are effective in reducing the use of antipsychotic drugs (Fossey et al., 2006) as well as agitation behaviors (Ballard & Aarsland, 2006; Chenoweth et al., 2009) among the demented population. Based on these clinical evidence, PCC has already been adopted as a key standard in dementia care management in Australia (Alzheimer's Australia, 2007) and most European countries, e.g. France, Netherland, Norway, and the UK (Alzheimer's Society, 2001; Department of Health, 2009). As such, PCC becomes synonymous with good quality care for demented older adults.

However, in the context of Hong Kong, little is known about whether and how the PCC approach has been understood and practiced in taking care of older adults with cognitive decline, particularly in residential care facilities. This study aims to examine the practices of PCC for demented older adults in residential care facilities in Hong Kong.

PCC and its Four Major Elements

In the last two decades, the notion of PCC has experienced a substantial development and become a dominant approach in dementia care. By literal meaning, PCC refers to "valuing people as individuals" in delivering health care (Winefield, Mueller, Clifford, & Farmer, 1996). The origin of the term "person-centered" can be traced back in the client-centered psychotherapy (Rogers, 1951). Kitwood (1988b) did the pioneer work to cite this concept to dementia care and gradually established an integrated and systematic conceptual framework of PCC (Kitwood, 1988b, 1993d; Kitwood & Bredin, 1992). At the heart of PCC, Kitwood argued that "no matter how severe the cognitive losses are, there is a 'core self' which remains recognizable and fundamentally intact" (Ballard & Capstick, 2007). Accordingly, high-quality interpersonal care becomes the most valuable outcome of Kitwood's PCC approach.

In the same vein, Brooker (2004) sketched four major elements of PCC in an equation: PCC=V+I+P+S, which means 1) "V": valuing persons with dementia and those who care for them; 2) "I": treating people as individuals; 3) "P": looking at the world from the perspective of the person with dementia; 4) "S": providing a positive social environment in which the person with dementia can experience relative well-being. Brooker's four major elements of PCC provide a more exercisable explanation of PCC, and thus have been applied to designing training programs and practicing guideline of PCC (CEAL, 2010). It has also been used to develop dementia care mapping, which is an observation tool for assessing the quality of life of demented older adults (Brooker, 2005). However, most of the previous studies examined Brooker's four major elements of PCC within the context of residential care facilities among the non-Chinese population, which led to a research gap.

Methodology

This study adopted a qualitative research method, in particular in-depth interviews were employed. In order to explore the practice of PCC in residential care facilities, superintendents are selected as the interviewees. The major reasons lie in that superintendent is the key person in care facilities, who could provide an overview of PCC practicing at residential setting. Brooker's four major elements of PCC have been applied to develop interview guidelines. A total of 11 superintendents from three non-government organizations were interviewed, with either nursing or social work background. A pilot study was conducted with a superintendent, which aimed to examine whether core questions in the interview guideline could be understood and answered. The semi-structured interview guideline was then adjusted after the pilot study. 10 in-depth interviews were conducted by the researcher, during which the interview process were audio-taped.

Table 1
Guiding Questions for In-depth Interview

	Key questions
1.	Please share your view on person-centered care.
2	In daily practice, how do you value demented older adults? What are possible barriers?
3	In daily practice, how do you provide individualized care? What are possible barriers?
4	In daily practice, how do you interpret the world of demented older adults? What are possible barriers?
5	In daily practice, how do you build up a positive environment for promoting the quality of life for demented older adults? What are possible barriers?

Thematic analysis was adopted to analyze the data, in which three stages were followed: organizing the data, interpreting the meanings, and developing a series of themes from the data (Boyatzis, 1998).

The 11 residential care facilities showed a variety of aged care settings in Hong Kong in terms of home size. There are 4 small-sized residential care facilities which serve less than 100 residents. Among the four, one mini-home offers only 32 places. There are also 5 medium-sized residential care facilities whose capacity are between 100-200 beds, and 2 large-sized residential care facilities which serve more than 250 residents were included as well. The ratios of residents with cognitive impairment among these 11 residential care facilities reach an average level of 40.3%, while the ratios range from 31.1% to 54.2%.

Findings

Through the thematic analysis, three major themes have emerged, which are 1) practicing PCC without a consensuses perception; 2) a range of good practice relating to Brooker's four major elements of PCC. (To be more specific, it refers to four sub-themes, which are valuing demented older adults and their caregivers as a stepping stone of practicing PCC, individualized care as a mechanism of practicing PCC, continuous assessment as a pathway to practicing PCC and nurturing environment as a facilitator in practicing PCC.); and 3) barriers in practicing PCC. Table 2 summarizes the themes.

Table 2
A Summary of Themes

Primary themes	Secondary themes
No-consensus perception toward PCC	Individualized care perspective Holistic approach perspective Care with dignity perspective
A range of good practice relating to Brooker's four major elements of PCC	Valuing demented older adults and their caregivers as the stepping stone of practicing PCC Individualized care as a mechanism of practicing PCC Continuous assessment as a pathway to practicing PCC Nurturing environment as a facilitator in practicing PCC.
Barriers in practicing PCC	Lack of knowledge and skills competence Increasing work stress and environmental constraints

Practicing PCC without a Consensus Perception

Regarding the understanding towards PCC, interviewees have three different perspectives. First, some interviewees put considerable weight on individualized care. They thought that the demented older adults themselves are the starting point of providing any services. That is to say, the formal caregivers should take the demented older adult's perspective to understand their needs, and the care arrangement for any individual resident should be suitable for their background, preferences, and habits. Therefore, getting to know a demented older adult is the initial step to provide services.

Second, some other interviewees viewed that the PCC approach is similar to the Holistic Approach (Alan, 1980) which requires integrated care towards one's physical, psychological, social and spiritual health. They interpreted that not only the person's physical health should be paid attention to, but also their needs in other aspects such as psychological/mental, social, and spiritual.

Third, other interviewees also believed that the heart of PCC is the dignity of demented older adults. Though the residents' cognitive ability is deteriorating, the caregivers should respect them as a person. An interviewee argued that caregivers should always remember that the one you are looking after is a "person". Only through PCC can demented older adults live a life with proper dignity. This shows a consistency with Kitwood's (1992) argument of personhood which is the key content of PCC.

A Range of Good Practice Relating to Brooker's Four Major Elements of PCC

During the in-depth interviews, all the interviewees introduced their practices related to each element of V/I/P/S. The major contents with representative examples are summarized as the following.

Valuing demented older adults and their caregivers as a stepping stone of practicing PCC

The element of "V" emphasizes two equally important counterparts: valuing demented older adults as well as their caregivers. Interviewees listed many concrete behaviors to illustrate how they value both the demented older adults and the staffs in their residential care facilities.

In respect of valuing demented older adults, three types of practice have been identified, which include: 1) showing courtesy and respect, 2) facilitating residents' freedom; and then 3) realizing residents' autonomy. First of all, interviewees thought the basic level of valuing demented older adults is showing courtesy and respect. This includes behaviors like demonstrating basic respects through language, expression and attitude, giving warm greetings and sincere regards to each resident every day, reminding residents of their own name when providing any service, and kindly explaining what is going to be done to the residents and so on.

Second, based on these basic respects, interviewees tried to facilitate residents' freedom, which shows a kind of deeper respect towards demented older adults. For example, interviewees are careful about the use of restrictions on demented older adults. An interviewee said that they tried their best to not restrain the demented residents. In her setting, only 4 out of 75 residents were restrained, which is a low level of using restraint in residential care facilities. Another interviewee gave an example that they allowed residents to worship Buddha in their home, even though it is a Christian organization. This example showed that the residents' religious freedom is respected in the residential care facilities. At another setting, an open door policy has been applied to let the residents with mild dementia access to the outside. The interviewees introduced that some residents lived in the same community with the residential care facility. Though they are diagnosed with dementia, they are still at the mild stage and familiar with the community. After seeking their family's consent, professionals will assess the residents' ability and health status, and determine whether to allow them to go out for a walk.

Finally, residents' autonomy has also been found to be valued to some extent at residential care facilities. For instance, in one residential care facility, demented older adults are allowed to decide what to do in their small group session. They make the decision, prepare the materials, and then take actions. Professionals help them to realize their idea, rather than design the activity for them. In another residential care facility, residents' opinion is collected twice a year through formal survey.

In respect of valuing caregivers, three major aspects can be recognized: 1) training; 2) providing incentive; and 3) taking suggestions from the staff. First of all, all the interviewees being interviewed attached considerable importance to the staff training issue. They expressed that enhancing personal working skill through systematic training is the best way to value their staff. They introduced different forms of training. Internally, they organized internal training instructed by professionals to front-line workers and appointed a supervisor to each front-line worker. Externally, they also encouraged staff to enroll in training courses provided by other organizations by offering time or a certain amount of cost. In a residential care facility,

the interviewees also tried a creative way to rotate positions among front-line worker so that staff can experience different work and learn new skills. Meanwhile, staff training covers a broad range of contents. On one hand, some regular training topics, such as infection control, bedsore prevention, carry skills, and fall prevention have been arranged in rotation during the year. On the other hand, a variety of dementia care training has been introduced, such as communication skills, behavioral problem control, cognitive training and etc. Moreover, staff's mental health, service spirit, and workplace safety are also important contents of training.

Second, superintendents argued that creating incentive is another efficient way of valuing staff. There are basically two kinds of incentive: spiritual and material. In terms of spiritual incentive, interviewees will give an oral prize, publicize those letters of thanks from residents' family, or have an individual talk to encourage excellent staff members. In terms of material incentive, interviewees will arrange a long-term contract with those who have excellent performance, or directly promote them. An interviewee bought small gifts by herself for those who worked more than 5 years in her residential care facility.

Finally, interviewees found that paying attention to the staff's opinion and taking their good suggestions could also express their respect to staff well. Several means of collecting staff's opinion have been identified, which include everyday hand-over briefing, regular staff meetings, superintendent mailboxes, and formal surveys. Interviewees found positive feedback when staff's suggestions were taken.

Individualized care as a mechanism of practicing PCC Regarding the "I" element, an individual care plan (ICP) has been found as a major mechanism to deliver PCC. Interviewees introduced that they would conduct home-visits before taking in new residents. The purpose of home-visits is to get a better understanding of the potential resident in his original environment. During the first month, professionals would assess residents' ability by using various psychometric tools. Then an individual care plan would be drafted for each resident based on one's own physical and mental health conditions and personal background. As such, ICP not only offers a treatment plan for disease or physical symptoms, but also facilitate proper cognitive interventions for each demented residents. ICP would be reviewed once or twice in a year. Interviewees believe that ICP is the most typical way to deliver individualized care.

Moreover, at two residential care facilities, demented residents have been arranged in a special ward, which is separated from other residents. This is called specialized care management for demented residents. Staff who work in this ward is offered more opportunities to attend dementia related trainings and courses, and thus they are supposed to be more skillful in taking care of demented older adults. Interviewees interpreted it as an extension of individualized care, because ICP has been well integrated into a specialized environment.

Furthermore, some innovative practices related to individualized care have been found. An interviewee introduced that they conducted a project called the "individual cognitive guidance book" or "personal life story book". This project aims to design a special album for each demented resident. It covers the subject's personal information, special dates and significant events in his or her life. By using this book, both caregivers and other visitors can help the demented older adults by recalling their old time, training memory and doing reality orientation.

Continuous assessment as a pathway to practicing PCC Element "P" refers to looking at the world through the perspective of demented older adults. Interviewees identified several ways to interpret the world of demented older adults. One of the most important ways is comprehensive assessment. Some interviewees argue that every demented resident has their own personal situation which differs from the others even if they are in the same stage of dementia. In order to understand one's real situation, they would do a series of assessments to measure resident's various kinds of abilities. Those regular assessment tools include the Mini Mental State Exam (MMSE), Geriatric Depression Scale (GDS), Beck Depression Inventory (BDI), Centre for Epidemiological Studies Depression Scale (CESD), Activity of Daily Living Scale (ADL) and so on. Such evaluation would be continuously conducted during certain periods, which provides a consistent interpretation of demented older adults.

Another important way to go into demented older adults' world is through communication. Some interviewees said that due to the cognitive deterioration, demented older adults normally fail to voice their own need and preference independently and actively, so that caregivers are required to ask them constantly and initiatively. Besides verbal communication, body language, facial expression and gestures are all significant hints to explore the ideas of demented residents.

Moreover, some other interviewees shared that observation is also a useful channel to interpret the demented older adults. Those who are in the middle and severe stage could neither express their own ideas nor reply to any inquiries. In this case, only through careful observation can the caregivers guess what the clients really want. For example, at one residential care facility, a physiotherapist arranged a pain healing intervention scheme for several demented residents, though they did not claim to have such problems. The therapist observed those clients for a long time, consulted their health record, and then predicted there is a large possibility for them to have this problem.

Nurturing environment as a facilitator in practicing PCC The "S" element means to provide a positive social environment in which the person with dementia can experience relative well-being. In residential care facilities, the captioned environment can be defined from three aspects, which are physical environment, social environment and interpersonal environment. First of all, concerning the physical environment, the safety issue is the priority among all concerns. As such, most of the residential care facilities in Hong Kong have a walking/escaping protection system, alarm system and wheelchair access. Some interviewees said that they follow the 5S (Structurise, Systematize, Sanitize, Standardize, Self-discipline) Management Guideline which helps to create a clean and clear, tidy, and handy physical environment (Hong Kong Association of Gerontology, 2004). Other interviewees contributed that they put up route signs, and other individualized marks to help the demented older adults find their way around.

Second, interviewees agreed that building up a positive social environment will benefit demented older adults. All the residential care facilities involved in this study provide a variety of dementia intervention projects, such as reality orientation therapy, reminiscence therapy, multiple scenery intervention, and etc. Social activities are also rich and varied. Besides the celebration for various festivals, there are monthly birthday parties, welcome parties for the new residents, visits and outings, and so on.

Third, the interpersonal environment is also a significant element to "S" element. Some interviewees shared that they put a lot of effort to build up an understandable and pardonable culture for demented residents. They focused on those cognitively intact residents and educated them about how to understand and support demented older adults. Some interviewees also invited volunteers to help organize activities for demented older adults. At one setting, demented older adults can regularly access the park nearby assisted by volunteers.

Barriers of Practicing PCC

During the interview process, two themes of barriers for practicing PCC emerged: 1) lack of competence on knowledge and skills among formal caregivers, and 2) increasing work stress and environmental constraints.

Lack of knowledge and skills competence Interviewees expressed that manpower is a crucial factor to realize PCC. However, the front-line workers in Hong Kong remain at a low competence level. The majority in the care worker's market are normally middle-age women, with less education and almost no nursing specific background except simple nursing training

courses. For those professional workers, there is no specific training on dementia provided during undergraduate study either. Increasingly, manpower shortage leads to high demand on on-site training and re-training which have been organized by individual organizations. As such, the competence level of manpower remains an irregularity. In addition, most residential care facilities are facing considerable challenges on manpower shortage and a high turnover rate. Reflected by some interviewees, the turnover rate reaches an average level of one fourth among the front-line care workers. Also, at some residential care facilities, the mixed ward in which demented residents and cognitively intact residents live together leads to extra challenges for care arrangement. Therefore, the service quality, especially the provision of PCC, is directly influenced by inefficient and less competitive manpower.

Increasing work stress and environment constrain Interviewees also reflected that the working pressure is increasingly accelerated in recent years. The reasons are mainly: heavy workload, higher expectation from residents' family and higher requirement from government (HKAG, 2004). Under such pressure, most residential care facilities are driven by task-focused goals. In addition, the physical environment in most of the residential care facilities in Hong Kong is less spacious and lack of outdoor space. In this situation, residents' privacy and freedom are restricted. As such, it remains a considerable difficulty to pursue PCC in a task-focused workplace and constrained environment.

Discussion

Based on the above findings, three observations deserve further discussion. 1) Lack of consensus about PCC may affect evaluating mechanisms on quality of care; 2) a variety of good practices of Brooker's four major elements of PCC shows a strong identity of practicing PCC at residential care facilities, and; 3) some components of Brooker's four major elements of PCC are still missing or under-developed, which calls for systematic training and promotion.

Lack of Consensus Needs Policy Interventions

First, the lack of consensus towards PCC poses potential peril to assessing quality of care. Though the interviewees have proper understanding about PCC respectively, they failed to show a high degree of agreement on PCC. Some interviewees focus only on the aspects of individualized care, which is what the "I" element is about; some interpreted PCC as a holistic approach; and others explained the heart of PCC is valuing dignity of demented older adults. In this case, there is not an agreeable standard to define PCC. One of the major reasons is that the policy framework and directions regarding PCC have not been in place in Hong Kong. In recent years we have witnessed an increasing attention on dementia care in Hong Kong (JCCPA & HKCSS, 2010). Hong Kong Council of Social Service drafted 9 acting objectives and goals for dementia care (HKCSS, 2011). However, PCC has not been formally recognized and its corresponding practice protocols have not been developed in the Hong Kong context. Since PCC is highly related to the quality of life of demented older adults (CEAL, 2010), a scientific and systematic dementia care strategy is urgently needed. Absorbing the experience of developed countries, the practicing guideline of PCC for residential care facilities should be put on the list of preferable tasks, followed by systematic caregivers' training and regular outcome assessment.

Diversified Practices Comes from a High Identification of PCC

Second, though lacking consensus, Brooker's four major elements of PCC can be identified in narratives of interviewees. They reflected a range of good practice relating to each V/I/P/S element. We can see that Brooker's four major elements of PCC have been tried in different ways through daily practice. Practices, such as ICP and occupational therapy are well developed. Some project-based practices, such as the open-door policy and individual life story book indicate staff's effort to promote PCC. Interviewees showed a strong identity of PCC approach, and believed that the PCC approach would benefit the demented older adults. Increasingly, they expressed a strong willingness to fulfill PCC with their best effort.

Possible explanations for the high identification of PCC could come from four major aspects. First of all, PCC is consistent with social work values – a person-centered, holistic approach. As all the interviewees have social worker or nursing background, their educational and professional background provides them with a solid foundation to grasp the soul of the PCC approach. Moreover, all residential care facilities are governmental subverted facilities which share similar quality standards, such as Service Quality Standards (HKCSS, 2011). Increasingly, sharing among NGOs has been practiced via conferences, symposiums and working groups under HKCSS. Finally, it is also strongly affected by urgent needs from the increasing number of demented older adults. Under such market pressure, service units need to work out daily practice protocol and consolidate good practices.

Some Components of Brooker's Four Major Elements of PCC Need to be Recognized

Third, regarding each element of V/I/P/S, some key components have been found underdeveloped or missing. The aspect of valuing demented older adults was identified largely on a basic level. Residents' freedom and autonomy need to be valued more. Meanwhile, the focus of valuing staff is now put on the aspect of skill training; more humanistic care is needed. Moreover, though the ICP is a major mechanism to deliver PCC, it also limits individualized care within a medical-oriented scope; psychosocial proportions need to be broadened. Increasingly, the practices of the "P" element rely too much on assessment rather than communication and empathy. In respect of the "S" element, we can see that great effort has been taken to build up positive social and interpersonal environments for the demented older adults. However, it seems that most of the social and cognitive activities are designed for the demented residents in the mild and moderate stage; on the contrary those in the severe stage still have less exposure to positive environment. Moreover, there also lacks evidence regarding to what extent the quality of life of demented older adults is improved. This remains a research gap for further exploration. That is to say, a systematic study of evidence-based practice on the PCC's effectiveness and outcome measures needs to be strengthened.

Finally, the difficulties in practicing PCC are mainly the lack of various kinds of resources. It seems that interviewees had a clear understanding about it and have been trying their best to promote PCC, although it is hard to solve in a short- term.

Conclusion

1. Interviewees in this study have a diversified understanding of PCC, but failed to meet a consensus conceptualization. This may affect the evaluation of care quality. Developing policy principle and practice guidance is highly recommended.
2. To some extent, Brooker's four major elements of PCC can be seen in place in daily practice. However, these four major elements (V/I/P/S) are mainly delivered in some well-established ways such as ICP and various kinds of interventions; more creative and efficient ways of delivering PCC are worthy to explore.
3. Lack of knowledge and skill competence, increasing work stress and environmental constraints are major obstacles that affect practicing PCC. Improving the long-term care situation for demented older adults is a more and more urgent issue, which calls for a joint-effort from government, society, business, and the academic field. ■

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Challenges in Disaster Medical Response

The management of the medical and public health effects of contemporary disasters, whether natural or man-made, is one of the most significant challenges facing medical providers today. Disaster medical care is not the same as conventional medical care. Disaster medical care requires a fundamental change in the care of disaster victims in order to achieve the objective of providing the "greatest good for the greatest number of victims".

The demands of disaster medical relief have changed over the past decade, both in the scopes of medical care, the spectrum of threats, and the field of operations. Increasingly, medical providers are being asked to respond to complex disasters, the spectrum of threats ranging from natural disasters to complex man-made disasters such as war and terrorism.

Natural disasters may be classified as sudden-impact (acute) disasters or chronic-onset (slow) disasters. Sudden-impact natural disasters generally cause significant morbidity and immediate mortality immediately as a direct result of the primary event (e.g. traumatic injuries, crush injuries, drowning) whereas chronic-onset disasters cause mortality and morbidity through prolonged secondary effects (e.g. infectious disease outbreaks, dehydration, malnutrition). Man-made disasters may be unintentional or intentional (terrorism). The spectrum of agents used by terrorists is limitless and includes conventional weapons, explosives and biological, chemical and radioactive agents. Seventy percent70% of terrorist attacks involves the use of explosive weapons and are is a significant challenge for medical providers due to the complexity of injuries (primary, secondary, tertiary and quaternary blast injuries).

Contemporary disasters follow no rules. No one can predict the time, location or complexity of the next disaster. Similar to the ABCs of trauma care, disaster medical response includes basic elements that are similar in to all disastersdisaster responses. The ABCs of the medical response to disasters includes:

- Search and rescue
- Triage
- Definitive care
- Evacuation

Mass casualty incidents (MCIs) are events causing numbers of casualties large enough to disrupt the healthcare services of the affected communities. Demand for resources always exceeds the supply of resources in a mass casualty incident. The difference in disasters is the degree to which certain capacities are needed in a specific disaster, and the degree to which outside assistance (regional, national or international) is needed. Rapid assessment by experienced teams of disaster responders will determine which of these elements are needed in the acute phase of the disaster to augment local capacities. Disaster management teams are based on "functional" capacities, not titles.

Search and Rescue

Many disasters, both natural and man-made, involve large numbers of victims trapped in collapsed structures. Many countries have specialized search and rescue teams as an integral part of their national disaster plans. Members of this team include:

- Cadre of medical/surgical specialists
- Technical specialists
- Trained canines

Triage

Triage is the most important, and psychologically challenging, aspect of disaster medical response, both in the pre-hospital and hospital phases of the disaster response. Triage is the process of shorting casualties according to the level of care they require in a MCI. Patients' needs are matched with available resources. Disaster triage is significantly different from conventional triage. The objective of disaster triage is to do the "greatest good for the greatest number of victims." The critical patients having the greatest chance of survival with the least expenditure of time and resources are the highest priority. Triage errors in the form of under-triage and over-triage are always present in the chaos of MCI.

Triage is a dynamic decision-making process of matching patients' needs with available resources. Three levels of disaster medical triage have been defined. The level of disaster triage utilized at any phase of the disaster will depend on the ratio of CASUALTIES to CAPABILITIES. Many MCIs will have multiple levels of triage as victims move from the disaster scene to definitive medical care. The three levels of disaster triage are:

- Field triage (Level 1)
- Medical triage (Level 2)
- Evacuation triage (Level 3)

Definitive Medical Care

Maximally acceptable care for all disaster victims is not possible in the early stages of the disaster given the large number of patients in a MCI. In the initial stage of the disaster, minimally acceptable care (crisis management care/altered standards of care) to provide life-saving interventions is necessary to provide the greatest good for the greatest number of victims.

Evacuation

In most disasters, the large number of victims needing evacuation, especially in austere environments, will mandate the use of non-convention medical transport aircraft. Evacuation decompresses the disaster area and improves care for the most critical casualties.

Conclusion

Good intentions and clinical expertise alone are not sufficient to achieve a successful disaster medical response. All medical providers must also incorporate the principles of disaster response into their training if they are to be effective "surge" capacity in today's complex disasters. ■







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Can the Accordion Stone Device Assist in Upper Ureteral SWL? In vitro and pilot clinical experience with a novel use of the device

Abstract

Background: Extracorporeal shock wave lithotripsy (SWL) of proximal ureteral stones has limited success rates. My objective was to determine whether an Accordion stone device might improve SWL effectiveness.

Methods: An in vitro model was used to determine optimal positioning of a 10 mm Accordion device during SWL. Three device positions were examined: (1) proximal to, (2) distal to, and (3) bracketing a simulated ureteral stone. Fragmentation efficacy was measured by drying and then weighing stones before and after SWL. Based upon the results of the in vitro study, with IRB approval and patient consent, five patients were evaluated during SWL with a 10mm Accordion device positioned either bracketing (2 patients) or immediately distal to the stones (3 patients). After SWL treatment (2000 shocks), the extent of fragmentation noted with fluoroscopic imaging was ranked as either low (minimal fragmentation), moderate (>60% of fragments >2mm), or extensive (<40% fragments >2mm).

Results: In vitro results noted positioning the Accordion device distal to or bracketing the stones was more efficient than placing the device proximal to the stones. In the clinical assessment, bracketing the stone with the film occlusion resulted in one moderate and one extensive stone fragmentation; positioning the occlusion distal to the stone resulted in one moderate and two extensive fragmentation rankings. There were no patient complications or damage to the devices employed. All 5 patients cleared their stones.

Conclusions: The Accordion device appears to assist stone fragmentation whether bracketing or positioned distal to the stone. The device provided guidance in localizing stones, did not interfere with the application of shock waves and reduced residual stone volume by sweeping fragments out of the

ureter after fragmentation in 3 of the 5 patients. These results warrant further clinical investigation.

Keywords:
Ureteral stone, SWL, Accordion device, fluid-filled chamber, film occlusion

Introduction

Extracorporeal shock wave lithotripsy (SWL) is considered one of the two first line treatments for patients with kidney stones which have migrated into the ureter.[1] This treatment procedure is non-invasive, but while it is highly effective for stones in the kidney,[2-3] treatment of stones in the ureter has a low initial success rate[4-7] and necessitates a second treatment in up to 50% of patients.[8,9] This lower success rate has been attributed to the lack of fluid surrounding stones in the ureter in contrast to much higher success rates when the stone is located within the fluid-filled calyces of the kidney.

Fragmentation of ureteral stones with SWL results from the combined actions of compression and tension as the shock wave passes through the stone,[10,11] but another factor in fragmentation is cavitation.[12] The negative pressure of the shock wave creates cavitation bubbles. The collapse of these bubbles results in a high pressure amplitude shock (essentially a jet) that also assaults the stone surfaces.[13] However, the cavitation bubble formation is suppressed if the urothelium is in contact with the stone and therefore minimizes the amount of fluid available in which bubbles can form.[14,15]

Creation of an expansion chamber with an endourological device was proposed in 1990,[16] but subsequently little progress has been published on this approach. A novel stone management device, the Accordion Stone Management Device, has been designed to limit stone migration during ureteroscopic guided laser lithotripsy with use of a film-based occlusion component. This film occlusion conforms to the walls of the ureter and fluid movement past the occlusion is minimal.[17] If this film occlusion component can push the urothelium away from the stone, then it may be possible to provide a method of creating a gap in order for fluid (urine) to accumulate around the ureteral stone. A fluid chamber surrounding a stone does result in higher fragmentation rate with SWL.[14,15] Pilot in vitro work has demonstrated that the Accordion Stone Management Device can withstand the assault of shock waves while remaining functional and intact.

In order to test this theory, first an in vitro study was first undertaken to determine which position of the Accordion device's film occlusion in relation to the stone is optimal for fragmentation by SWL, followed by an assessment of SWL fragmentation in patients in a pilot clinical study.

Methods

In vitro Study

The Accordion Stone Management Device (PercSys) consists of a two-part guide wire with a polyurethane film near the device's proximal end (Figure 1). After the device is advanced past the targeted stone, the film is pulled together to form an occlusion (Figure 2). This occlusion limits the migration of stone fragments during lithotripsy and can be used to sweep fragments to the bladder. The Accordion device has U.S. Food and Drug Administration marketing clearance and CE marking; it is not considered to be an experimental device and its use in SWL procedures is not off-label. For this study, the 10 mm Accordion device was used.

Figure 1. The Accordion Stone Management Device is a two-part guide wire-based design, with a shaft diameter of 0.97 mm, which forms a 10 mm diameter occlusion.

Figure 2. The 10 mm film occlusion formed by the Accordion device once it is past the targeted stone.

The objective of this study was to visually assess the extent of surface defects and/or fragmentation of artificial stones when the Accordion device was placed in one of three positions: (1) the film occlusion formed distal to the stone; (2) the film occlusion bracketing the stone; and (3) the film occlusion proximal to the stone. As control, SWL was conducted on stones without an Accordion device present.

A test tank was constructed of acrylic panels with a Mylar window on the lower surface of the tank in order to simulate the skin surface, following a design of Neucks et al.[18] The test tank was filled with de-ionized water and placed on the treatment table of a Storz Modulith SLX ESWL machine into the focal point using biplanar fluoroscopy, such that the Mylar membrane was in contact with the water cushion of the treatment head. The electromagnetic therapy head of the SWL machine is integrated with the fluoroscopic imaging system isocentrically so when the imaging system is in focus with the target stone, the shock wave focus (F2) also is centered on the target stone.

An artificial stone, constructed of UltraCal with dimensions 7 mm x 10 mm and a mean dry weight of 0.59 grams, was introduced into an artificial ureter. Artificial stones constructed from UltraCal 30 have been reported to have physical characteristics similar to those of human kidney stones.[19] The artificial ureter was constructed of silicone and has characteristics of porcine ureters.

The artificial ureter containing the stone was submerged in the de-ionized water within the test tank and its proximal end connected to a reservoir of de-ionized water via tubing with a stop-cock. De-ionized water was instilled into the lumen until all air bubbles were removed from the artificial ureter.

Once the stone was in position and the artificial ureter free of air bubbles, an Accordion device was advanced within the lumen of the artificial ureter to the stone and the film occlusion engaged at one of three positions: distal to the stone; proximal to the stone; or bracketing (encompassing) the stone (Figure 3). In addition, a stone was placed in the artificial ureter without the presence of an Accordion device and subjected to the same SWL treatment regime as a control.

A. B. C.

Figure 3. Positioning of an Accordion device (A) distal to the targeted stone, (B), proximal to the stone, or (C) bracketing the stone. When the film occlusion is engaged, the radiopaque discs within the film coalesce.

In each run of the study, the acrylic tank was placed on the SWL machine in the position normally occupied by the patient's lumbar region during treatment for ureteral stones. The shock wave head was positioned approximately 10 cm (4 in) from the targeted simulated stone, with the focal point of the shock wave source (F2) targeted onto the center of the stone.

The treatment regime applied was modified slightly from that typically used for stones contained within the ureter (for the sake of time), but did cover the parameters typical for SWL treatments at this stone center: a cumulative number of 1000 shock waves provided over 17 minutes (power

starting at 3.3 mJ and ending at 22.7 mJ).

Following application of the shock waves, the stones and fragments were removed from the simulated ureter, air dried for 48 hours, and then weighed. A total of five stones were used in each position and as controls; mean weight for each position and control were calculated. The percentage weight reduction was calculated for each position and compared to the weight reduction in the control stones.

Pilot Clinical Study

The primary endpoints of the clinical pilot study were the capacity of the Accordion device's film occlusion to maintain the stone in position during the SWL regime, and the extent of stone fragmentation following application of the SWL treatment cycle. The extent of fragmentation was rated as low [no to minimal fragmentation noted], moderate [many fragments created but most (> 40%) of them larger than 2 mm], or extensive [many fragments created but with few (<40%) fragments larger than 2 mm].

The secondary endpoints were the capability of the Accordion device to sweep fragments into the bladder following the SWL treatment, and patient complications noted during or following the treatment.

With IRB approval and after gaining informed consent, patients included in this study were those who had been diagnosed with a solitary stone in one ureter, were 18 years of age or older, and scheduled to receive SWL treatment. Patients were excluded from the study pool if they had a bleeding disorder, had a urinary tract infection, were pregnant or nursing, and/or known to have ureteral strictures.

At my facility, typically patients are treated under sedation (often a general anesthetic agent) so that their movement during the SWL procedure is minimal. Once the patient was anesthetized, the location of the targeted stone was determined with the fluoroscopic imaging modality of the procedure table.

With the stone's location identified, a flexible cystourethroscope was advanced up the patient's urethra until its tip resided in the bladder. The ureteral orifice (UO) was visualized and an open-ended ureteral catheter was advanced to the distal ureter and a contrast agent injected into the renal pelvis. After removing the catheter, an Accordion device was advanced into the UO via the working channel of the cystoscope. Once the Accordion device was within the ureter, it was advanced, under imaging, until its film component was near the stone. In a nonrandomized scheme, the film occlusion bracketed the stone in the first two patients and then was positioned distal to the stone in the next three patients.

With the film occlusion in position, SWL treatment begun with the Storz Modulith SLX Lithotriptor and a total of 2000 shocks were applied to all stones.

After the treatment has concluded, using fluoro imaging, the extent of the fragmentation was rated as low, moderate, or extensive. The Accordion device was used to sweep fragments into the bladder as the device was removed from the patient. A total of five patients were enrolled in this pilot study.

Results

In vitro study

The film occlusion of the Accordion device resulted in higher levels of stone fragmentation than occurred with shock waves striking control stones (Figure 4). Following application of the SWL treatment regime, the control stones had a mean residual weight of 0.56 g, a reduction of 5% by weight from stones not treated with the SWL regime. With the film occlusion distal to the stone, the mean residual weight was 0.38 g, a 36% reduction from the stones' original weight. Placement of an Accordion device so that its film occlusion bracketed the stone caused a 29% reduction in stone weight, with a mean residual weight of 0.42 g; placement of the occlusion proximal to the stone resulted in a 15% reduction in weight (Table 1). The mean reduction in weight was significant when the film occlusion of the Accordion device either was positioned distal to the stone or when it bracketed the stone ($p = 0.03$ and $p = 0.05$ respectively). Based upon these results, the positions of the device's film occlusion used in the clinical study were bracketing the stone and the distal to the stone.

Figure 4. The typical reduction in core volume of UltraCal 30 artificial stones following SWL when (B) no Accordion device was used, (C) when an Accordion device was placed distal to the stone, or (D) encompassed the stone, or (E), or was placed proximal to the stone, as contrasted to an artificial stone prior to SWL (A).

Table 1. Reduction in weight following shock wave lithotripsy in stones with the film occlusion of the Accordion device positioned proximal to, distal to, or braketing the stone.

	Number	Mean weight (g)	Mean percentage weight reduction
Virgin stone	5	0.59	--
Control stones (no occlusion)	5	0.56	5%
Stones with occlusion proximal	5	0.5	15%
Stones with occlusion distal	5	0.38	36%
Stones with occlusion bracketing	5	0.42	29%

Pilot clinical study

The Accordion device was engaged distal to the stone in three patients and bracketing the stone in two patients. All five patients received the SWL treatment without complications; the device did not interfere with the SWL procedure or require the patient to be positioned in a manner that was not typical for the procedure.

The stones were all in the proximal ureter, with two approaching the ureteropelvic junction. The stones ranged in size from 5 X 3 mm to 7 X 7 mm (Table 2). The Accordion devices advanced easily to all five stones and the film occlusions were noted to assist in maintaining the stone in position during the procedure. Positioning the Accordion device distal to the stone assisted in targeting of the stones for SWL, especially in the one case of a patient with a radiolucent stone (Figure 5).

Table 2. Ranking of the extent of stone fragmentation during shock wave lithotripsy in 5 patients with the film occlusion of the Accordion device positioned bracketing the stone or distal to the stone.

Patient number	Stone size (mm)	Occlusion position	Extent of Fragmentation
1	5 x 8	Bracketing	Moderate
2	7 x 7	Bracketing	Extensive
3	5 x 7	Distal	Extensive
4	5 x 3	Distal	Extensive
5	7 x 7	Distal	Moderate

Figure 5. Accordion device immediately distal to a radiolucent stone (arrowhead) in order to assist in targeting.

None of the stones were ranked as having a "low" level of fragmentation, and more fragmentation was ranked as "extensive" than as "moderate" (Table II). The film occlusion was used to sweep fragments down the ureter and into the bladder in the three instances where the level of fragmentation was extensive. This sweeping permitted the majority of the residual stone burden to be removed from the ureter and did not result in hematuria or other complication subsequent to removal of the Accordion device.

Use of the Accordion device did not interfere with the application of the shock waves and appeared to promote fragmentation. While this was not a comparison study, my experience is that SWL of ureteral stones typically require 4000 shocks in one SWL session and, in this pilot study, sufficient stone fragmentation was achieved with only one application of 2000 shocks. The progression of fragmentation was monitored by pulling on the stone with the film occlusion of the Accordion device while shock waves were being provided. A change in the orientation of the stone on the fluoro image provided a visual clue that fragmentation was occurring (Table II). Another advantage provided by the film occlusion was that it maintained the contrast agent in the kidney and ureter proximal to a radiolucent ureteral stone (Figure 6) during the entire time of the SWL procedure, which eliminated the need to inject additional contrast during the procedure.

Figure 6. Retention of contrast agent in the kidney and ureter proximal to the film occlusion during shock wave lithotripsy.

Discussion

Use of an Accordion device in shock wave lithotripsy may provide advantages not only in increasing fragmentation efficiency of the SWL machines but also permit reduction of the volume of fragments in the ureter following the procedure. The early SWL publications were based upon a machine that required the patient to be immersed in a water bath.[20-22] The fragmentation success and stone-free rates reported with the Dornier HM3 lithotripter and formed the basis for establishing this modality of lithotripsy.[23] However, these machines were cumbersome and required general anesthesia, so SWL technology evolved to a design where the shock wave is generated within a fluid-filled arm of the machine that is placed in contact with the patient's skin so that the waves travel into the body via a wider shock path. This results in a smaller focal point and requires more precise targeting.

This approach has higher patient acceptance since there is minimal preparation required, but over the years the treatment success rates have declined to a point that some are questioning the utility of SWL as a treatment option in urethralureteral stones.[24-26] In order to increase the success rate, manipulation of the environment within the patient's body has been examined. Coordinating the application of shock waves to the patient's respiration has been examined as a way to maintain the stone within the target zone of the shock waves,[27] as has using more efficient pathways to the stone based upon the patient's body mass index.[28]

Another factor that has received attention in the past several years has been increasing the fluid volume around stones in the ureter. While different stone composition is associated with the success rate of SWL, presence or absence of fluid surrounding ureteral stones has been associated with fragmentation success.[14,15,29-31] As the shock wave from an SWL generator moves through the human body, cavitation bubbles are created by the negative pressure of the shock wave itself. As these cavitation bubbles collapse, a microjet of fluid is formed. This jet has been measured to have a speed approaching 100 meters per second[12] and to some researchers the impact of the microjet has a larger effect on fragmentation than the shock waves, since the acoustic emission produced by the collapsed cavitation bubbles have a peak positive pressure similar to the focused shock waves.[32,33] This concept of the utility of cavitation bubbles is bolstered by research that notes that the presence of fluid surrounding a stone doubles the fragmentation effect of SWL.[14,15,34,35]

Among the endourological tools available for use within the ureter, the Accordion device's film occlusion is unique. Other antiretropulsion devices are capable of minimizing migration of stone fragments during laser or pneumatic lithotripsy,[36,37] but typically they contain a barrier component that is mesh-like and open to movement of fluid.[17] As such they are incapable of maintaining fluid around a ureteral stone targeted with SWL. Several bench top studies have pointed to the capability of the Accordion device's film occlusion to maintain fluid within the ureter and point to an effect of enhancement of SWL fragmentation.[17,34,35] In the in vitro study reported here, fragmentation of artificial stones was increased significantly with the use of the device's film occlusion to create a fluid-filled chamber around the stone. Placing the film occlusion distal to the stone provided the highest level of fragmentation both in the in vitro study and in the pilot clinical study. This position fits with other observations of increased efficiency in SWL with fluid surrounding the stone.[14-16,29-31]

In addition to providing the mechanism for a fluid-filled chamber around ureteral stones, the film occlusion assisted in targeting the stones and elimination of stone fragment burden after the procedure. The film occlusion contains ten radiopaque discs in order to for the position of the occlusion to be monitored by fluoroscopic imaging during endourological procedures. These discs coalesce as the film occlusion is formed such that the imaging presents a grouping of the discs (Figure 5). The film occlusion is distinctive in such imaging and, once the occlusion was formed distal to the stone, it provided a means to assist in SWL targeting. Not only did the film occlusion maintain the stone in a specific location within in the ureter, but also one patient in this series also had a radiolucent stone which would have been difficult to visualize over the length of the procedure due to respiratory displacement of the ureter from the initial plane of the imaging focus had not the film occlusion remained highly visible. With the film occlusion present in the imaging, it was possible to continue the application of shock waves to this radiolucent stone within without needing to stop repeatedly in order to determine the location of the stone.

When used in ureteroscopic-guided lithotripsy of ureteral stones, the Accordion Stone Management Device often is often used to sweep fragments from the ureter and into the bladder at the end of the procedure. This technique allows removal of fragment burden, reduces the need for placement of a ureteral stent, and eliminates the use of stone baskets. Sweeping of fragments from the ureter with the Accordion device is safe due to its capacity to disengage the film occlusion at a force of 0.67 N[38] rather than produce a static barrier that potentially could avulse the ureter if a fragment becomes immovable. I used the Accordion device to sweep fragments from the ureter into the bladder following SWL in three of the five patients in this pilot

study. While I did not quantify the volume of stone fragments removed in these 3 patients, the fragments visualized in the bladder after sweeping were numerous and follow-up imaging found all patients to be stone-free at 3 months post-procedure.

Even though these data points to the beneficial effects of using an Accordion device in SWL procedures, one criticism to this technique is that its use moves what is presented as a minimally invasive procedure to the patient to a procedure with some additional manipulation. Outside the USA, SWL often is provided with minimal to no anesthesia, so placement of a cystoscope in order to place the Accordion device would result in a substantial departure from the current practice. In the USA, some level of anesthesia, often sedation, is applied, not only for patient comfort but also to limit movement of the patient during the procedure, which can result in the stone moving out the optimal zone for application of the shock waves.39 In my practice, ureteral stones larger than 1 cm typically require more than one session of SWL over a period of time. Even if minimal sedation were provided to these patients, SWL can be painful to the patient and the need to repeat the treatment two or three times is not always a welcome consultation with the patient. If the residual fragment burden following SWL of ureteral stones is high, I will place a ureteral stent at the end of the session, which requires the use of a cystoscope. So, use of a cystoscope in a SWL treatment session is not atypical. Therefore, having the cystoscope available at the start of the session to inject a contrast agent to assist with visualization of the stone and also to introduce an Accordion device is not a substantial deviation in my current practice. In addition, if this initial assessment of the Accordion device resulting in extensive fragmentation with just one SWL session is confirmed in larger studies, the prospect of having their ureteral stones addressed in only one SWL session with the use of a cystoscope rather than returning two or three more times for a minimally invasive session may be acceptable to patients with ureteral stones.

Conclusion

The Accordion device appears to have assisted in increasing the efficiency of shock wave lithotripsy in Vitro vitro and in vivo. The Accordion device provided assistance in localizing stones, did not interfere with the application of the shock waves, and reduced residual stone volume by sweeping fragments out of the ureter after effective fragmentation in 5 patients. These results warrant further clinical investigation. ■

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Pain Relief and Tissue Healing Using PEMF Therapy: A Review of Stimulation Waveform Effects

Abstract

Over the past seventy years, pulsed electromagnetic field (PEMF) therapy has been revealed as an effective means of reducing pain and inflammation in a wide variety of conditions while often promoting healing (Rohde et al. 2009; Hedén & Arthur a Pilla 2008; C. A. L. Bassett, R. J. Pawluk, et al. 1974; C. a Bassett, R. J. Pawluk, et al. 1974; C. a Bassett et al. 1977; Strauch et al. 2007; Strauch et al. 2011; Strauch et al. 2006). Observations and mathematical models suggest that one of the primary anti-inflammatory mechanisms

of PEMF is via the Calcium-Calmodulin (Ca2+/CaM) dependent nitric-oxide synthase pathway (M. Markov & A Pilla 1997; a Pilla et al. 1997; David J Muehsam & Arthur a Pilla 2009b; David J Muehsam & Arthur a Pilla 2009a; A A Pilla et al. 1999; Robert J Fitzsimmons et al. 2008; a a Pilla 1974; Arthur a Pilla 2002; Diniz, Shomura, et al. 2002; Diniz, Soejima, et al. 2002). Specifically, it is hypothesized that electromagnetic pulses of appropriate parameters will preferentially induce calcium binding to CaM (A A Pilla et al. 1999). Of utmost importance are the waveform parameters—with the most effective parameters falling within a range producing induced electrical fields on the order of 1 V/cm (W. Pawluk 2003; A A Pilla et al. 1999).

Unfortunately, the majority of the PEMF literature fails the basic scientific requirement of repeatability. By our accounting, more than 90% of all published reports fail to include adequate waveform parameters to fully define the dosimitry of the applied treatment. This shortcoming in the literature is very unfortunate as it tends to drive reputable clinicians and scientists away from the scientific study and clinical acceptance of PEMF, even though there is strong evidence to suggest that PEMF, when properly applied, is safe and can be very effective at reducing inflammation and pain while also accelerating healing of otherwise refractory injuries.

Herein we seek to review past and current technologies, effective waveform parameters, and propose a summary of the current theories regarding the mechanism of PEMF. Our goal is to establish clearly those experiments which are properly executed and have well-described stimulation parameters, and show that PEMF is an effective treatment for pain and inflammation given the appropriate stimulation waveforms.

Introduction

Electromagnetic therapies have been in use for many years. Electrical stimulation of tissues has been studied since Galvani's experiments using electricity and frog legs (Galvani 1954). The systematic study of the effects of electrical and magnetic fields on living and dead tissues began with Galvani in the late 18th century, whose research led to the discovery that one of the primary methods of information transfer within nerve and muscle tissues is via electrical pathways. In the middle of the 20th century, it was discovered that bone is piezoelectric in nature, and therefore was hypothesized to also transfer information electrically (Fukada & Yasuda 1957; Yasuda 1954). Soon thereafter, many experiments demonstrated that directly-applied electrical currents can be employed to induce bone formation and remodeling (Duriez & A. Bassett 1980; C. A. L. Bassett, R. J. Pawluk, et al. 1974; C. a Bassett, R. J. Pawluk, et al. 1974; C. a Bassett et al. 1977). One problem with these early methods of direct electrical stimulation of bone tissue was that they required the implantation of electrodes into and around the bones to be stimulated. The deeply invasive nature of direct electrical stimulation of bone led to the development of non-invasive methods, such as the use of induced electrical fields. These inductive methods employ magnetic fields from external magnets or solenoids that change over time to induce the desired electrical fields within the tissues, based on the well-understood Faraday's Law of Induction (Halliday et al. 2000). Electrical fields induced in this non-invasive manner were subsequently shown to be effective in eliciting accelerated bone formation and healing (C. A. L. Bassett, R. J. Pawluk, et al. 1974). With the advent of inductive stimulation methods came the study of the effects of non-depolarizing electromagnetic fields on tissues other than bone. Non-depolarizing electric fields are those which are too low to induce overt depolarization of the cell membrane as in the case of an action potential, but strong enough to presumably have other effects on molecular mechanisms within cells and in the extracellular space. Nerve regeneration became a topic of interest as it was shown that non-depolarizing electromagnetic pulses could improve nerve lesion healing. Further studies showed that inflammatory factors could be reduced in tissue inflammation in humans post operatively (Rohde et al. 2009; Hedén & Arthur a Pilla 2008). Pilla et al. developed a theory of interaction between pulsed radio frequency (PRF) waves and tissues which makes use of the frequency response of tissues and places lower bounds on waveform parameters based on the thermal noise threshold (David J Muehsam & Arthur a Pilla 2009a; A A Pilla et al. 1999; a a Pilla 1974; David J Muehsam & Arthur a Pilla 2009b; D J Muehsam & a a Pilla 1999; McLeod & AA Pilla 1983; M. Markov & A Pilla 1997; a Pilla et al. 1997; M. S. Markov et al. 1993). More recently, PEMF has been studied in terms of behavioural modulations—specifically the effects of PEMF on bipolar disorder, autism spectral disorder (ASD), Alzheimer's, and Parkinson's disease (R Sandyk 1998b; R Sandyk 1997; R Sandyk 1999a; R Sandyk 1999c; R Sandyk 1998c; R Sandyk 1998a; R Sandyk 1999d; R Sandyk 1999b; R Sandyk 1998d; Rohan et al. 2004). Prior to discussing the effects of PEMFs on cells, tissues and systems, it is necessary to discuss the important parameters which govern how tissues will respond to electromagnetic radiation.

Waveform parameters

There are three key levels of signals that need to be specified in order to properly define the waveform parameters that are to be used when inductively stimulating:

1. Current flowing into the coils from the stimulation unit. This is the original driving signal that is produced by the electronic circuit within the PEMF device to drive the coil that will then produce the magnetic field.
2. The time-varying magnetic flux in and around the coils resulting from the electrical current driving the wire coils.
3. The induced electric field in the tissue volume resulting from the time-varying magnetic flux generated by the coils.

Based on our detailed review of the literature, we have determined that in most cases investigators report only a partial description of the original driving signal emanating from the electronic circuit (#1 above), but do not measure, calculate, report, or estimate the resulting magnetic field vs. time (#2 above) or the electrical fields that are ultimately induced within the target tissues (#3 above). For the most part, the second level signal—magnetic flux—is the most relevant signal to specify because it is prone to deviate from theoretical values when calculated based upon the presumed driver circuit performance, it is readily measured using modern analog signal Hall effect sensors, and when measured accurately yields good estimates of the induced field within the tissues. It should be noted that it is the final signal—the electric field induced within the tissues—which is the hypothesized mediator of the responses seen in vivo and in vitro, but that it is difficult to directly measure these induced fields within tissue.

Current Flowing into the Coils (Primary or First-Level Signal)

In time-varying magnetic field stimulators it is the primary signal from the electronic device that drives the coil(s) to produce the magnetic field. For the purposes of this discussion, we will not consider "static" magnetic devices such as permanent magnets or solenoids driven by steady DC current. In these cases the magnetic fields are largely steady and non-varying over time, so their ability to induce electrical fields is essentially zero because the first time derivative of the magnetic flux in steady magnetic fields is by definition equal to zero. That is not to say that such devices would have no biological effects, because they certainly may have effects through such mechanisms as the Hall Effect, in which charged particles (ions) ubiquitous in biological systems would be influenced as they move through the steady magnetic field. The induction of electrical fields within tissues requires magnetic fields that vary in time, and typically this is accomplished using a computer or a microcontroller-based platform to drive current waveforms through solenoid coils. To induce the desired electrical fields it is essential to control the slew-rate (rate of change or first time derivative of the magnetic flux) of the signal. Thus, it is of utmost importance that the primary driving electronics have adequate dynamic performance. However, since most investigators do not measure or report the second- or third-level signals (above) they generally cannot guarantee that the primary driver electronics had adequate dynamic performance to achieve the desired biological effect. The primary signal also allows one to determine the

upper limit of the overall stimulus signal power. Basically the maximum power into the system can be calculated by knowing the maximum current flowing into the coils and the impedance of the coils (though empirically, the power transfer to the body is much lower because of inefficiency). Because the undesirable effects of non-ionizing radio frequency (RF) energy generally are regarded to arise from thermal effects within the tissue, it is conservative and correct to consider the total PEMF system power when determining the upper limit of potential harmfulness of any PEMF or RF stimulation system, and the power consumption of the primary driving electronics provide a direct and convenient opportunity to measure and determine the upper boundary for power for the entire system.

Magnetic Flux Produced by Coils (Secondary or Second-Level Signal)

Because there are electrical (Ohmic and reactive) energy losses in driving the primary signal through the coils, it is most accurate to directly measure the dynamic magnetic flux produced by the current flowing into the coils. From these measures one can disregard the need to correct for dynamic limitations of the primary driver circuit, and the induced electric field within the tissues can be accurately estimated. Faraday's law of induction shows that the induced circular electric field in a conducting surface is proportional to the inverse of the rate of change of the magnetic flux (defined as the magnetic field strength times the area through which it is passing). The key parameters involved with the induced electric field are the rate of change of the magnetic field (i.e. dB/dt, which is the first time derivative of the magnetic flux B) and the radius around which one examines the field of interest. Specifically, the larger the rate of change of the magnetic field, the larger the possible induced electric field. Maxwell's relationship explains why the driving electronics must have good dynamic performance: to provide adequate magnetic flux slew rate to induce the desired electric field in the tissue. For a given magnetic flux change, the larger the radius of interest (up to the inner radius of the stimulating coil), the larger the induced field; and the smaller the radius, the smaller the induced field. The induced electric field for a Helmholtz coil (i.e. separation distance of the coils approximately the same as the radius of the coils) decays linearly to zero within the boundaries of the coils and falls off as the inverse of the distance from the outer edge of the coil outside of the boundaries of the coils (Figure 1). The internal surface of the graph in figure 1 is a cone, representing the induced electrical field strength between the coils where the induced electric field decreases toward zero linearly as the radius of curvature of the induced field drops to zero in the x-y plane. The inner conical surface is perhaps most relevant because it is the volume of tissue between or within the coils that generally is intended to undergo treatment with PEMF.

Induced Electric Field within Tissues (Tertiary or Third-level signal)

Finally, it is necessary to briefly discuss the induced electric field—specifically with regard to the tissue volumes of interest. For example, if one considers a stimulation volume on the order of 10 μm (average cell diameter), then with a magnetic flux slew rate of 1,400,000 Gauss/second (=140 Tesla/second), the magnetic pulse will induce a peak electric field of approximately 3.5 x 10-4 V/m around the perimeter of a typical cell. If one considers thermal noise averaging and cellular response, then the predicted threshold induced field for a measureable response is on the order of 10-3 – 10-5 V/m (Weaver & Astumian 1990). However, if one considers a conduction pathway on the order of the radius 35 mm (ex: the outer edge of a 6-well plate well), then the peak electric field produced by the same magnetic pulse is on the order of 1.23 V/m. We would like to point out that in fact, the model being used to explain the induction of electric fields within a tissue volume is identical to the model of eddy currents (Halliday et al. 2000). In the case of eddy currents within a tissue, one can consider the conducting pathways to be represented by the fluid in the pericellular space, just outside the cell membrane and between cells and thus, circular pathways around cells are those of interest. Since there are many cells in a tissue mass, there are various conducting pathways, some circular, but most are not. Considering that the field strength in a plane varies with respect to the radius of interest, one can determine that if cells meet in locations where the cross sectional radii are not identical, then the currents where the cells meet will not cancel, and there will be a net flow of current around the larger radius of interest. However, if two cells meet at a location such that their cross-sectional areas are approximately the same (and they are both relatively circular cross sections) then circular currents flow around each cell, and should approximately cancel where the cells meet—producing a conducting path around both cells (Figure 2). Because of these geometric effects, it is possible that amplification effects might be seen for signals that fall below stimulation thresholds. Such circumstances may dominate the geometry in tissues with relatively high cellular density such as muscle and skin in which the cells occupy well over 50% of the volume in any representative sample of tissue. In the case where cells are separated by relatively larger distances, the induced electric fields in the pericellular fluid spaces surrounding each individual cell may not interact as shown, each cell being subjected to an induced electric field. If all cells in the target tissue have approximately the same geometry, then each individual cell in the target tissue would be stimulated very nearly uniformly throughout the tissue within the coils. This geometry could dominate in tissues with relatively lower cellular density with widely distributed (not clumped) cellular arrangement, such as bone, tendon, all types of cartilage, ligament and crucially, the interfaces where these tissues meet (Nordin & Frankel 2001).

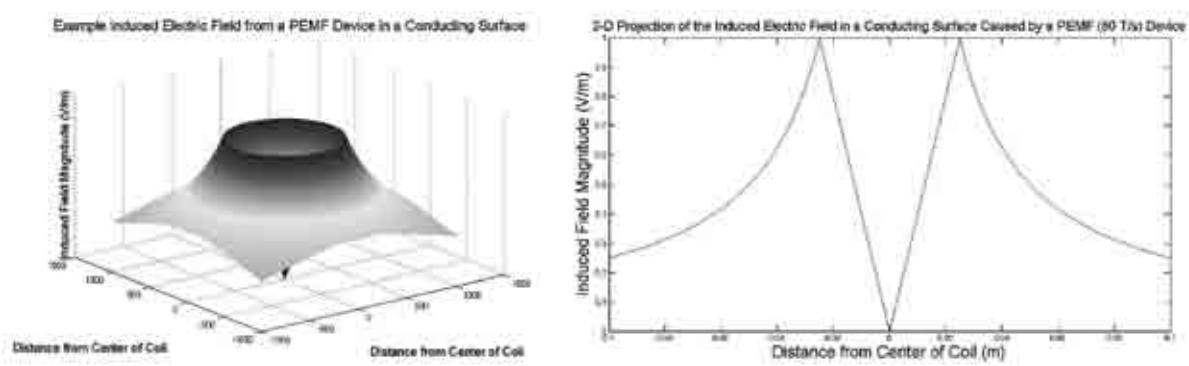

Figure 1. (Left) Representative plot of induced (tertiary or third level) electric field strengths within a conducting surface as caused by a Helmholtz configured set of PEMF coils. Any path within the circumference of the coils with radius less than the coils will have an induced electric field dictated only by its radius, not its axial position within the coils. Outside the circumference of the coils, the radius of interest must be concentric with the axis of stimulation in order for the plot above to apply. Note that the peak magnetic field is induced around a pathway of radius equal to the stimulating coils. (Right) Representative 2-dimensional slice of the surface on the left showing a cross section of the conical interior and 1/r behaviour of the induced (tertiary or third level) electric field in a conducting surface. The diameter of the representative coils is 50 mm and the plot is constructed for a magnetic flux slew rate of 80 T/s.

The above arguments generally hold true for the simplest of cell geometries: 10 micron diameter spherical cells.

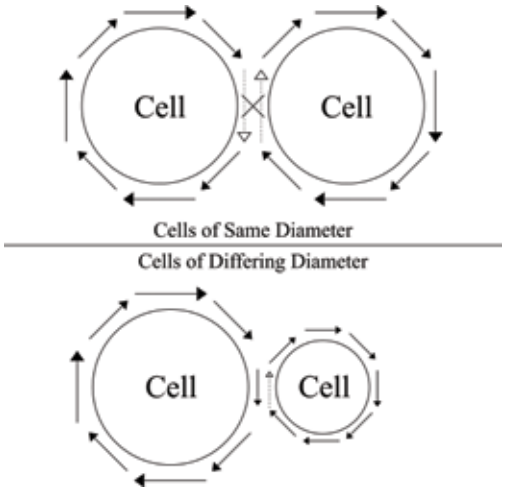

Figure 2. A cartoon of the current flow induced around cells. Top.) Cells of equivalent radius have offsetting electric fields between them, resulting in a net current flow around the perimeter of both cells, but not between them. Bottom.) Cells of different radii of intersection will have a net current flow around their perimeter and in the direction between them determined by the larger cell.

Though this assumption of simple geometry may be adequate for the estimation of tissue properties, such as estimating the number of cells in a given volume of tissue, the spatial details of cell membrane geometry and receptor distribution may well dominate when considering the mechanisms that relate to electrochemical transduction and mechano-transduction in cells and tissues. The assumption of a simple and smooth cellular geometry thus runs the risk of falling into the scientific error known as the "assumption of a spherical cow", a scientific simplification than makes calculations easier at the cost of ignoring the most important details of the system being studied. Many cells in the musculoskeletal system are known to have a complex surface structure containing thin filaments that stretch out into the space between cells. For example, osteocytes (cells in bone tissue) are known to have cytoplasmic processes which extend into canaliculi (tiny canals) in the hard bone matrix (Klein-Nulend et al. 2005; Nordin & Frankel 2001). These thin extensions of the bone cell membrane are known to be involved in the collection of nutrients and elimination of waste, but it is hypothesized that osteocytes may detect mechanical loads through the detection of signaling that arises from the mechanically-induced flow of fluids and ions through the lacuno-canicular network surrounding each osteocyte (Klein-Nulend et al. 2005). It is our working hypothesis that pulsed magnetic field stimulator systems work at this level to emulate the mechanical signals in musculoskeletal tissue systems that would normally induce a functional adaptive response, such as bone growth and remodeling to increase bone density as a result of exercise. We further hypothesize that the emulation of these signals by PEMF stimulators has the additional benefit of employing the natural signal amplification systems within the musculoskeletal system without actually applying the mechanical loads to the tissues being stimulated, thus allowing musculoskeletal tissues to adaptively respond to the emulated signals without also being subjected to the structural micro damage that would otherwise occur from the mechanical loads.

PEMF as a Biological Signal

Biologically relevant signals often have the property of being very low-level; either very low amplitude, low energy, infrequent, or otherwise subtle. As a result these signals are often difficult to detect experimentally. But through millions of years of evolution the molecular or cellular responsiveness to these low-level signals has evolved in many cases to become highly specific and responsive only to a very precisely defined signal, so as to prevent amplification of spurious background noise that might elicit inappropriate cellular or molecular response. Within the receptive bandwidth of these low-level biological signals the signal itself therefore has a high signal-to-noise ratio, with minimal energy being expended upon parameters of the signal that do not contribute to the intended message. This allows all other signals that fall outside of the receptive bandwidth to be essentially ignored. The evolutionary process tends to make good use of such highly selective and efficient processes once they have passed the test of natural selection, so it is reasonable to hypothesize that a signal that might elicit a functional adaptive response in one tissue, for example bone, might also be employed by other tissues for similar purposes. This would be especially true for tissues within the same functional groups such as musculoskeletal tissues, cardiovascular tissues, nerve tissues, etc. On the basis of this reasoning we hypothesize that specific signals that induce tissue growth and regeneration in one tissue in the musculoskeletal system might elicit the same general response in many or all other tissues of the musculoskeletal system. So a specific signal that is known to elicit acceleration of bone repair might also elicit accelerated repair in cartilage, ligament, tendon, and muscle as well. Our review of the literature reveals that this general assumption may be implicit, but is generally not explicitly articulated in the description of any of the PEMF technologies that have been reported. In most cases we believe the PEMF signals that are employed, often referred to as PEMF "waveforms", have been arbitrarily selected and often not developed and refined based upon this line of reasoning. Therefore many PEMF technologies do not take advantage of the inherent natural mechanisms of biological signal amplification, preferring instead to use a brute-force approach to coerce the target tissue toward the desired response rather than employing high fidelity signals that work with innate biological filters and amplifiers. The literature suggests that this latter approach, though crude, is in fact effective to a limited degree. However, this approach has no basis from which to develop increasingly sophisticated, efficient, and effective PEMF signals, and as a result most commercially-available PEMF technologies simply are not improved over time. Once they can be demonstrated to be statistically significant in their intended biological effects the evolution of the PEMF waveform protocols toward increasingly better signals generally does not occur. The unintended consequence of this crude approach to the development of PEMF waveforms has been that most PEMF systems are very inefficient, bulky, costly, and they subject the target tissue to unnecessary levels of electromagnetic energy. But more rational approaches to PEMF waveform design are certainly possible.

PEMF Waveform Shapes

Many different methods exist for inducing an electric field within tissues and all of these have been employed at various times by different PEMF systems. These can be divided into four distinct waveform categories: pure sinusoidal, triangular/sawtooth/trapezoidal/square, asymmetric pulses, and pulsed radio frequency (PRF)/Modulated signals. We will not consider steady (DC) magnetic fields though they are frequently employed, for the reasons stated above. We must also keep in mind that there are three levels of signals, as discussed above. For the following discussion the signal waveforms refer to signals in Level #2—the magnetic field generated by the coils.

Sinusoidal This is by far the most common form of PEMF stimulation, based upon a pure sinusoidal magnetic waveform. In the literature it is well established that tissues typically respond to radio frequencies (RF) from 0 Hz to 10 kHz—outside of this range, tissues and cells are essentially transparent (with the exception of PRF signals). The smallest wavelength of such signals in an electrolyte environment is on the order of 3000 meters—thus cells are unlikely to be acting as antennae at such frequencies. Furthermore, a frequency of approximately 30 THz would be required to induce resonance in a cell of size on the order of 10 μm in a saline solution. Interestingly, because tissues have been found to be responsive in such a low frequency range, one must consider the mechanisms by which cells or

molecules might transduce these signals. Much of the biological response is dependent upon the bulk electrical properties of tissues (direct and reactive impedances), which dictate how electrical energy is absorbed through a medium. In the case of a magnetic field, because the vast majority of mammalian tissues are not known to interact with magnetic fields, one must consider magnetically induced electric field pathways as the primary method in which magnetic fields can interact with tissues. Because the induced electric field is proportional to the rate of change of the magnetic field, the amplitude and frequency of the magnetic field dictates the strength of the cellular response. Thus, higher frequency and amplitude signals should be more effective in eliciting a response. It should be noted that there is significant theoretical evidence that suggests that there is a lower bound for frequencies as well due to the thermal noise threshold (A A Pilla et al. 1994; Weaver & Astumian 1990; David J Muehsam & Arthur a Pilla 2009a). Interestingly, there have been a number of studies that find effects well below the theoretical frequency and amplitude limits predicted mathematically, suggesting either a placebo effect or an alternative transduction mechanism (R Sandyk 1998b; R Sandyk 1997; R Sandyk 1999a; Reuven Sandyk 1993; R Sandyk 1999c; R Sandyk & Iacono 1993; R Sandyk 1998c; R Sandyk 1998a; R Sandyk 1999d; Goodwin et al. 2005; R Sandyk 1999b; R Sandyk 1998d; R Sandyk & Iacono 1994; Weaver & Astumian 1990).

Triangular/Trapezoidal/Square Triangular, trapezoidal and square waves fall into a similar category because they represent Fourier sums. While the multi-frequency aspect of such signals may be a reason that they are effective, it may equally be the case that their efficacy is due to the high slew-rates that can be produced. For practical purposes, pure square waves are impossible to create electronically: there is always a finite rise-time and fall-time for the primary electrical signals—they cannot change instantaneously. Thus, this category of three waveforms can be collapsed into triangle and trapezoidal, which includes square waves which are actually trapezoids because their rising and falling slopes are not perfectly vertical. Both triangular and trapezoidal waveforms provide bipolar induced fields, which depend upon the slope of the sides of each trapezoidal waveform—the main difference being that there is a delay between positive and negative peaks in a trapezoidal pulse given by the length of the signal plateau.

Asymmetric Pulses Asymmetric pulses are typically triangular or trapezoidal in nature, but have a differing rising and falling edge. Such waveforms can be useful for inducing non-equal bipolar induced electric fields. Examples of asymmetric pulses include saw-tooth waves such as those shown in (Figure 3).

PRF/Modulated Signals Pulsed radio frequency (PRF) signals provide a high-frequency method for encoding low-frequency signals, similar to the way in which an FM radio works. Because tissues will integrate low-frequency signals (i.e. they act as a high-pass filter), they can demodulate pulsed PRF signals. The advantage of such a stimulation paradigm is that tissue penetration can be increased. Since radio frequency signals can penetrate tissues easily, PRFs can provide an effective means of stimulating deep tissues without using very strong external fields. The efficacy of PRF stimulation has been explained by Pilla et al. on the grounds of a proposed biochemical model (David J Muehsam & Arthur a Pilla 2009a; David J Muehsam & Arthur a Pilla 2009b; Strauch et al. 2011; a a Pilla 1974; M. Markov & A Pilla 1997; Rohde et al. 2009; M. S. Markov et al. 1993; A A Pilla et al. 1999). Under appropriate stimulation parameters, PRFs can modulate first order kinetics of ion binding to enzymes. Pilla's work is focused on modulating calcium binding to calmodulin in vivo—providing a method by which downstream targets such as endothelial nitric oxide synthase (eNOS) and neuronal nitric oxide synthase (nNOS) can be affected (A A Pilla et al. 1999).

Waveform Parameters All waveform categories and shapes are defined by a set of waveform parameters. These include amplitude, frequency, slew rate, and other parameters. Some waveforms are well described by only two parameters, such as continuous pure sine waves which can be defined by the two parameters amplitude and frequency. Other waveforms are more complex and may require six or more parameters for a complete description. An example of this is asymmetric trapezoidal waves that are generated in short bursts of pulses followed by periods of no stimulation. In this case the waveform would be fully defined by at least twelve parameters: start time, initial slope, peak amplitude, duration (time) held at peak amplitude, final slope, terminal amplitude (can be zero or have opposite sign for bipolar pulses), duration of zero or opposite-sign plateau, return slope (if non-zero), time between pulses, number of pulses in each burst, dwell time between bursts, and at least one additional parameter to define the periodicity of the bursts of asymmetric trapezoidal pulses.

Amplitudes The mechanism for the biological effects of PEMF as they relate to magnetic flux peak amplitude, and thus the relative importance of this parameter, remains slightly ambiguous at this point because there is a large range of experimentally effective amplitudes that fall well below thermal noise limits. However, generally speaking, larger amplitudes are more effective in direct tissue stimulation until high amplitudes that begin to cause collateral tissue damage are reached. This damage is most likely because more energy is dissipated into the tissues in each unit of time. Energy per unit time yields the physical units of power, and electromagnetic power is associated with tissue damage when the power level begins to reach a level with significant thermal effects (temperature rise) within the tissue. This effect is put to positive use in modern surgery when radio ablation is utilized to destroy tumors or other unwanted tissues. Assuming that the RF power is below a damaging level, we have noted in a wide variety of literature that induced electric fields on the order of 0.01 – 10 V/m appear to be most effective in treating chronic pain and inflammation. Generating such field strengths can be done using several magnetic waveforms. It should also be noted that much lower amplitude magnetic fields, on the order of picotesla (10-12 T), have been reported to be clinically effective for treatment of multiple sclerosis and Parkinson's patients (Reuven Sandyk 1993; R Sandyk & Iacono 1994; R Sandyk & Iacono 1993; R Sandyk 1998b; R Sandyk 1999c; R Sandyk 1999a; R Sandyk 1998d; R Sandyk 1997; R Sandyk 1998c; R Sandyk 1998a; R Sandyk 1999d; R Sandyk 1999b). So, we can con-

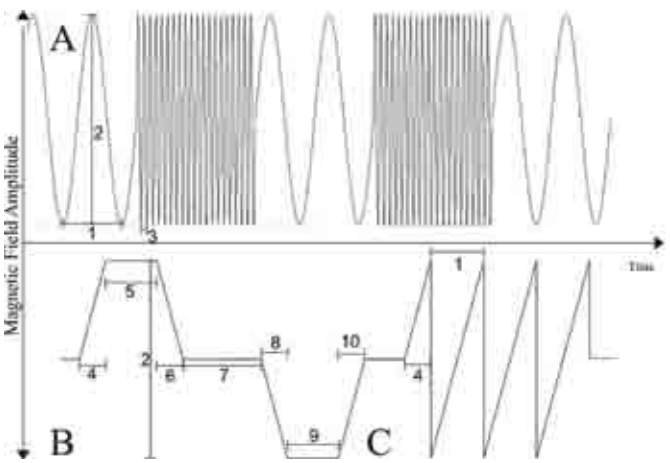

Figure 3. Representative images of waveforms used in PEMF. A.) Sinusoidal waveforms have smoothly varying edges, and can also be pulsed at high frequencies to produce PRF signals. B.) Trapezoidal and square waveforms represent waveforms with large rising and falling edge slopes and non-changing peaks and troughs. C.) Asymmetric pulses, such as the saw-tooth waveform shown, represent waveforms that have large rising and/or falling edge slopes, but provide non-symmetric induced electric fields within tissues of interest. A description of the numbered portions above can be found in Figure 4.

clude that waveform amplitude certainly plays a role in both the efficacy and the potential risk involved in the use of PEMF stimulators, but the precise role and the underlying biological and electromagnetic mechanisms remain to be elucidated.

Frequency The waveform frequency parameter is also considered of vital importance when considering periodic signals. The precise role of frequency is somewhat obfuscated by the imprecise use of this very well-defined engineering term. As noted previously, tissues typically only respond to frequencies below 10 kHz, with the exception being that FM signals can be demodulated by tissues, provided the low frequency encoding falls below 10 kHz. Because the frequency of a sinusoidal magnetic flux signal dictates the time derivative dependence, and therefore the induced electric field magnitude, it follows that higher frequency signals are capable of inducing electric fields with greater peak amplitudes in the target tissue. However, as we shall see later, there are theoretical limits that help narrow down the range of frequencies that would be theoretically effective. For example, a 1 Hz wave would require a peak amplitude of approximately 100 tesla in order to induce an electric field on the order of 1.75 V/m around the perimeter of a 35 mm disk. This peak field strength is approximately 100 times higher than the average field produced in a clinical MRI unit, which is a very large amplitude indeed. One tesla = 10,000 gauss, so a 100 T field = 1 MG, which is about 200 times the average magnetic field strength of the Earth. At higher frequencies the calculus, a simple derivative of the sinusoidal waveform, indicates that significantly lower magnetic flux amplitudes could theoretically become biologically effective. For example, by increasing the frequency from 1 Hz to 1 kHz, the required peak magnetic field becomes approximately 0.1 T, which is more reasonable and technically is much easier and less expensive to achieve—but it remains very large.

Slew Rate As an alternative strategy to employing magnetic fields of very high amplitude it is both possible and sometimes advantageous to use high rates of change (steep slopes) coupled to otherwise low frequency pulses. It is in this use of the term frequency that confusion sometimes arises. For pure sine waves the meaning of the term frequency is defined as "the first time derivative of phase angle", whereas the meaning of the term frequency in reference to non-sinusoidal pulses is "how frequently the individual pulses are generated". Improper or imprecise use of the term frequency can lead to considerable confusion when defining the precise parameters for non-sinusoidal magnetic pulse waveforms. Trapezoidal and triangular magnetic pulses can be generated individually with long periods of inactivity between pulses, but it is possible by this approach to generate very large induced electric fields by driving the trapezoidal waveforms with very steep rising and falling edges, that is, incorporating large slew rates to each edge of each trapezoidal or triangular pulse. Such signals are easily capable of producing 1.5 V/m induced signals while keeping peak magnetic field strength well below 0.1 T provided the pulse can be delivered in a short enough time (approximately 100 μs). Frequency modulated signals provide an alternative method for producing high slew-rate signals by encoding low frequency signals in high frequency (1-27.12 MHz) sinusoidal carrier waves.

The Thermal Noise Threshold

An interesting and important discussion must be had regarding the thermodynamic effects of electric fields. Specifically, as one decreases the magnitude of the induced electric field, there comes a point where thermal fluctuations due to random motion within the sample can easily produce field strengths large enough to mask the applied signal. This masking is referred to as the thermal noise threshold and is on the order of 9x10-2 V/m when signal averaging is not taken into account. However, cells are able to integrate applied signals, which allows the theoretical noise threshold to fall even further to levels as low as 10-3 – 10-5 V/m (Weaver & Astumian 1990).

Review of Past Literature/Focus on Systems/Tissues:

Bone Studies

The majority of the evolution of PEMF therapy in the 20th and 21st century has been driven by the development of bone-growth stimulators. When Fukada and Yasuda discovered that bone is piezoelectric and subsequent studies implicated that bone remodeling could be driven by this property, it was only a matter of time before people began exploring the possibility that applied electromagnetic fields could drive other biological processes. Thus, much of the pioneering work done by Bassett et al. laid the foundation for subsequent work in other tissues.

Cell Studies

Effects of PEMFs on cells have been studied extensively in those cells of bone- or cartilage-derived lineage. In vitro studies on both primary and immortalized cells have been conducted, and there is evidence to suggest that each responds differently to PEMFs (De Mattei et al. 1999). Cell studies done on osteoblast-like cells have mainly focused on the nitric oxide synthase (NOS) pathway of cells such as MC3T3 cells (Diniz, Shomura, et al. 2002; Diniz, Soejima, et al. 2002). Proliferation in several different cell types has been extensively studied and found to be increased in the presence of low-magnitude PEMFs on the order of 0.002 V/m (Pezzetti et al. 1999; Tepper et al. 2004; Liboff et al. 1984; Takahashi et al. 1986; Sollazzo et al. 1997; Robert J Fitzsimmons et al. 2008). In addition to modulating proliferation, PEMFs have been implicated in the upregulation of DNA synthesis , and IGF-2 (osteosarcoma) (R J Fitzsimmons et al. 1995; R. J. Fitzsimmons 1995), FGF-2 (endothelial cells) (Tepper et al. 2004) and BMP-2 mediated osteoblastic differentiation in human mesenchymal stem cells (HMSCs) (Schwartz et al. 2008). In addition to the studies on bone, there have been questions as to the efficacy of PEMFs in nerve regeneration. In particular, a study conducted at NASA by Goodwin and McCarthy (Goodwin et al. 2005) and Dennis (2011) showed that human neuronal cells could be modulated by time-varying electromagnetic fields (TVEMF). They

Summary of Important Secondary Wave Structures Necessary for Fully Defining PEMF Waveforms

Sinusoidal (A)	PRF (A)	Trapezoidal (B)	Asymmetric Pulse (C)
Period (1) Amplitude (2) Peak Slope	Bulk Pulse characteristics Carrier Period (3) Amplitude (2) Encoded frequency Peak Slope	Amplitude (2) Positive Rising Edge Slope Positive Rising Edge time (4) Time at Max (5) Positive Falling Edge Slope Positive Falling Edge time (6) Time at Zero (7) Negative Falling Edge Slope Negative Falling Edge time (8) Time at Minimum (9) Negative Rising Edge Slope Negative Rising Edge time (10) Peak Slope	Period (1) Amplitude (2) Rising Edge Slope Rising Edge time (4) Falling Edge Slope Falling edge time (6) Peak Slope

Figure 4. Summary of important waveform parameters necessary to completely define a PEMF waveform. All numbered items are labeled in figure 3 on their respective waveform type letter. Unlabeled components are those which cannot easily be drawn on a figure, however are absolutely necessary. Trapezoidal waveforms are assumed to be constructed of straight lights—if lines are curved, a function may be required to define the edge slopes. It should be noted that this table is not comprehensive, as more complicated waveforms may require additional information to fully define one full cycle of stimulation.

found differences in cell morphology as well as proliferation rates in cells that were cultured in the presence of TVEMFs. While cell culture studies are important to understanding biochemical and cell-level responses to PEMFs, they cannot provide the tissue and organism level responses that can be gleaned from in vivo, animal and human studies.

Soft Tissue Studies

To understand the effects of PEMF therapy on a system level, we feel it is easiest to break the existing literature into the broader categories of nerve healing and anti-inflammatory studies. Because PEMF is so well established as an effective treatment in bone-healing, we choose not to review that literature—however the reader should be aware that there is a vast literature concerning bone remodeling (a good reference to start with is the 1974 Bassett reference).

Nerve Healing To understand the effects of PEMFs on nerve regeneration, we have broken the in vivo studies into three broad categories: peripheral, spinal cord and cortical studies. We have chosen to separate the cord from central and peripheral studies because it is the junction point for both central and peripheral nerves, and thus has the potential to affect both simultaneously.

Peripheral Nerves The focus of the majority of peripheral nerve studies has been to examine the ability of PEMFs to temper pain and stimulate regrowth. As previously mentioned, the studies performed at NASA by Goodwin et al. indicated that neuronal proliferation could be significantly affected by low frequency pulses much lower in magnitude than the earth's magnetic field. Studies performed by Raji et al. have shown that rat peroneal nerve regeneration can be enhanced by the use of PEMF (a M. Raji 1984; A. Raji & Bowden 1983).

Cord Nerves The majority of the published controlled laboratory studies examine the effects of PEMFs on sciatic nerve lesions. Significant evidence from animal studies suggests that PEMFs are potentially effective in accelerating sciatic nerve healing. Square wave pulses (~600 T/s magnetic flux rate), as studied by Sisken et al. (1989), seem effective in increasing sciatic nerve regeneration regardless of the orientation of the Helmholtz stimulation coils. However, Baptista et al. (2009) showed that there was no significant effect from treating sciatic crush lesions in Swiss mice using a stimulation protocol that induced a 20 kT/s magnetic flux rate—a relatively large stimulus.

Cortical/Central Nerves Finally, it is important to discuss the potential cortical effects of PEMFs. Cortical effects should be considered from two different views: direct stimulation (ex: rTMS, low magnitude PEMF, etc.) which stimulates the brain directly, and indirect stimulation that causes cortical remapping or modulation by stimulating peripherally. Direct stimulation methods such as those used in the studies published by Sandyk et al. have indicated that very small induced fields may be effective in alleviating some of the difficulties associated with multiple sclerosis and Parkinson's disease (Reuven Sandyk 1993; R Sandyk & Iacono 1994; R Sandyk & Iacono 1993; R Sandyk 1997; R Sandyk 1998a; R Sandyk 1998b; R Sandyk 1998c; R Sandyk 1998d; R Sandyk 1999c; R Sandyk 1999b; R Sandyk 1999a; R Sandyk 1999d). However, it should be noted that the field strengths in question fall far below the thermal noise threshold and that the majority of these studies are case studies, not controlled laboratory studies. Unfortunately the literature regarding the central effects of peripherally applied PEMFs on central nerve function is rather sparse. Because peripheral neurons play a very large role via the feedback mechanism in cortical plasticity, it follows that if PEMF affects these neural feedback loops, then fMRI and PET studies would reveal potentially significant effects of peripherally applied PEMF on cortical plasticity.

Anti-inflammatory Effects There are two notable studies that shed significant mechanistic light on the anti-inflammatory and pain reducing effects of PEMF: those of Per Hedén et al. and Christine Rohde et al. Both studies examined the post-operative effects of PEMF on breast augmentation and breast reduction patients respectively. In the former, a pilot study of patients undergoing breast augmentation, PEMF (2-ms bursts of 27.12 MHz PRF, 32 mV/cm peak applied for 30 minutes every 4, 8 or 12 hours on different post-operative days) was shown to significantly reduce pain scores (Hedén & Arthur a Pilla 2008). The second study, performed by Rohde et al. using similar PEMF parameters showed significant pain reduction, and interestingly a drastic reduction in IL1-β levels in wound exudate as compared to sham groups (Rohde et al. 2009). Reduction in inflammatory factors suggests at least one possible biochemical mechanism—perhaps the Ca2+/CaM dependent NOS pathway suggested by Pilla et al. (A A Pilla et al. 1999). It is interesting to note that although these reports and others have demonstrated very significant and repeatable reduction in post-operative pain when PEMF is correctly applied, and that the use of narcotics to manage pain has severe and well documented health and social effects, there does not appear to be any increase in the clinical acceptance of PEMF stimulation for the management pain. Essentially—despite growing support in the peer-reviewed literature, the availability of many commercial PEMF products, and the lack of evidence indicating adverse effects—the use of PEMF for any form of pain management remains outside even the fringe of standard medical practice.

Possible Mechanisms

While there are many possible mechanisms by which PEMFs could influence cells, tissues, organs and whole systems—there are only a few basic mechanisms that are adequately explored in the scientific literature. First is an implicit theory which is not always discussed explicitly: eddy current interactions with signaling proteins. The fundamental idea of this first theory is based on Faraday's law of induction which states that electromagnetic eddy currents can be induced in a conducting surface (such as a slice of tissue) by a time-varying magnetic field. In the presence of a changing magnetic field, the electrolyte surrounding cells can act as a conducing medium and eddy currents can flow in these spaces. If there are free ions in solution, presumably they could be placed into organized motion and their frequency of interaction with their receptors of interest might be preferentially increased or decreased, causing a cell response. Another possibility is that proteins are affected directly—since every biochemical reaction is driven fundamentally by the electromagnetic force, it follows that protein binding pockets could be modulated by induced EMFs or eddy current flow. A more specific proposed mechanism is that put forth by Pilla and his collaborators, which states that PEMFs of the appropriate waveform and pulse duration (specifically pulsed radio frequencies) are able to modulate the Michaelis-Menten binding kinetics of the Calcium-Calmodulin dependent nitric oxide synthases (David J Muehsam & Arthur a Pilla 2009a; A A Pilla et al. 1999; a a Pilla 1974; David J Muehsam & Arthur a Pilla 2009b; M. Markov & A Pilla 1997; Rohde et al. 2009; Hedén & Arthur a Pilla 2008; M. S. Markov et al. 1993; C. a Bassett, R. J. Pawluk, et al. 1974; C. A. L. Bassett, R. J. Pawluk, et al. 1974; Arthur A Pilla 1970). Modulating such a fundamental pathway could result in modulated levels of NO production and therefore have very drastic downstream effects in the body. Finally, for low amplitude magnitude fields, a Larmor precession model is discussed which states that the Larmor precession behaviour of certain atoms or molecules (such as water) can be modulated in the presence of a magnetic field. In the case of water, modifying the Larmor precession can impact the ability of thermal fluctuations to drive chemical reactions—shifting the amount of energy required by a ligand to displace water from a binding site on a target molecule (M. Markov & A Pilla 1997; a Pilla et al. 1997; Barnes & Greenebaum 2007). These three theories are far from complete or comprehensive; however, they serve as a good beginning to the development of an understanding of the basic mechanisms to elucidate the effects of PEMF on the body.

Summary, and the future of PEMF

The PEMF literature is rather sparse when one considers the vast continuum of electromagnetic frequencies and amplitudes. The problem of

organizing and classifying effective PEMF waveforms in tissues is similar to the problem faced by Mendeleev and other chemists who faced the growing problem of classifying elements into the periodic table. More recently a similar problem was faced by subatomic particle physicists such as Glashow, Weinberg and Salam in trying to develop what we now call the Standard Model—a method for classifying and understanding the subatomic particles and their interactions. The problem faced by these influential scientists is not completely held in simply organizing information—it was in taking a large amount of completely unorganized information and convincing a scientific community of an effective means of organizing the information. The importance of such organization is twofold. First, organization helps to circumvent vicious arguments between those seeking answers to the same problems by giving objective grounds on which to make rational arguments. And secondly, possibly more importantly, it allows outside viewers—those not directly involved in the scientific community—the opportunity to understand clearly the methods and goals of the study. If organization can be achieved, then the PEMF community as a whole can make research progress at an incredible pace. As a research community we must apply several simple principles in our experiments and articles that will help to alleviate the questions that are often generated by those not directly involved in the research. First, we must strive to be scientifically rigorous—any published experiment MUST include adequate information to completely replicate the experiment. This means that waveform parameters must be fully and carefully defined such that an induced electric field can be calculated. In some cases the parameters should be measured and determined experimentally, using well-calibrated instruments suitable to the task. Secondly, it is important that authors choose effective and specific titles for articles. Titles such as "PEMF is Not an Effective Means of Treating Rotator Cuff Injury" do not help the already confused literature (unless every single frequency, amplitude, waveform structure and treatment regimen was tested). Consider the possible title for a study in which aspirin (a drug) was found to be ineffective in reducing post-operative pain. The resulting manuscript titled "Drugs are not effective in the treatment of post-operative pain" is non-specific to the point of being both misleading and incorrect. Just as there are many types of drugs, there are vast numbers of different PEMF stimulation protocols. One of the authors of this paper (Dennis) estimates this number to be on the order of 10 trillion different possible PEMF stimulation protocols (unpublished estimate). Therefore, titles should include at minimum a descriptor of the magnetic field waveform such as "75 Hz, 250 mH Sinusoidal PEMF is Not an Effective Means of Treating Rotator Cuff Injury." This allows those in the field to quickly isolate articles based on their treatment parameters, and it gives those outside the field an understanding that different PEMF protocols are used for different reasons. Just as ultrasound has different clinically effective waveforms for different applications (imaging, targeted ablation, ARFI, etc.), both clinical practitioners and the educated public must understand that the same is likely true of PEMF. Secondly, it is important, as the PEMF literature progresses and waveforms are grouped based on efficacy, that we use consistent terms to define PEMF stimulation protocol parameters (Figure 4). Until a well-defined set of terms is established, understanding and forward progress in the use of PEMF will be limited. However, if we are strict with definitions and clear in our methods and scientifically approach the many questions posed by the interactions of PEMFs with tissues, then we can take the field from being in a questionable and disorganized state toward a respected and organized body of knowledge that has earned the respect of scholars and physicians. ■

List of Abbreviations:

ARFI – Acoustic radiation force impulse
BMP-2 – Bone morphogenic protein 2
Ca2+ – Calcium (2+) ion
CaM – Calmodulin
DNA – Deoxyribonucleic acid
eNOS – Endothelial nitric oxide synthase
FGF-2 – Fibroblast growth factor 2
HMSC – Human Mesenchymal derived stem cell
IL1-β – Interleukin-1 Beta
NASA – National Aeronautics and Space Administration
nNOS – Neuronal nitric oxide synthase
NOS – Nitric oxide synthase
PEMF – Pulsed electromagnetic field
PRF – Pulsed radio frequency
rTMS – Repetitive transcranial magnetic stimulation
TVEMF – Time varying electromagnetic fields

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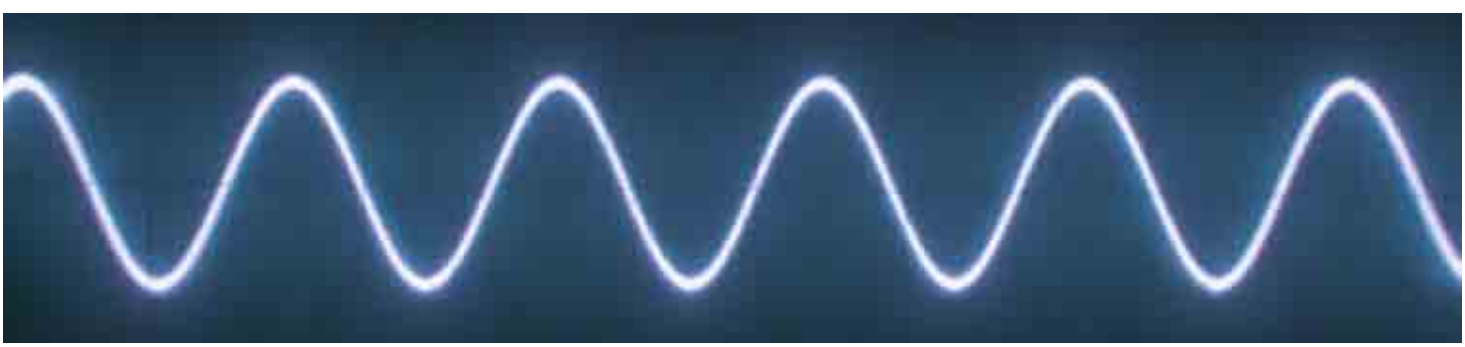

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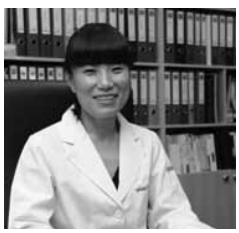

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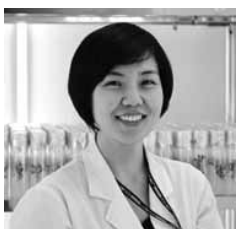

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A Reliable Supply of Natural Products through Cambial Meristematic Cell Culture*

Plants are probably the best cell factories as they produce more than 100,000 different natural products, such as alkaloids, terpenoids, phenolics steroids and flavonoids, with a large number of products continued to be discovered every year[1]. These natural plant products are not only used as flavor, color enhancers, agricultural chemicals and food ingredients, but also serve as an important historical source of medicine[2].

Most natural products cannot be produced on an industrial scale by chemical synthesis due to their structural complexity. Moreover, extraction from plants is often not feasible as plants can be rare or slow growing[3]. Therefore, plant cell culture offers an attractive production platform for some natural products[4], but is often not a commercially viable strategy because of the difficulties associated with culturing dedifferentiated plant cells (DDCs) on an industrial scale[5]. DDCs, as known as callus (Figure 1), can be induced from the explants from most plant organs through a dedifferentiation process. Since the cell population from the original plant organ is a mixture of specialized cell types, which vary in cell cycle participation[6] and other properties, DDCs are heterogeneous such that it leads contributes to the instability of many culture properties, such as slow growth rate and large cell aggregation, and complicate scale-up of bioreactors. Also, deleterious genetic and epigenetic changes that occur during the dedifferentiation process[7, 8] will result in inconsistent and low yields of natural products[4, 5].

To circumvent the dedifferentiation process and problems in the production of natural products from DDC culture, The Unhwa Corp. developed an innately undifferentiated cambial meristematic cell (CMC) from cambium (Figure 2), which functions as vascular stem cells. CMC isolation and culture technology marks an important departure from traditional plant cell culture and has broad utility since it can be applied to produce CMCs from a variety of plant species, including ginseng (Panax ginseng), ginkgo (Ginkgo biloba) and tomato (Solanum lycopersicum) (Figure 3).

Based on a variety of approaches, the Unhwa Corp. confirmed that cultured CMCs are consistent with CMCs in nature. Microscopic analysis of cultured Taxus CMCs revealed the presence of small and abundant vacuoles, whereas Taxus DDCs derived from needles or embryos showed only one large vacuole, typical of such plant cells (Figure 4). Also, cultured Tax-

Figure 1. Induction of DDCs.
DDCs induced from the cut edge of a needle explant. Scale bar, 0.5 mm.

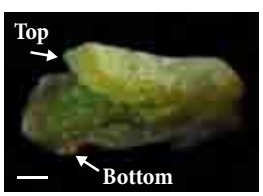

Figure 2. Isolation of innately undifferentiated cambial meristematic cells(CMCs) from cambium.
Natural split of CMCs from DDCs induced from phloem, cortex and epidermal cells. The top layer is composed of CMCs whereas the bottom layer consists of DDCs. Scale bar, 1 mm.

*This article is a summary of a paper entitled, "Cultured cambial meristematic cells as a source of plant natural products"[9] and "Plant natural products from cultured multipotent cells"[10].

us CMCs had increased ability to differentiate into tracheary element (TE; i.e. tracheids and vessel elements found in xylem in vascular plants) (Figure 5) and hypersensitivity to radiation compared to Taxus DDCs. A comparison of molecular signatures of CMCs and DDCs revealed that more than 500 differentially regulated genes confirm the upregulation of several genes known to be overexpressed in cambial cells. In aggregate, cultured CMCs show stem cell properties, are consistent with the identity of CMCs in nature, and are inherently distinct from DDCs typically used for plant cell tissue culture.

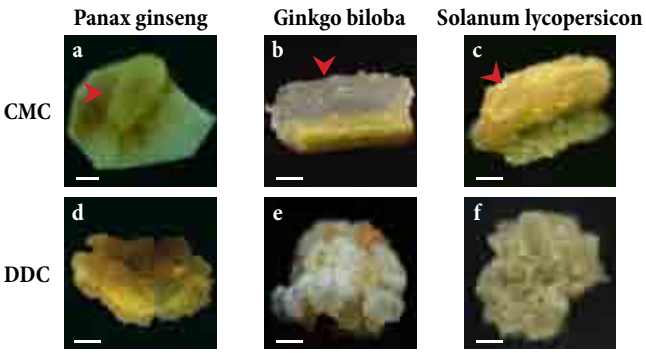

Figure 3. CMCs and DDCs generated from a variety of plant species.
a, Proliferating CMCs derived from ginseng (Panax ginseng) tap root. b, Proliferating CMCs derived from ginkgo (Ginkgo biloba) stem. c, Proliferating CMCs derived from tomato (Solanum lycopersicon) stem. d, DDCs produced from P. ginseng tap root pith. e, DDCs produced from G. biloba stem. f, DDCs produced from S. lycopersicon stem. In a,b and c, CMCs are indicated by a red arrow head. Scale bar is equivalent to 1 mm for a, b, c and 2 mm for d, e, f.

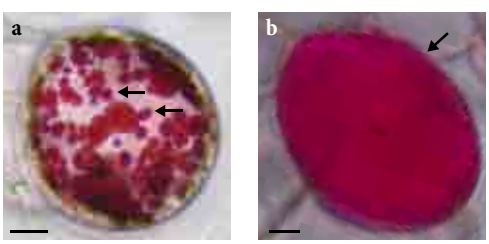

Figure 4. Vacuoles of CMC and DDC.
a, Single CMC stained with neutral red, which marks the presence of vacuoles. Two of many stained vacuoles are denoted by black arrows. Scale bar, 10 μm. b, Needle-derived DDC stained with neutral red. The single large vacuole present in this cell is marked by a black arrow. Scale bar, 10 μm

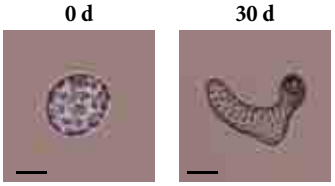

Figure 5. CMC differentiation.
Conditional differentiation of T. cuspidata CMCs to tracheary elements, at the times indicated, after addition of differentiation media. Scale bar, 25 μm

The performance of CMCs as an applied bioprocessing technology is shown to be far superior to that of DDC cultures established at the same time, in terms of cell aggregation size (Figure 6), growth rates (Figure 7); susceptibility to shear stress (Figure 8) and variability in growth over repeated subculture cycles (Figure 9). Thus, CMCs have greater potential to produce useful natural products at both the laboratory scale (125 ml) and pilot scale (up to 20 liters) than DDCs, such as paclitaxel (Figure 10). These advantages of CMCs can also be applied to the production of various valuable natural products from different plants.

A reliable, cost-effective supply of natural products for use as pharmaceuticals, fragrances, dyes and insecticides remains a major challenge for many systems. Plant cell tissue culture has been limited by inconsistent performance and the economic constraints associated with slow growth and low product yield. Additionally, there were problems such as cell aggregation, susceptibility to shearing, variability in growth and profusion of necrotic cells. CMCs, however, appear to enhance cell culture performance in all of these areas and, notably do not require selection of specific cells and aggregates for consistent growth over repeated subcultures, thereby minimizing maintenance requirements. CMC-based strategies should therefore facilitate the development of economically viable plant cell tissue culture processes for many natural products.■

Figure 6. CMC differentiation.
Conditional differentiation of T. cuspidata CMCs to tracheary elements, at the times indicated, after addition of differentiation media. Scale bar, 25 μm

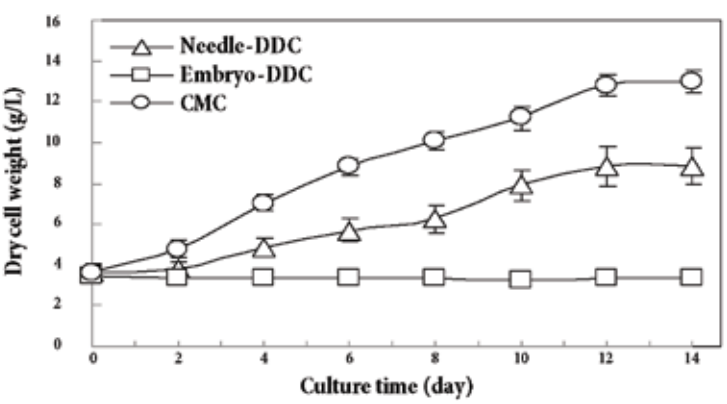

Figure 7. Growth curve of T. cuspidata CMCs and selected needle and embryo derived DDCs in a 3 L air-lift bioreactor.
During 1.8 years growth on solid media more vigorously growing needle and embryo derived DDCs were selected where apparent at each 14 day-subculture. CMCs were grown in a similar fashion for 1.8 years without selection. The growth rate of the resulting cells was subsequently determined in a 3 L air-lift bioreactor.

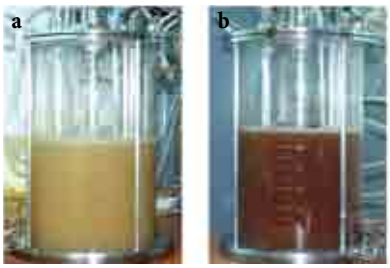

Figure 8. Susceptibility to shear stress in a 10 L stirred tank bioreactor.
a, CMCs following 14 days of culture. CMCs are resistant to shear stress that the survival rate of CMCs were strikingly higher than DDCs. b, DDCs after 14 days of culture. DDCs were sensitive to shear stress that the cells had largely turned necrotic and had stopped growing at the end of the culture. In a and b agitation speed was 200 rpm to promote shear stress.

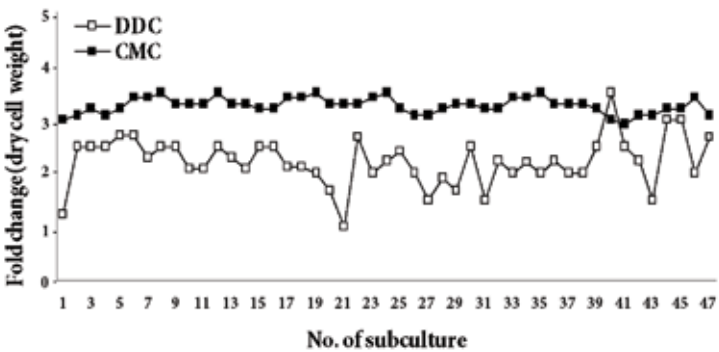

Figure 9. Growth stability of T. cuspidata CMCs.
The growth stabilities of T. cuspidata CMCs or selected DDCs derived from needles were monitored over 1.8 years in a 20 L air-lift bioreactor with subculturing every 2 weeks.

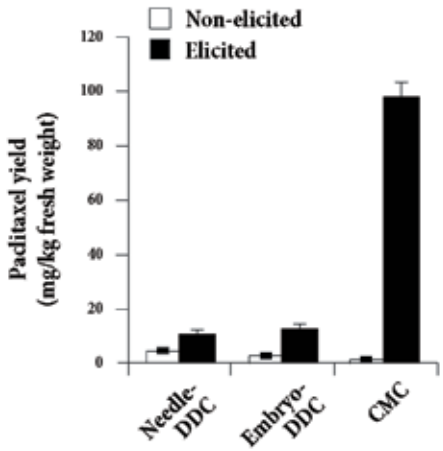

Figure 10. Paclitaxel production of CMCs and DDCS.
Total paclitaxel production following elicitation of the indicated 6-month-old repeatedly subcultured cell suspensions, after batch culture in a 3 liter air-lift bioreactor.

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A Special Sino-Luso Surgery "Grand Rounds"

By Ralph Novotney

Macau's medical community continued to grow tighter at a special skills forum held in April 2012.

Over 50 local surgeons from San Jaunario Hospital, the University Hospital of the Macau University of Science and Technology (MUST), and Kiang Wu Hospital, along with Chinese mainland and international experts discussed cutting edge surgical techniques, personal perspectives and thought-provoking issues.

The 5-hour session reviewed cases in current surgical management strategies and advanced endoscopic and laparoscopic paradigm for a broad spectrum of diseases.

The special Sino-Luso Surgery Grand Rounds event was open to all the surgeons in Macau. This on the job training panel provided local doctors a great opportunity to hear prominent and influential surgeons who are in the forefront of their respective specialties.

Visiting professor from Portugal, Dr. Vitor Ribeiro said, "I am proud to be here to attend this meaningful Sino-Luso International Medical Forum, the Grand Rounds that we have this morning fosters collaborations across three local hospitals here in Macau and my faculty based in Porto, Portugal.

This indeed promotes the wonderful work and strong commitment of the Faculty of Health Sciences of MUST."

Two highly regarded surgeons from the Chinese mainland, the Vice President of the First Affiliated Hospital of China Medical University, Vice Chairperson of the Scientific Branch of Surgery and Pre-elect Chairperson of China Medical Organ Transplant Association of Chinese Medical Association, Prof. Liu Yong Feng and Vice President of the Liaoning Cancer Hospital, Prof. Song Chun were amongst the experts in advanced minimally invasive surgery.

Prof. Liu said, "Today's session gave the opportunity to many local junior surgeons in acquiring the knowledge and skills management in some complex and uncommon surgical procedures that generally require additional trainings. This has been a unique contribution to the local doctors."

Associate Dean of the Faculty of Medicine of the University of Hong Kong, Prof. NG Patil and President of International HepatoPancreatoBiliary (HBP) Association and Professor and Chief of the Division of HPB Surgery at the Prince of Wales Hospital, the Chinese University of Hong Kong, Prof. Joseph Lau,were also present at the Grand Rounds.

Dean of the Faculty of Health Sciences of MUST, Dr. Manson Fok explained, "This panel discussion provided practical information needed for our local Macau doctors. This event gave us the most interactive approach to the presentations. We are committed to provide local doctors and medical professionals with quality educational opportunities. The presenters here today are absolutely world-class, they are chosen as experts in their surgical field to highlight the latest scientific evidence and clinical knowledge."

Prior to the presentation, a "Meet the Experts" session was held for attendees from all three local hospitals. Our Sino-Luso (Series 6) event chairpersons, Chief of Service in Surgery, Dr. Pang Heong Keong, Dr. Edward Lai, Dr. Peter Tung and the President of the Association of Macau Portuguese Speaking Physicians, Dr. Rui Furtado, presented their latest findings in their research and treatments with six local clinical case studies in general surgery.

They did so with the strong commitment to strengthen Macau medical community.■

Jacky Kwan
Chairman, Bamboos Group
Honorary Professor, Guangdong Food and Drug Vocational College, Guangdong Province Health Department

Jacky is the Chairman of Bamboos Group. Founded in 2003, Bamboos is the largest private nursing service supplier and a leading medical service company in Hong Kong. Bamboos currently has approximately 9,500 medical professionals, including more than 5,000 registered and enrolled nurses, supporting most private hospitals, HA hospitals and nursing homes in the territory.
Jacky holds a Bachelor and a Master degree in Economics from The University of Hong Kong and an Executive Master of Business Administration (EMBA) degree from the Chinese University of Hong Kong. He also serves as the President of Hong Kong Health Care Federation and has been actively participating in social and healthcare service, with a focus on the healthcare management. In 2009, he was granted full scholarship from Harvard Business School for an executive training course at its campus. Effective management of enterprise is one of his key study themes.

Effective Management Strategy for Product Recall

Product recalls have become a fact of life in Asia. As quality control regulatory systems in Asian regions became more sophisticated over the years, this practice has been on the rise. The Internet has also facilitated rapid dissemination of product news and information, rendering timely management of product recall issues important and necessary. In Hong Kong, over 1000 medical related products recalls take place every year.

Product recall refers to the removal of products from the market, either on the wholesale, retail or consumer level. Companies often find product recalls creating substantial damage to themselves, manufacturers and distributors. This brings adverse effects to their financial status, credibility as well as brand image of their products. One of the most infamous examples recently is the Chinese milk scandal in 2008, where melamine was found in tainted milk. This incident caused a large-scale product recall in the consumer market and also aroused much fear among the consumers.

The safety of medical products is one of the most challenging public health issues of all time. Medical products safety crises are similar in nature to ticking time-bombs and have been exploding in cities around the world often at times when they are least expected.

The increasing trend of product recall may be attributed to several reasons. Firstly, given the rigorous supervision mechanisms put in place by governments, the detection rate of faulty products reached its highest point ever. Secondly, Asian companies have yet to recognize the importance of crisis management. Thirdly, managerial staff in Asia lacks the skills and receives inadequate training for product recall management. Errors could happen even in the most conscientious and professionally-managed companies. Then the problem is – what can companies do to conduct effective product recalls?

Review on the Product Recall Literature

One of the must-knows of companies is what steps should be taken when defective products were found. A lot of commentators and researchers have written articles on the procedures for recalling products (e.g., Duffy & Hamory, 1987; Malickson, 1983; Berman, 1999).

Malickson (1983) suggested four essential steps that ought to be taken:

(1) effective initial announcement to users, the public or stakeholders about the recall;
(2) easy product-model identification by consumers and retailers;
(3) decision on adjustment offer; and
(4) adjustment fulfillment.

In addition, he highlighted the significance of forming a group of dedicated personnel – a recall task force – to help get the job done in an efficient and timely manner.

In fact, companies often hesitate to form such a dedicated group of personnel just to handle something that may possibly happen. From small-medium firms' point of view, they lack the financial and labour resources to set aside for product recall pre-planning. For large-medium firms, they consider planning for product recall is equivalent to planning for failure of their products, and thus they find investment in recall task force unjustifiable.

On the other hand, Duffy and Hamory (1987) suggested nine steps to product recall that which extend beyond the product recall procedures recommended by Malickson (1983):

(1) recognize the problem;
(2) verify and characterize the problem;
(3) define extent of problem;
(4) notify in-house personnel;
(5) notify manufacturer or supervisory bodies;
(6) decide to replace or retain product;
(7) replace product or document corrective action;
(8) follow-up, including education and information dissemination; and
(9) keep anecdotal record.

One of the key steps that Duffy and Hamory paid much attention to is the documentation and record maintenance of the product recall procedures. In particular, they suggested to keep a centralized, organized record and to identify the person who will act as the recorder for the anecdotal events. This would avoid a lot of legal complications and ensure that documentation is ready for future reference.

A common feature found among articles on product recall is the significance of pre-planning. Companies vary in the degree of readiness for product recall (Berman, 1999). Some executives have an aforementioned "this can't happen to me" mentality and do not find it justifiable to devote resources in product recall pre-planning. Others simply underestimate the impact of product recall on current sales, profits or other business activities. The fact is that a lot of product managers are trained to think in terms of new product planning and in forward channel flows rather than product recalls and reverse channel flows. Regardless of the reasons, these companies are prone to experience great shocks when product recall does happen.

A Focus Group on Product Recall Training and Services Needs

A company's knowledge and skills of product recall allows it to respond to recall incident timely and effectively. Early this year, an informal focus group study was conducted to understand the training needs and product recall services of companies in the pharmaceutical and medical industry. Results indicated that there is a common uncertainty on whether a company should proactively take the initiative to undertake product recalls in the face of minor defective products in the market, given that an empirical study found proactive strategies having more negative effects on firm value than more passive strategies (Chen, Ganesan & Liu, 2009). Most companies are uncertain about the role and function of product recall, and lack the communication skills to liaise with regulatory authorities. For this reason, a lot of companies are willing to seek training specialist from overseas to equip their staff with recall knowledge and skills. In product recall incidents, they also prefer hiring external recall specialists to handle the recall process and aftermath issues.

Medical Product Recall Procedures that Involves Third Party Recall Specialist

Systematic pre-planning and implementation of product recalls bring a number of advantages. It helps to (1) control damage to the company reputation and image; (2) minimize disruption to operation; (3) minimize financial loss; (4) educate internal staff on importance of product safety; and (5) make better use of the mass media attention to communicate corporate message, maintain branding, and reinforce company's values, mission and operation.

Nevertheless, not every company can afford having their own recall task force to handle the preparatory and action phases of product recall. The product recall procedures, as illustrated in Figure 1, are thus developed upon the literature to take into consideration a third party recall specialist. Notably, it is suggested that constant monitoring of local and international news regarding the company's products is necessary even before the actual process of product recall. If the company does not have dedicated staff to monitor news, an external recall service provider may help. The third party recall specialist may be made up of a team of experts, including public affairs consultants, regulatory experts and lawyers as well as staff that provides logistic support.

As mentioned above, preparation for product recall is as important as the implementation of the recall itself. For product recalls, sufficient personnel should be assigned to handle all aspects of recalls with the appropriate degree of urgency. In order to ensure that quick and appropriate actions can be taken, a comprehensive training is very important. A successful program to train recall teams on current regulatory issues and recall managerial staffs may include training on laws and policies related to recall process, preparation for recall, media training and liaison skills.

Furthermore, setting up an enquiry hotline may improve the transparency of the product recall process and eliminate any unnecessary rumors spurred by media propaganda. A specialized product recall service provider should be able to provide administrative support, which includes establishing hotline services, self-serve recall websites and an email inquiry response system. Other support measures include reviewing recall manual and mechanisms regularly and arranging transportation to and from the return or exchange spots.

Conclusion

The costs involved in achieving such readiness do not necessarily have to be substantial. There may be little incremental expenses for a firm to designate responsibility for a product recall, prepare a recall plan, monitor overall safety during in-home product testing, institute lot tracing, and develop customer repair and warranty reports that communicate safety-related information. In contrast, other elements of recall planning, such as implementing a formal safety inspection process and updating customer databases to reflect a product's current owner can be costly. These more costly approaches should nevertheless be considered when the degree of safety risk is high due to the nature of the product, the type of consumers, the high possibility of foreseeable misuse by consumers, or a situation under which an additional recall would seriously impair the company's future image and sales. In such cases, companies may consider employing third party recall specialist to fulfill the need for recall expertise for the companies.

Any entities that are involved in the manufacturing, distribution, marketing or sale of products must take the initiatives to prepare for product recall. With the proliferation of products and brands in the consumer market, regulatory bodies and consumers across different countries are being more concerned about the quality and standards of products. Companies may choose to either equip internal staff with the capability to handle product recalls or employ external service providers to supplement inadequate recall knowledge and skills. Either case, wise companies must not overlook the potential damage brought by product recalls. ■

Note from Editor

If you would like to have a further discussion on product recall projects and services, please feel free to contact us on (852) 2575 5191 or contact@bamboos.com.hk. A group of experts and service providers are available to offer more views on this matter.

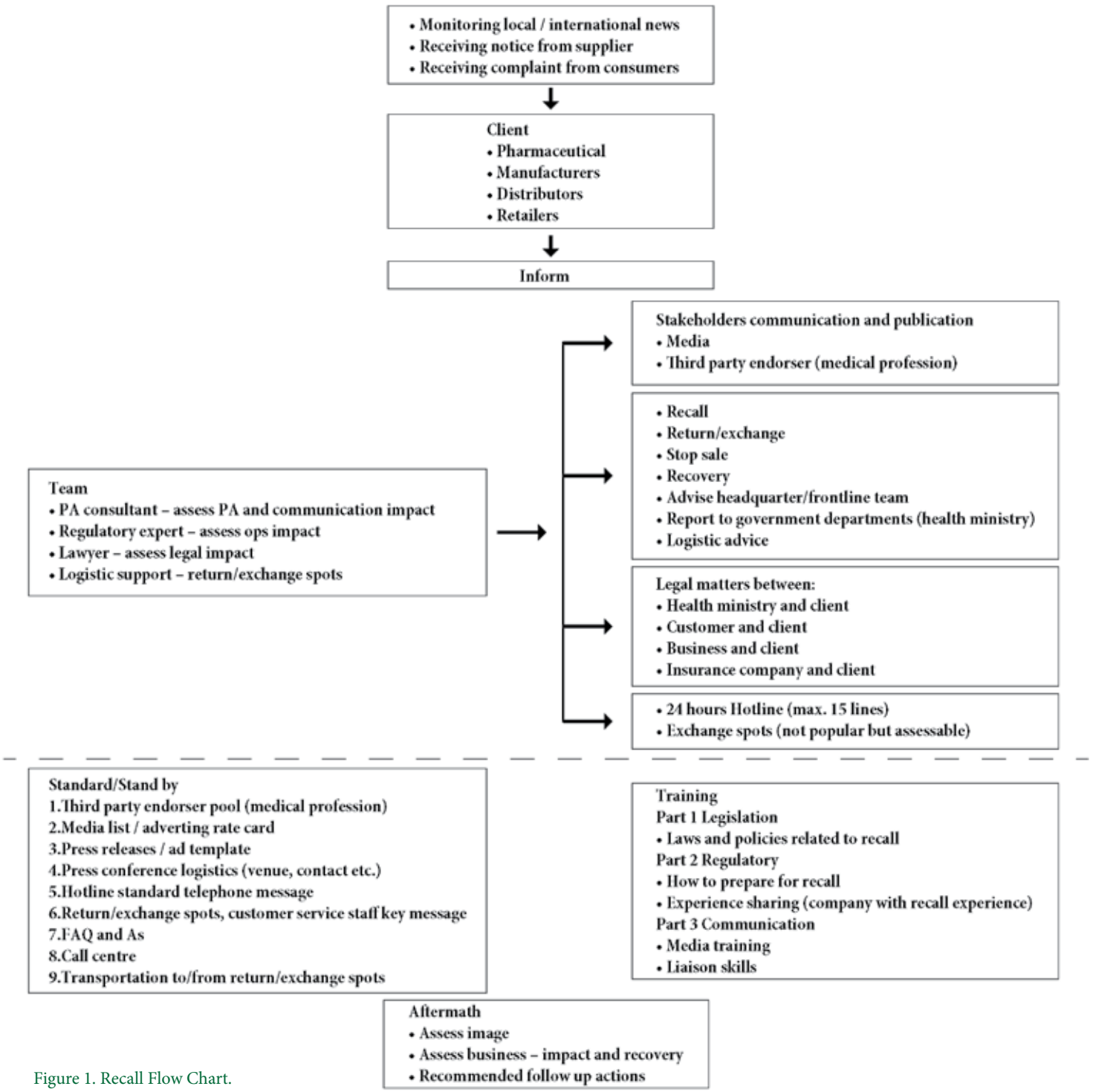

Figure 1. Recall Flow Chart.

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Product Recall
Certificate Course

Why Attend?

In the pharmaceutical and medical devices industry, product recall is almost bound to happen no matter how well prepared the company is. As a result, if we cannot change that fact, we should improve our skill set and learn to do it well. This course is organized to help companies to deal with product recall smoothly by attaining soft skills and practical tips in recall.

Instructor

Prof. Jack Wong:

Jack is now Head of Regulatory Affairs, Johnson & Johnson, APAC. Prior to joining J&J, Jack was the Vice President of Regulatory, BSI, Hong Kong. Jack has been in Pharmaceutical and Medical Devices Regulatory area for more than 15 years. He is also teaching in a number of universities in Asia including Hong Kong Polytechnic University, The Chinese University of Hong Kong, Hong Kong University, the National University of Singapore, National University of Taiwan etc..

Content

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Hong Kong Health Care Federation launches the Asia Health Care Journal with its first issue published in 2011. The Journal provides coverage and analysis of the related issues in healthcare and medical regulatory issues. The Journal features a diversity of topical issues ranging from market examination, traditional Chinese medicine, pharmaceutical regulatory affairs, medical breakthroughs, case studies, research or book review. The Journal's circulation is approximately 10,000 hard copies and 100,000 electronic copies will be sent to the subscribers. The primary audience includes healthcare professionals in hospitals, clinical practice groups, corporate healthcare systems, healthcare consulting firms, vendor organizations, and government settings in professional levels ranging from senior staff to COOs and CEOs.

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Author biographies are limited to 80 words and should appear at the end of text.

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