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Editorial: Bioethics, Stress and Moral Responsibility

One of the ultimate issues of bioethics is who takes responsibility for our health and the questions of life and death. If we can live a life according to the principle of bioethics as the love of life, perhaps we can reduce the stress that life brings to us. This issues has two papers exploring two different perspectuves of this question.

Nasrin Akhter et al. conducted experiments and review some of the research studies that address one of the most popular drugs that is used all around the world – caffeine. Maybe some of you are reading this paper and issue are in arm's length of caffeine, in a delivery form such as coffee, or soda based drinks. Please put your drink down while you read the study! As someone who almost never drinks these substances, I feel somewhat relieved to have not become addicted to them, nor list them as something which I need or desire.

Perhaps an alternative solution is bioethics education, as presented in the findings of Alex Waller in use of environmental ethics among teenagers in an international school in Khao Yai, Thailand. Even in the vicinity of the nature of famous National Park, there were positive effects in the health and academic performance of students taking those courses.

This issue of *EJAIB* also includes a review by Patrick Foong of laws regulating stem cell therapies that are so popular among many persons, that a growing number of medical tourists travel in order to avail of this technology. How do we regulate this?

Jasper Doomen reviews the ethics and law of euthanasia in the Netherlands, which is a topic of much interest to persons around the world, who usually live in countries that do not allow active euthanasia.

Joseph N. Ogar, Ushie Abel Idagu and Samuel Akpan Bassey discuss how some of the ethical principles of medical ethics affect the responsibility of physicians, and how this is applied in Nigeria today. Please enjoy the articles, and be encouraged to submit your own!

- Darryl Macer

(Please note the print edition is always in Black and white, but the pdf version online is in colour)

Repeated administration of high dose caffeine induces oxidative damage of liver in rat: Health and ethical implications

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Abstract

Caffeine, a known CNS stimulant is given as an adjunct component in most abused drugs which could be fatal with repeated administration in many circumstances. This paper presents a study to investigate the effect of repeated administration of caffeine at high dose on rat liver, and discusses ethical and policy issues of caffeine use.

Long Evans rats were treated with pure caffeine solution in distilled water through intragastric route once daily for consecutive 56 days. Three groups of rats recognized as low dose, high dose and control group received 6mg caffeine / kg BW, 12mg caffeine / kg BW and distilled water, respectively. Rat plasma was examined for liver transaminases (ALT, AST) and alkaline phosphatases (ALP) concentrations which were significantly increased in plasma as compared to the control. Both rat plasma and liver homogenate were subjected to estimate malondialdehyde (MDA), advanced oxidation protein product (AOPP), nitric oxide (NO), antioxidant enzyme catalase (CAT), glutathione (GSH) and superoxide dismutase (SOD) activity. MDA, AOPP, NO levels increased and SOD activity decreased significantly in both plasma and liver as compared to those of control where as CAT and GSH activity remain unchanged. Rat liver tissues were studied histochemically with Hematoxylin and Eosin, and Picro Sirius Red staining. Significantly increased infiltration of inflammatory cells and progressive deposition of collagen fibre were visible in liver tissue of caffeine treated both dose groups as compared to the control.

Long term administration of caffeine at higher dose, significantly contributes to liver inflammation and consequent fibrogenesis. This raises significant ethical and policy issues .

Key Words: Caffeine, Liver, Inflammation, Fibrogenesis.

Introduction

There are many legal ways available for caffeine intake including soft drinks, chocolates, drinking coffee, beverages, energy drinks and so on. There is expanding caffeine consumption around the world with the rise of global brands such as Starbucks. There is an apparent lifestyle choice in many societies to demand more chemical stimulants through soft drinks and coffee to keep awake and active for longer hours. Recreational use of CNS stimulant are rising globally. Most recreational drugs contain caffeine as an adjunct stimulant.

Development of addiction eventually increases caffeine intake due to repeated use of those drugs. Regular coffee intake has been reported as an attenuator of liver fibrosis progression in several studies. Sung Gon and Dae Won found caffeine inhibits hepatic stellate cells (HSCs) adhesion and activation and increased HSC apoptosis (Shim et al., 2013). Another study suggested that regular coffee intake lowers plasma liver transaminase level, inhibits the cAMP/PKA/CREB signal pathway through adenosine A2A receptors in HSC (Wang et al., 2015). However, caffeine has shown variable stimulating effect on acetaminophen induced hepatotoxicity mediated by microsomal CYP3A subfamily (Jaw et al., 1993). Caffeine increases respiratory rate and exert broncho-dilatation effect. On GIT, caffeine exerts stimulating effects on gastric acid and pepsin secretion and is sometimes reported to increase acid reflux by weakening lower esophageal sphincter (Robertson et al., 1978; Pincomb et al., 1985; Williams et al., 1985; Davis et al., 1988; Prineas et al., 1980; Sutherland et al., 1985; Benowitz et al., 1985; Smits et al., 1985; Murat et al., 1981; Gong et al., 1986; Benowitz, 1990).

Overall the literature identifies that caffeine consumption is associated with lower risk for multiple diseases including type II diabetes, heart disease and stroke, but the mechanism underlying these protective effects is not known. Interestingly, epidemiological studies have also established an association between the common consumption of coffee, or other caffeinated beverages, and a reduced risk of developing Parkinson's disease. Caffeine (1, 3, 7-trimethylxanthine) exerts dose dependent effects on nervous system, heart and metabolic process. On average 250 mg of caffeine may be administered to get bodily positive effects like feelings of alertness, decreased fatigue, and eased flow of thought and so on.

Caffeine intake more than 250 mg and up to 500 mg can result in adverse effects like restlessness, nervousness, insomnia, and tremors (Yew et al., 2014). The fatal dose of caffeine for adults is more than 10g. Renata et al. suggested that chronic coffee and caffeine ingestion protected the endogenous antioxidant system in rat brain and reduced lipid peroxidation of brain membrane; thus prevented age related cognitive function turn down. Caffeine mainly acts by antagonizing adenosine receptors (A_1 &A_2) non selectively and

reversing the action of adenosine. On central nervous system, caffeine induces low blood flow by vasoconstriction and releases catecholamines from presynaptic neurone by opposing action of adenosine (Abreu et al., 2011; Fredholm, 1985; Mathew et al., 1985).

On the cardiovascular system, caffeine, by a moderate intake, induces peripheral vasoconstriction, slight increased blood pressure, reduced heat rate, systemic release of catecholamine and renin, a balanced change in cardiac output and contractility. Chronic coffee consumption is found to be associated with increased level of serum LDL cholesterol and cardiac arrhythmia. In contrast, high dose of caffeine decreases blood pressure by vasodilatation and increases systemic catecholamine extremely. Glomerular filtration rate and tubular reabsorption, increased by caffeine creates hyponatraemia. Contribution of caffeine to increased body temperature is not supported by any strong evidence.

Investigation on rats treated with caffeine revealed that coffee or caffeine intake inhibits calcium metabolism and results in higher levels of calcium in the urine and plasma as compared to bone, decreased bone mineral density and bone volume. Moreover, caffeine has negative effects on osteoblast function and bone matrix formation and thus bone repairing process is delayed. Caffeine suppresses calcium absorption from intestine to some extent. Thus people, with a habit of caffeine intake and lack of calcium in diet, are highly at risk of developing osteoporosis. A separate study reported that high dose caffeine intake inhibits the secretion of parathyroid hormone (PTH) through the mechanism of decreasing intracellular cAmp. PTH contributes directly to the survival and differentiation of osteoblast cell and hence increased population of osteoblasts useful for the treatment of osteoporosis and bone formation. A correlation between high coffee consumption and low PTH serum levels has been observed in men which was opposite in a separate study with young women. However, this relationship requires further detailed investigation.

Caffeine undergoes N-demethylation and/or ring oxidation through its biotransformation process and metabolites produced are theophylline, paraxanthine, theobromine and 1, 3, 7-trimethyluric acid in man. Further decomposition of these compounds takes place to give rise dimethylated uric acids, monomethylxanthines and monomethyluric acids. A separate study suggested that CYP1A2 isozyme catalyzes the demethylation process of caffeine which is further reportedly acetylated to 5-acetylamino-6-formylamino-3-methyluracil (AFMU) by the polymorphic acetyl transferase (Huang et al., 2002; Tassinari et al., 1991; Wink et al., 1996; Lacerda et al., 2010; Heaney, 2002; Lu et al., 2013; Jilka et al., 2007; Landin-Wilhelmsen et al., 1995; Paik et al., 2010; Tang-Liu et al., 1983; Butler et al., 1992).

To investigate liver toxicity by caffeine we have estimated liver marker enzymes (ALT, AST) and alkaline phosphatases (ALP) level in rat plasma; antioxidant enzyme activity such as catalase CAT), glutathione (GSH), superoxide dismutase (SOD) and oxidation end products like advanced oxidation protein product (AOPP), lipid peroxidation product, malondialdehyde (MDA) and level of nitric oxide (NO) in both plasma and liver tissue after long term administration of caffeine on rats. Histopathologic study of rat liver tissue was performed for inflammation and fibrosis from all groups.

Methods

Chemicals and reagents

Pure caffeine of pharmaceutical grade used in our study was kindly supplied by Pharmadesh Laboratories Limited. Alanine aminotransferase (ALT), aspartate amino transferase (AST) and alkaline phosphatases (ALP) assay kits were obtained from DCI diagnostics (Budapest, Hungary), Thiobarbituric acid (TBA) was purchased from Sigma Chemical Company (USA), 50,50-dithiobis-2-nitrobenzoate (Ellman's reagent) from Sigma (USA), glutathione (GSH) in reduced form and trichloroacetic acid were purchased from J.I. Baker (USA) and sodium hydroxide from Merck (Germany). All other chemicals and reagents used were of analytical grade.

Animal experiments

18 male Long Evans rats (180-200g) were obtained from animal production unit of Animal House in the Department of Pharmaceutical Sciences, North South University, Dhaka, Bangladesh (aged between 10-12 weeks old). The animals were kept in ordinary cages (18 inch X 12 inch per individual) at room temperature of 25±3˚C with 12 h dark / light cycles (65% relative humidity). They had free access to standard laboratory feed and water. The present study protocol was approved by the Ethical Committee of the Department of Pharmaceutical Sciences, North South University for animal care and experimentation.

To study the effects of caffeine on liver, the animals were equally divided into three groups (6 rats in each). Animals of group 1, considered as low dose group, were treated with 6mg caffeine / kg of body weight intragastrically, once daily. Rats of group 2, considered as high dose group, were treated with 12 mg caffeine / kg of body weight intragastrically, once daily. Group 3 considered as control group where rats received only distilled water. Rats of all groups were treated for eight weeks. Body weight, water and food intake of animals were monitored and recorded daily.

After 56 days, all the animals were weighed and sacrificed. Blood samples were collected and plasma separated from it and stored at -20˚C until used. Some major organs like liver, kidney, heart, spleen were also collected and weighed immediately. Half of the organs were stored at -20˚C until used for biochemical tests and half were processed for histological study.

Assessment of liver enzymes

Rat plasma of three groups was assayed for liver transaminases, ALT and AST and another isozyme, alkaline phosphatases (ALP). Chemical analysis was conducted by following the standard protocols of manufacturer provided with DCI diagnostics kits (Hungary).

As biochemical markers of liver dysfunction, some of the enzymes and end products of the metabolic pathway, such as serum bilirubin, alanine amino transferase, aspartate amino transferase, ratio of aminotransferases,

alkaline phosphatase, gamma glutamyl transferase, 5′ nucleotidase, ceruloplasmin, α-fetoprotein, are said to be very sensitive, reported by several studies. Among them the three enzymes ALT and ALP, AST are considered as the classical markers of any kind of liver cell injury whose levels are elevated in plasma in liver disease. (Gowda et al.;2009).

Assessment of oxidative stress markers and antioxidant enzyme activity

Oxidative stress markers and antioxidant enzyme activity were measured in both blood plasma and liver tissue. Liver tissue was homogenized in 10 times volume of ice cold phosphate buffer having pH 7.4 and centrifuged at 12,000X g for 30 min at 4°C. The supernatant was collected and used for the determination of protein and enzymatic studies.

Estimation of malondialdehyde (MDA)

Following a colorimetric method, we measured MDA, one of the products of lipid peroxidation in plasma and liver tissue extract using thiobarbituric acid (TBA) as per method described by Niehaus and Samuelsson (Niehaus et al., 1968). The procedure briefly described as treatment of 0.1 ml of tissue extract or plasma in Tris-HCl buffer (pH 7.5) with 2ml of TBA-TCA-HCl reagent mixture taking equal amount of each (thiobarbituric acid 0.37%, 0.25 N HCl and 15% TCA). The final mixture was heated in hot water bath for 15 min and then cooled. The clear supernatant was taken and absorbance measured against reference blank at 535nm.

Assay of nitric oxide (NO)

Nitric oxide, in the form of nitrate, was measured following the method described by Tracey et al.(1995). In the present study, Griess-Illosvoy reagent was modified by replacing 5% 1-napthylamine with naphthyl ethylene diamine dihydrochloride (0.1% w/v). The reaction mixture containing tissue extract or plasma (2ml) and phosphate buffer saline (0.5ml) was incubated at 25°C for 150 min. The mixture color changed into pink due to formation of a pink colored chromophore. Using corresponding blank solutions, the absorbance of these solutions was measured at 540 nm. A standard curve, expressed as nmol/ml, was prepared to measure plasma and liver tissue content of nitric oxide.

Measurement of advanced oxidation protein products (AOPP)

The methods described by Witko-Sarsat et al.(1996) and Tiwari et al.(2014) were followed with slight modification to detect AOPP level. In brief, 2 ml mixture was made by diluting plasma or tissue extract with PBS in 1:5 ratio; then 0.1 ml of 1.16 M potassium iodide was added to each tube; after 2 min, 0.2ml acetic acid was added to it. The absorption of the reaction mixture was measured immediately at 340 nm using a blank containing 2ml of PBS, 0.1ml of potassium iodide and 0.2 ml of acetic acid. AOPP concentrations were expressed as nmol/L as chloramine-T equivalents where the absorbance of chloramine–T was linear within the range of 0 to 100 nmol/L at 340 nm.

Estimation of catalase (CAT) activity

The method described by Khan et al. (2012) was used to test catalase activity with some modifications. The 3 ml reaction mixture used for CAT activity contained: 0.1 ml of plasma or liver tissue enzyme extract, 2.5 ml of 50 mmol phosphate buffer (pH 5.0) and 0.4 ml of 5.9 mmol hydrogen peroxide. 1 min later changes in absorbance of the reaction mixture were determined at 240 nm. An absorbance change of 0.01 as units/min corresponds to one unit of CAT activity.

Assay of glutathione (GSH) in reduced form

Reduced glutathione in liver was estimated by the method of Mitchell JR et al. (1973). 1.0 ml of 4% sulfosalicylic acid was added to 1 ml of 10% tissue homogenate. Then the precipitated mixtures were kept for one hour at 4ºC. After 1 hour, mixtures were centrifuged at 1200 × g for 20 min at 4ºC. 0.1 ml filtered aliquot, 2.7 ml phosphate buffer (0.1 M, pH 7.4) and 0.2 ml of 100mM DTNB (5,5-dithiobis-2-nitrobenzoic acid) were mixed to make 3 ml assay mixture. A yellow color of the mixture developed which is immediately subjected to take absorbance at 412 nm using Smart SpecTM plus Spectrophotometer. The calculated result was expressed in ng/mg protein.

Estimation of superoxide dismutase (SOD) activity

SOD was assayed in plasma and tissue homogenates by using previously described method (Tripathi et al., 2010). Sufficient amount of tissue extract mixed with PBS to make the volume 2.94 ml. Then 0.06 ml of 15 mM epinephrine is added to the mixture to start the reaction. Taking an interval of 15 sec, change in absorbance of reaction mixture was recorded for one min at 480 nm. Blanks prepared with all the ingredients, except enzyme preparation were used simultaneously for taking absorption. Auto-oxidation of epinephrine present in sample solution will be reduced to 50% with the action of one unit enzyme.

Histopathological observation

Liver tissues of all groups were prepared for histology study according to standard procedure. In short, tissues were fixed neutral buffered formalin, treated with ethanol and xylene, then embedded in paraffin. Using microtom, tissue paraffin blocks were sectioned at 5μm. Tissue sections were then stained with Hematoxylin and Eosin and Picro Sirius Red separately for microscopic observation of the inflammatory cell invasion and deposition of collagen fibre respectively in liver. Stained tissue sections were examined under light microscope at 40X magnifications.

Statistical analysis

The experimental results were evaluated by using the student's *t* test in Graph Pad Prism Software. The values were expressed as mean±standard error of mean (SEM). In all cases, statistical significance was considered $p< 0.5$.

Results

Physical and behavioral changes observed in rat during caffeine treatment

During the period of experiment, rats of both dose treated groups were found restless with palpitation. No

lesions were observed on skin. Body temperature was normal after caffeine administration.

Effects of caffeine on body weight, food and water intake in rat

During the experimental period, daily body weight, food and water intake of rats of all groups were recorded. Body weight of rats increased equally (Figure 1) in drug treated and control groups. Food and water intake was the same for all groups (Figures 2 and 3).

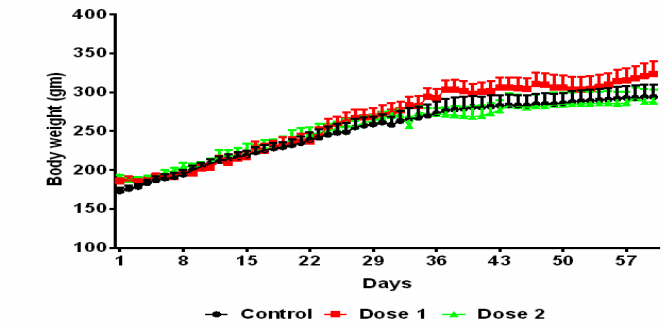


Figure 1: Daily body weight record of rats during caffeine treatment

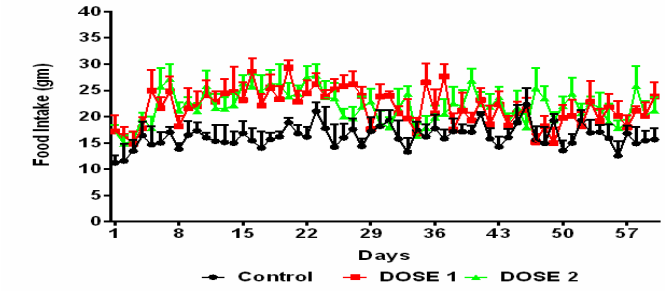


Figure 2: Daily food intake record of rat during caffeine treatment

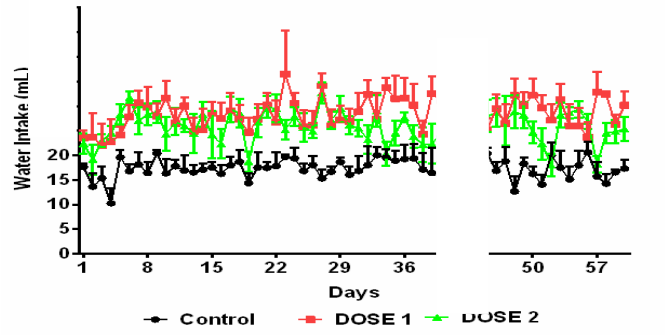


Figure 3: Daily water intake record of rat during caffeine treatment

Effects of caffeine on organ weight in rat

Liver weight of caffeine treated rats increased significantly from that of control in high dose group ($P < 0.05$, $n = 6$). Other vital organs such as heart, kidney and spleen showed no significant change in weight as compared to control values.

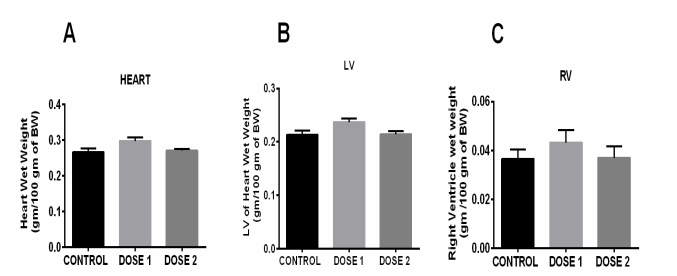


Figure 4: Comparison of weights of whole heart, left ventricle and right ventricle of caffeine treated rat with control group

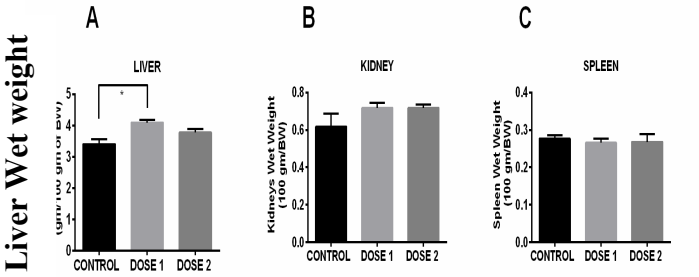


Figure 5: Comparison of liver, kidney and spleen weights of caffeine treated rat with control group

Effects of caffeine on liver marker enzymes in rat

By caffeine treatment, transaminase ALT increased significantly to 71.78 ± 8.22 in low dose group and to 73.21 ± 5.33 in high dose group from 43.07 ± 4.45 U/L ($p< 0.01$, $n= 6$ in both groups). Another liver marker enzyme AST increased significantly to 41.63 ± 3.46 in low dose group and to 47.37 ± 4.85 in high dose group from 22.97 ± 2.87 U/L($p< 0.01$, $n=6$ in both dose groups). Alkaline phosphatase (ALP) increased significantly to 51.10±3.85 in low dose group and to 48.75 ± 3.88 in high dose group from 30.88 ± 4.59 U/L($p< 0.01$, $n=6$ in both groups). The liver transaminases, ALT increased 1.7-fold in both dose groups; AST increased 1.8-2.0 fold in low dose and high dose group, respectively; ALP increased1.6-1.7 fold in low dose and high dose group respectively as compared to control value.

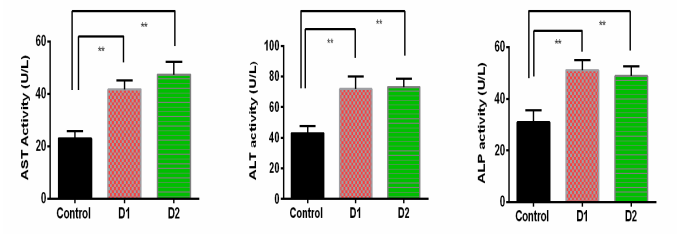


Figure 6: Effect of caffeine on liver transaminases and alkaline phosphatases in rat

Effects of caffeine on oxidative stress in rat

In our study, we have evaluated the MDA, nitric oxide and AOPP content in rat plasma and liver homogenates as markers of oxidative stress. The level of lipid peroxidation product, MDA in caffeine treated rats significantly increased from 97.72 ± 7.30 to 169.79 ± 11.09 by low dose and to 146.85±14.08 nmol/ml by high dose ($p< 0.01$, $n=6$) in plasma. In liver homogenate,

this value increased from 130.82±10.89 to 179.08±6.76 by low dose and to 194.46 ± 5.85 nmol/ml by high dose ($p< 0.01$, n=6). Caffeine increased MDA 1.5-1.7 fold by high and low dose respectively in rat plasma and 1.4-1.5 fold by low and high dose respectively in liver.

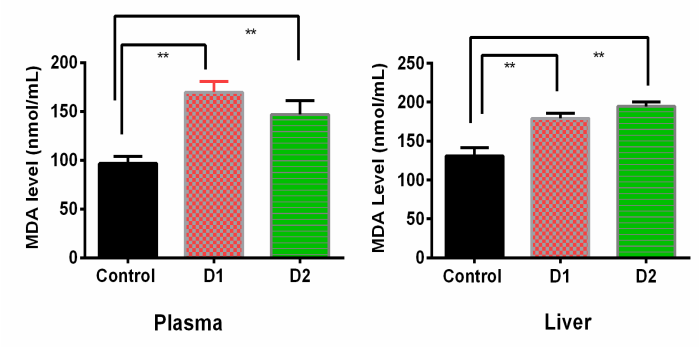


Figure 7: Effect of caffeine on lipid peroxidation in plasma and liver in rat

NO, measured as nitrate, increased significantly from 14.1 ± 0.91 to 17.24 ± 0.34 nmol/ml ($p<0.05$, n=6) by low dose in plasma and in liver tissue, from12.63 ± 0.48 to 29.05 ± 2.01by low dose and to 35.57 ± 4.08 nmol/ml ($p<0.05$, n=6) by high dose when compared with control values. Caffeine induced increase in NO level 1.2-fold by low dose in plasma and in liver 2.0-2.3 fold by low and high dose respectively as compared to control values.

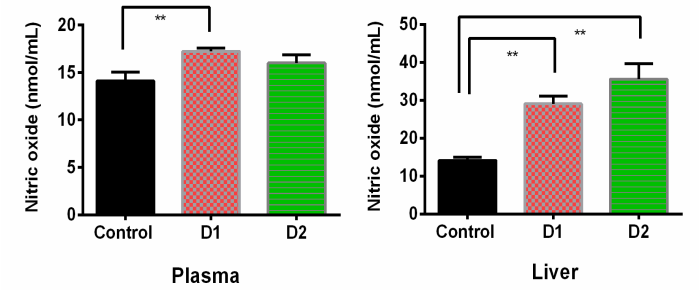


Figure 8: Effect of caffeine on nitric oxide level in plasma and liver in rat

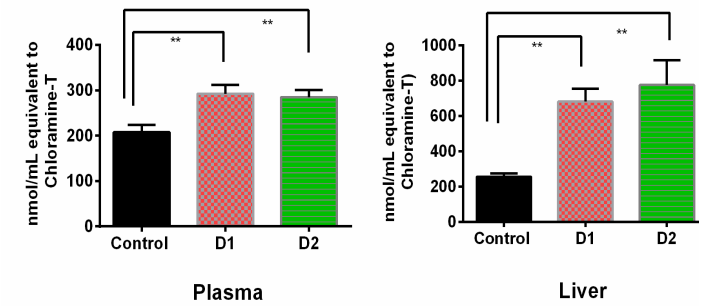
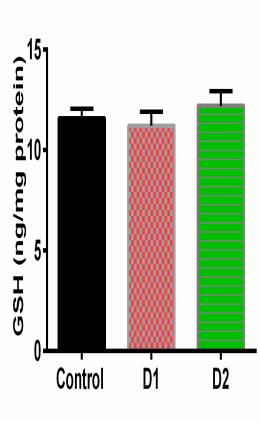


Figure 9: Effect of caffeine on advanced oxidation protein product level in plasma and liver in rat

Caffeine treatment induced significant increase in AOPP concentration to 292.62 ± 19.03 and to 285.08 ± 15.40 from 207.70 ± 16.05 nmol/ml equivalent to chloramines-T ($p<0.01$, n=6) in plasma by low and high dose respectively. In liver it increased to 682.06 ± 72.34 and to 776.51 ± 139.36 from 256.11 ± 18.44 nmol/ml equivalent to chloramines-T ($p<0.01$, n=6), by low and high dose respectively. AOPP increased 1.3-1.4 fold by high and low dose respectively in plasma where as 2.6-3.0 fold by high and low dose respectively in liver as compared to control.

Effects of caffeine on antioxidant enzyme system in rat

Caffeine treatment significantly reduced superoxide dismutase activity by low dose from 20.83 ± 3.52 to 10.00 ± 1.83 in plasma; from154.17 ± 17.77 to 83.33 ± 8.82 by low dose and to 94.17 ± 6.38 by high dose in liver. SOD activity reduced 2-fold by both dose groups in plasma and liver. Activities of other antioxidant enzymes such as GSH and CAT found unchanged in plasma and liver tissue in both dose groups when compared to control values.



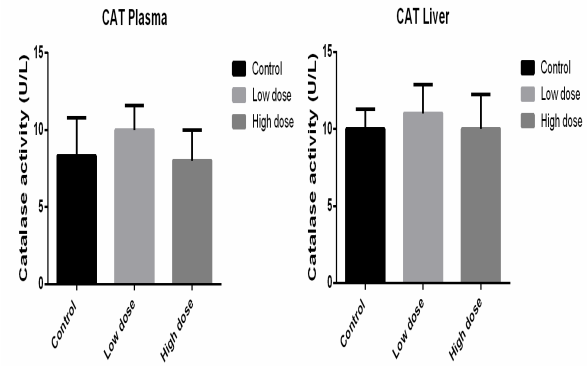


Figure 10: Effect of caffeine on glutathione and catalase activities in plasma and liver in rat

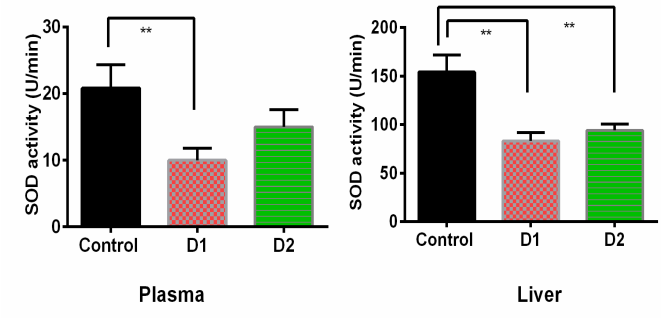


Figure 11: Effect of caffeine on superoxide dismutase activity in plasma and liver in rat

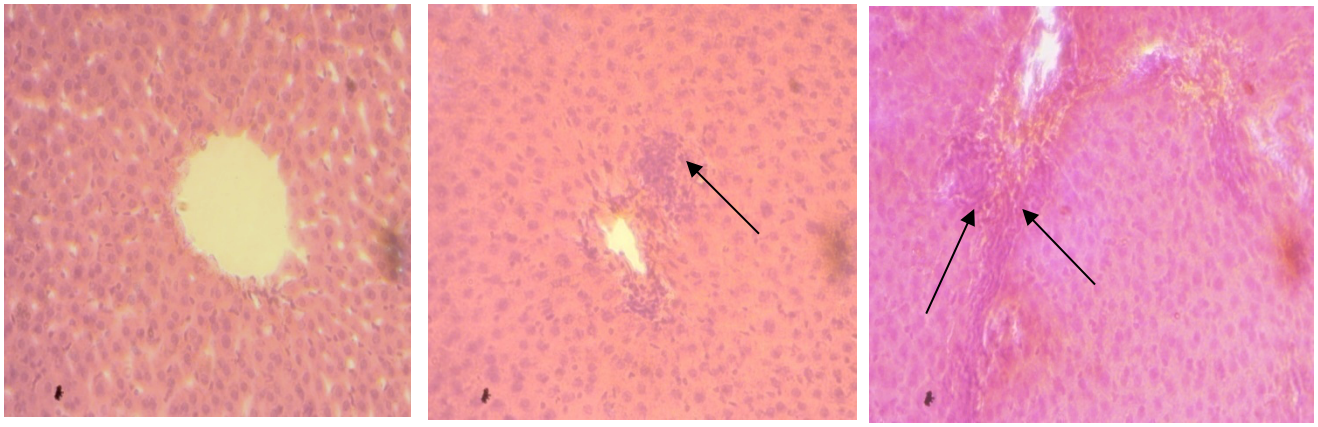
Histological changes after caffeine treatment in rat liver

Inflammation in drug treated rat liver was seen in stained tissue section. Massive invasion of inflammatory cells was found in the centrilobular part of liver section stained with H &E in low dose group, which progressively increased in the high dose group (Figure 12).

Liver fibrosis was evaluated histologically by visualizing the red color of collagen fibres deposition using Sirius red stain in both dose groups. The collagen fibres were heavily deposited around portal tracts and central veins in caffeine treated group and extended from central vein to portal tract resulting in the formation of pseudolobules which was not seen in control rats. Extent of collagen fibre deposition was enormous in high dose group than that of low dose group (Figure 13).

Discussion

In the present study, we have performed investigations to figure out the effect of caffeine on liver. This study illustrates how biochemistry can be applied to investigate potential health affects of a popular dietary compound. The biochemical test results indicated the contribution of caffeine on ROS induced liver cell damage through lipid peroxidation or protein oxidation. Other effects such as increased nitric oxide and decreased activity of antioxidant enzymes suggest the stressed condition with reactive oxygen or nitrogen species produced by caffeine. High and low doses of caffeine induced elevation of serum ALT, AST and ALP levels as compared to control.



Control Low dose High dose

Figure 12: Invasion of inflammatory cells in the centilobular part of rat liver after caffeine treatment

Control Low dose High dose

Figure 13: Deposition of collagen fibre in rat liver after caffeine treatment

In our study, we have focused on the oxidative damage of liver cells with chronic administration of high dose of pure caffeine targeting reactive oxygen species (ROS) and reactive nitrogen species (RNS) mediated damage of cell components. To observe liver cell damage the plasma levels of three liver marker enzymes (ALT,AST,ALP) have been estimated. As a proof of increased oxidative stress some antioxidant enzymes (CAT,GSH, SOD) level in plasma and liver tissue have been measured. Moreover, to check damage by oxidation some reaction end products such as AOPP, MDA, NO were determined in plasma and liver tissue.

The cytotoxic effects of caffeine have been demonstrated as indirect action with several enzymes or xenobiotics in some studies included-

i. Caffeine increased glioma cell death by decreasing HDAC1 activity and/or by increasing p300 activity (Jin-Cherng Chen et al., 2016).

ii. The synergistic cytotoxic activity of caffeine with different anticancer agents to treat several cancers has also been reported (Line. Saeb H et al., 2017).

iii. Caffeine has been shown to induce apoptosis and autophagy in different cancer cells. (Bøhn, et al., 2014).

iv. Importantly, caffeine has also been shown to inhibit ATM and ATR -two important protein kinases involved

in DNA damage– and to induce cell cycle arrest/apoptosis signaling process (Wang, et al., 2015).

v. In a different study, combined effects of caffeine with alprazolam (Alp), a member of benzodiazepine group of drugs, have been shown to elevate level of ROS and depletion of GSH. Presence of caffeine augmented necrosis in a well-regulated pathway whereas alprazolam alone induced apoptosis in human cells. (Saha et al., 2009).

The magnitude of aminotransferase alteration defines the severity of liver disease as "mild" (elevation less than 5 times of normal) "moderate" (elevation 5–10 times of normal) or "marked" (elevation more than 10 times of normal). Besides liver, alkaline phosphatase level indicates bone disease even though this enzyme may also be released from other tissue damage included the placenta, kidneys, intestines or leukocytes. In drug induced liver damage, alcoholic liver disease and non-alcoholic fatty liver disease, viral hepatitis (hepatitis B and C) and hemochromatosis, liver transaminases (ALT,AST) exhibit mild elevation (Green et al., 2002; Pratt et al., 2000; Gopal et al., 2000; Robert et al., 2011; Fishman, 1990). In present study, we found the magnitude of ALT and AST elevation in caffeine-treated rat as representing mild liver disease when compared with control values.

Drug toxicity can play significant role by triggering inflammatory response and activating innate immune cells by release of damage –associated molecular pattern. Resident kupffer cell, neutrophils, monocytes are activated in the liver after toxic induction of drug. ROS produced by the phagocytes mediates killing of target cells (e.g. the invaded organisms). In absence of bacteria, especially when injury is drug induced, hepatocytes and other liver cells becomes target of ROS; hence the damaged host cells initiate chronic inflammation. However, the nature of oxidative stress specifies the target and damages particular cellular component. The mechanism of ROS induced cell killing involves mitochondrial dysfunction leading to oncotic cell necrosis rather apoptosis.

Very few studies presented the effect of caffeine on metabolism as:

i. Caffeine mobilizes fatty acids from adipose tissue and increases its plasma level at rest in an exercising muscle (Graham et al.; 2008)

ii. Few studies supported the fact that the carbohydrate and fat metabolism in active muscle was generally unaltered after caffeine ingestion (Graham et al. ; 2000)

iii. Oral doses of caffeine increase the urinary excretion of calcium, magnesium, sodium and chloride for at least 3 h after consumption. Uncompensated losses of calcium would be a risk factor for development of osteoporosis (Linda et al., 1993).

iv. A Retrospective cohort study presented that consumption of green tea, coffee, and total caffeine was associated with a reduced risk for type 2 diabetes. However, the mechanism of action of caffeine for reducing risk for type 2 diabetes has not been studied yet (Iso et al., 2006).

Chronic release of cell contents amplifies the inflammatory injury. Jaeschke et al. described that inflammatory ROS cause cell death in sufficient concentration where as insufficient ROS triggers the resistance against future inflammatory oxidative stress by inducing transcription of antioxidant genes and thus promoting tissue repairing process (Jaeschke, 2011). Among ROS, superoxide anion ($O2^{-}$) and hydrogen peroxide (H_2O_2) mostly capable of damaging biochemical molecules including nucleic acids and aminoacids. However, the most damaging effect is the induction of lipid peroxidation. The cell membrane, composed of poly-unsaturated fatty acids, is a primary target for reactive oxygen attack leading to cell membrane damage (Ghiassi-Nejad et al., 2008). Our study revealed that caffeine administration resulted in a significant reduction of SOD in plasma and liver by both doses variably which was accompanied with a significant increase in lipid peroxidation product TBARS as compared to the control group. This finding suggested the elevated production of superoxide anion by caffeine treatment in rats.

It is known that stress on rats dilates the endoplasmic reticulum (ER), and that caffeine induces release of calcium from the ER (Macer and Koch, 1988). Further investigation of the effects of caffeine related to stress response will be useful. As indicated at the beginning of the paper, the effects of caffeine on various body systems, and overall health requires more clarification. Also given the genetic diversity of all human populations, persons with particular genotypes (and epigenetic patterns) may respond differently. This study may be particularly important to those with a genetic predisposition to liver damage, who will suffer more from the effects described in this paper. Will we apply nutrigenomics to those who are contemplating different forms of stimulants?

Also people in particular life stages, such as during pregnancy may be particularly vulnerable. Prospective observational studies have indicated that maternal caffeine intake during pregnancy is associated with a higher risk of excessive infant growth and overweight in childhood. Studies such as these support the current advice to reduce caffeine intake during pregnancy.

Increased level of oxidized protein is an indicator of increased oxidative stress. Oxidized protein product equivalent to chloramines-T increased significantly in plasma and liver after caffeine treatment indicated increased ROS production by both doses of the drug. Catalase and glutathione, which protect body from oxidative harm by reactive oxygen species, showed unchanged activity in caffeine treated groups when compared with control value. Nitric oxide (NO), another component of reactive species, takes part in lipid peroxidation. Role of NO in apoptic cell death of neuronal cells was described by Taotao et al. The same paper suggested that NO- induced apoptosis is partly mediated by ROS. In our study, caffeine induced significant increase in NO level in rat plasma and liver as compared to control indicating hepatic cellular apoptosis or necrosis.

In response to liver inflammation, the pro-fibrotic mediators are stimulated and initiate liver fibrogenesis (Cui et al., 2003; Galli et al., 2005). Sign of liver inflammation, due to significantly increased inflammatory mediators, detected by biochemical tests, was supported by the histopathological assessment of liver tissue. Typical hepatotoxic signs appeared in

histopathological study of caffeine treated rat liver tissue as described in previous literature of Nabeshima et al., 2006 and Jin et al., 2013. Inflammatory cells were accumulated in the necrotized region and along the bile ducts and blood vessels in liver of drug treated rats.

However, we could not identify the inflammatory cell type in present study. Research suggested that immune cell infiltration coupled with liver-resident kupffer cells, contribute significantly to the development of liver fibrosis. Investigation on mice with drug induced liver injury revealed the involvement of monocytes in both acute and chronic inflammation (Karlmark et al., 2009). At the initial stage of fibrosis, macrophages derived from monocytes release several cytokines which initiates chronic inflammation through the activation of hepatic stellate cells. The activated hepatic stellate cells, proliferated and trans-differentiated into myofibroblasts start to produce collagen (Imamura et al., 2005). In our study, dose dependent collagen fibre deposition was seen in Sirius red staining of rat liver. Progressive deposition of collagen fibre supported the sustained inflammatory cell damage of rat liver, treated with caffeine.

Conclusions

As discussed in the introduction the effects of caffeine on human beings is complex. To our knowledge, the cytotoxic effect of caffeine have been investigated as combined therapy or using human cell line in vitro. In our study, we have used **pure caffeine alone in vivo** to monitor its cytotoxic effect on rat liver after long term administration at high dose. In the present study, inflammation and consequent fibrogenetic effect on liver by caffeine was uncovered. The possible mechanism might be increased lipid peroxidation of hepatocytes and protein oxidation by increased ROS (especially O_2.) or RNS (especially nitric oxide); consequent chronic inflammation stimulated by damaged cells and progressive collagen fibre deposition by myofibroblasts. Additionally histochemical findings revealed the existence of inflammation and fibrogenesis in liver. However, in contrast with inflammatory response, antioxidant enzyme catalase and glutathione activity remain unchanged. Another enzyme superoxide dismutase activity significantly decreased suggesting abundance of superoxide ion as compared to other reactive species. Further study on other molecular mechanisms might be conducted to clarify the process of fibrogenesis mediated by caffeine.

There are significant ethical implications of this study given the widespread use of caffeine in society. There is an urgent need to further studies to assess the effects of lifelong use, given that many persons start use of caffeine at a young age. This is more than a significant public health issue, but also a question of social policy. How do we assign risks to popular substances when the overall health affects likely vary between individuals.

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Some beneficial effects on the physical heath and academic achievement of middle years secondary school students through studying environmental ethics

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Abstract

Some of the results from a case study at a small international school in Thailand indicate a possible relationship between increased naturalistic intelligence, physical health and subsequent academic performance. These rises follow the introduction of an Environmental Ethics and Renewable Energy Education (EEREE) programme into the curriculum for middle years students. The health estimations are from Body Mass Index (BMI) and records of students seeking medical attention. The tools to assess naturalistic intelligence are statistically validated and the results from subsequent International General Certificate of Secondary Education (IGSCE) are analysed. There is a suggestion for a possible causal link, although this is not proven.

Key words: self-esteem, body mass index, bioethics, environmental ethics, naturalistic intelligence

Introduction

During the four academic years 2013/14 to 2016/17 a one year Environmental Ethics and Renewable Energy Education (EEREE) course was delivered to Year 10 students at St Stephen's International School, Khao Yai (SISKY). It consisted of forty one hour lessons that were included within the Personal Health and Social Education Programme (PSHE) or within Science lessons, depending on the timetable allowances each year. The course introduced the main ethical frameworks, principles applied in ethical decision making as well as introducing a range of socioeconomic topics related to sustainability, the science behind renewable energy technologies and related environmental issues. A case study was conducted to determine the benefits of studying EEREE for the students and the wider school community. The specific objectives were to determine if there were changes in multiple intelligences and values or attitudes towards sustainability. This paper refers some data that emerged from searching for long term benefits within the school that arose during the years of these trials.

In this case study two indicators of health were used. Firstly, the Body Mass Index (BMI) of students was calculated. Secondly, records of visits to the medical to seek medical attention were tallied for students from each academic year group. The BMI records were available for six years prior to the introduction of the EEREE course as well as the years 2013 to 2017 during which the course was taught at SISKY. The log visitors to the medical room was only available from 2013-14 until 2016-17, which were the years that the EEREE course was delivered.

The hypothesis is that learning EEREE required the frequent use and development of higher order thinking skills such as analysis and evaluation. This induced an increase in naturalistic intelligence. This increase of intelligence lead to higher confidence and self-esteem that in turn lead to measurable improvements in physical health. Collectively these factors supported students learning Sciences in general and Biology in particular.

A brief review of some relevant literature

The third UN Sustainable Development Goal (SDG)[1] is specifically concerned with health and wellbeing; surely there is little point in aiming for unsustainable development without ensuring sustained or improved good health. Therefore it is appropriate to consider physical and mental health in the case study of the impacts of studying EEREE on students' attitudes towards sustainability.

Following a survey of 757 adults in Australia, Kermode and MacLean (2001) determined a positive correlation between quality of life (QOL) and self-esteem, long term stress lowered QOL as did illness. Although some researchers such as Ross and Broh (2001) argue that self-esteem has little benefit on academic achievement, it is generally agreed that ideally students will grow in self-esteem. Booth and Gerard (2011) conducted a case study in two Western schools that demonstrated a fall in self-esteem was directly related to subsequent poorer academic performance. Trzesniewski *et al* (2006) found that low self-esteem in teenagers is a predictor of poor health in later life. Von Hinke Kessler Scholder *et* al (2010) used genetic markers to check findings that increased adipose tissue levels correlated with lower academic achievement. They cite bullying, absenteeism, sleep apnoea and ostracism by their peers as all being contributing factors to these lower achievement levels. Al Drees *et al* (2016) correlate higher levels of physical activity with higher academic performance in medical students. Alswat *et al* (2107) found, in a survey of 424 students from 14 Saudi secondary schools, a correlation between obesity and poor performance in Physics, but not in their overall Grade Point Average (GPA) scores. Oketayo *et al* (2010) that within a group of 110 Nigerian Physics students there was a strong negative correlation between BMI and academic performance. One of the most compelling studies is from Korea involving over 72 000 adolescents aged 12 - 18 years, which shows very strong correlations between obesity and poor academic performance (Kim and So, 2013).

Several studies also report no significant difference in achievement comparing individuals with different BMI values (Wehigaldeniya *et al,* 2017; Fletcher and Lehrer, 2009; Kaestner and Grossman, 2009). In addition to there being a possible link between BMI and academic performance there are many other factors that do or could influence achievement, such as socio-economic background, parental education levels, regular quality sleep, access to online learning support and resources, travel times to and from school. This list is not exhaustive, for example Wang *et al* (2017) found that the consumption of nutrient fortified milk lead to increased performance in mathematics, ethics and languages.

Methodology

The nursing staff at SISKY calculated the Body Mass Index (BMI) of all students each year. The BMI is calculated using:

$$\text{BMI} = \text{mass (Kg)} / \text{height}^2 \text{ (m)}$$

The BMI value is used an indicator of potential for ill health related to body mass issues such being chronically underweight, overweight or obesity. The significance of the BMI value is dependent upon the age and gender of the student as shown in Figures 1 and 2 below.[2]

Figures 1 and 2 show the World Health Organisation (WHO) BMI chart for boys (above) and girls (below) aged 5 to 19 years old. Interpretation: The numbers of the coloured lines are standard deviations (SD) from the median (50th percentile): >1SD is overweight (equivalent to BMI 23.7 kg/m^2 at 15 years for girls and 22.7 kg/m^2 for boys of the same age), >2SD is Obesity <-2SD is thinness, and <-3SD is severe thinness. The number of students with "healthy" BMI values within each academic year group was calculated.

The number of visits to seek medical attention was simply a tally of the recorded visits. These included those seeking genuine medical attention for physical problems and visits from students seeking emotional support as the nurses are often a first port-of-call for students needing comfort.

[1] listed on the UN website http://www.un.org/sustainabledevelopment/sustainable-development-goals/

[2] These graphs of the percentiles related to BMI age and gender interpretations are available from the WHO website at http://www.who.int/growthref/who2007_bmi_for_age/en/

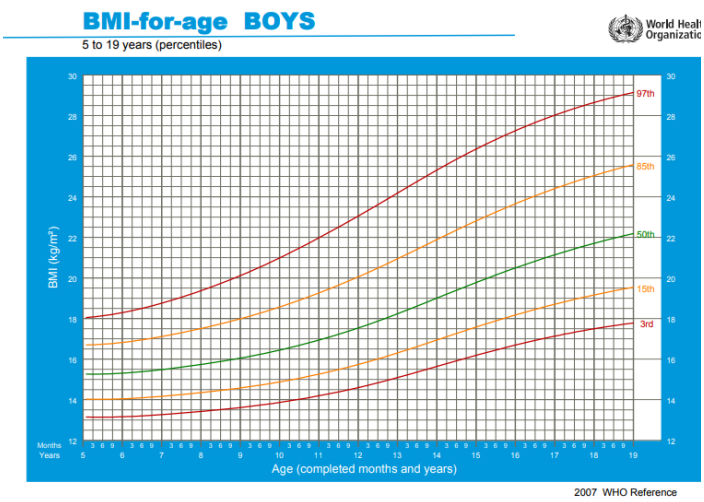

Figure 1: Graph for interpretation of boys BMI values taken from WHO (2007)

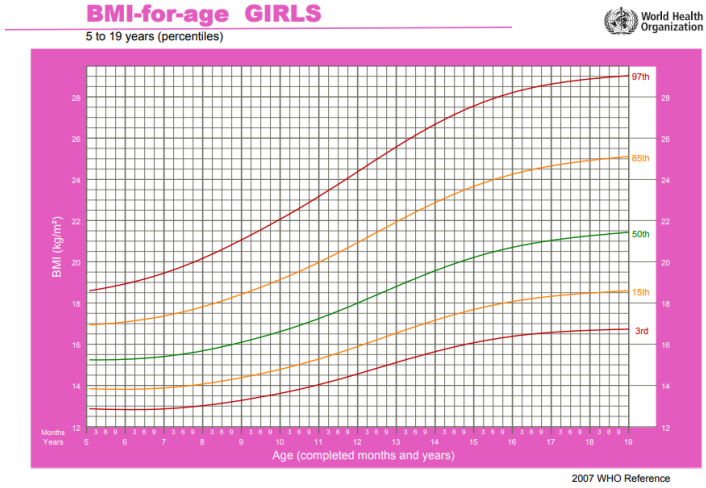

Figure 2: Graph for interpretation of girls BMI values taken from WHO (2007)

Table 1. Demography of SISKY students with BMI values within first quartile "healthy" showing the numbers of students below Year 10 as well as in Years 10 and 11.

Number of students who are neither overweight, obese, underweight or at risk						
< Y10	N⁰ on roll < Y10	Y10	N⁰ on roll in Y10	Y11	N⁰ on roll in Y11	Total SISKY N⁰ on roll
29	56	9	12	11	16	84
29	61	5	7	10	12	80
41	64	5	8	5	8	80
47	73	10	11	2	3	87
64	101	5	6	4	5	112
60	85	16	18	5	7	110
75	119	3	4	16	18	141
86	138	8	9	N/A	0	147
93	142	9	10	N/A	0	152

Naturalistic intelligence was assessed using a pre-test post-test assessment tool based on that developed by Tirri and Nokelainen (2008). It was also assessed using a 64 item Multiple Intelligence Diagnostic Assessment Scale (MIDAS) questionnaire. Both the naturalistic intelligence tool and the MIDAS tool were trialed on a control group to determine the repeatability of these instruments.

The academic progress of the students from the 2013-2014 cohort of the EEREE course was also tracked to their performance in subsequent internationally standardized examinations that are certified by the Cambridge International Examination (CIE) board. The performance of this cohort is compared to previous the performances of previous examination cohorts at SISKY.

Results

1. Health related

The results of the BMI calculations for all students at SISKY from 2008 until 2017 are summarized in Table 1.

There is a clear trend in the BMI data that older students in Y10 and Y11 have historically (since 2008) tended to have healthier BMI values than younger students at SISKY. There is no significant change to this pattern in the years 2013-2014 onwards.

The demography of the school changes during the timescale of this data, partly due to growth in numbers on roll of younger students. However it was also due to a number of older students leaving the school before completing Y11, to complete secondary education at other institutions.

Prior to 2013-2014 in the years 2008 to 2013 the percentage of Y10 who were within the first quartile of the BMI was 77%. Following the introduction of the EEREE course in 2013-2014 the percentage of Y10 in the years 2014 – 2017 within the first quartile of BMI scores is 88%. This indicates a small rise in health in Year 10 compared to former years, as measured by BMI.

The Y11 cohort in 2014 -2015 were the first students to have completed the EEREE and maintained their percentage of 89% being within the first quartile of BMI values. The percentage of Y11 prior to 2015-2016 in Year 11 in this healthy range of BMI is only 73%. Therefore, these data indicate that not only did Year 10 EEREE students have become more "healthy" they also maintained these healthy BMI values for the year following the EEREE course. A possible, and lasting,

relationship between studying EEREE and physical health, however does not prove a causal relationship, but a pattern can be seen.

To summarise this data Table 2 contains a comparative tally of all senior students at SISKY before and after the introduction of the EEREE course to Year 10 students in 2013-14. This data generates a Pearson-Chi Squared value of 4.064 with one degree of freedom and *p* 0.044 which demonstrates a statistically significant association at the 95% confidence limit, using Minitab Pearson Chi Squared test.

Table 2: The tallies of senior SISKY students healthy and unhealthy BMI values with expected values for Pearson-Chi Squared test in parentheses.

Academic Years since 2008/2009 to 2016/17	Combined number of students with healthy BMI in Y10 and Y11	Combined number of students with unhealthy BMI in Y10 and Y11	Total
Prior to EEREE course	71 (75.88)	24(19.12)	95
Post first EEREE course	52 (47.12)	7 (11.88)	59
Total	123	31	154

Table 3. Number of visits to medical room by students below Year 10 as well as students in Years 10 and 11

	2013 - 2014	2014 - 2015	2015 - 2016	2016 - 2017
total visits	1295	1293	1232	1042
Nº visits by <Y10	1090	1180	1171	988
Nº visits by Y10	122	44	61	54
Nº visits by Y11	83	69	0	0
% visits by < Y10	84.2	91.3	95.0	94.8
% visits by Y10	9.4	3.4	5.0	5.2
% visits by Y11	6.4	5.3	0.0	0.0
Total nº on roll	110	141	147	152
Nº on roll <Y10	85	119	138	142
Nº in Y10	18	4	9	10
Nº in Y11	7	18	0	0
% on roll < Y10	77.3	84.4	93.9	93.4
% on roll = Y10	16.4	2.8	6.1	6.6
% on roll = Y11	6.4	12.8	0.0	0.0

The records for visits to the medical room were tallied and then calculated as ratios of visits per year group. The data was only available from 2013-14 until 2016-17. It is summarized in Table 3. The data in Table 3 shows that the total number of visits to seek medical attention has decreased in recent years even though the number of students on roll has increased. It also shows that students below Year 10 tend to require more attention than more senior students. On closer study the data also shows that for the academic years, 2013-14, 2015-16 and 2016-17, Y10 (EEREE) students (*n*= 37) made relatively less visits to the medical room than the students who were younger than them. For these three years of the trial collectively Year 10 made up 9.7% of the school community and yet Y10 constituted only 6.6% of the visits to the medical room. This trend was also true and showed a further improvement for the 2014-15 Y11 (former SISKY (2013) EEREE) students (*n*=18) who represented 12.8% of the school population but were recorded as being 5.3% of the population seeking medical assistance. However, the Y11 students (*n*= 7) in013-14 had not studied the EEREE course. They represented 6.4% of the school population and also made 6.4% of the visits to the medical room.

Multiple Intelligence assessments

The mean average values for the naturalistic sensitivity and MIDAS test in Table 4 provide a baseline value against which the test groups can be measured. The results of the Wilcoxon Signed Rank (WSR) statistical analysis for non-parametric data are shown in Table 5

Table 4 Control group Pre-test Post-test data

		mean	sd
EnvS	Pre-test	3.1	0.54
	Post-test	3.3	0.44
MIDAS	Pre-test	3.4	0.30
	Post-test	3.4	0.35

The WSR analysis of the environmental sensitivity and MIDAS assessment of the control group in Table 5 both give *P* values that are greater than 0.05 so it can be concluded that there are no significant differences between the pre-test and post-test scores in the control group. This demonstrates the repeatability of these assessment tools.

Having established the validity of the assessment tools the results of the pre-test post-test data from the test groups could now be collated from all students who have completed the EEREE course in the years since 2013.

In Table 6 it can be seen that there is a rise in the post-test results for both environmental sensitivity and MIDAS scores compared to the pre-test mean average values. To determine the statistical validity of these results WSR test was employed. The results of this are in Table 7.

The results of the WSR analysis in Table 7 show that the environmental sensitivity test showed a significant increase at the 95% confidence level as the *P* value generated by the WSR analysis is less than 0.05. The WSR analysis of the pooled MIDAS test results shows that the rise indicated are not statistically significant at the 95% confidence level. However, it must be remembered that this MIDAS score is the mean average score of the ratings for all eight intelligence dimensions. Therefore, a closer analysis of the changes of the naturalistic intelligence in the test groups at SISKY have been summarized in Table 8 and the results of the WSR analyses are presented in Table 9.

Table 5. Results of WSR statistical analyses of environmental sensitivity (EnvS) and MIDAS control group pre-test and post-test data from non EEREE students at SISKY (2013)

	number in group	number of differences	W value	P value	median of differences
EnvS	14	9	36	0.062	0.1500
MIDAS	14	12	36	0.608	0.0000

Table 6. Collated Pre-test and Post test Environmental sensitivity and MIDAS data from SISKY (2013-2016) (n=41)

	EnvS		MIDAS	
	Pre	Post	Pre	Post
mean	3.2	3.4	3.7	3.8
Sd	0.41	0.37	0.93	0.83

Table 7. Results of WSR statistical analyses of environmental sensitivity and MIDAS testing at SISKY (2013-2016) pre-test and post-test EEREE students (n=41)

	number in group	number of differences	W value	P value	median of differences
EnvS	41	36	511.5	0.003	0.1500
MIDAS	41	39	442.5	0.234	0.1250

Table 8 SISKY (2013 - 2016) Changes in Interpersonal, Intrapersonal and Naturalistic Intelligences pre-test post-test means and standard deviations

Multiple intelligence Dimension	Pre -test		Post-test	
	mean average	standard deviation	mean average	standard deviation
Naturalistic MI 8	2.9	1.55	3.8	1.41

Table 9 Results of WSR statistical analyses MI 6, MI7, and MI8 domains of MIDAS at SISKY (2013-2016) pre-test and post-test EEREE students (n=41)

Multiple Intelligence	number in group	number of differences	W value	P value	median of differences
MI 8	41	31	411	0.001	1.0000

MIDAS test consisted of eight items for each of the eight intelligences The EEREE course did not include any opportunities for students to develop musical intelligence, and few opportunities to exercise bodily-kinesthetic intelligence. So the inclusion of these in the analysis in Table 7 partly explains why the increase in MIDAS scores between 2013-16 is not significant.

The naturalistic dimension of MI in Table 8 shows a rise in the mean averages between the pre-test and post-test scores. Therefore the data in Table 8 has been analysed using WSR test to determine if the changes in Naturalistic Intelligence were statistically significant. The results of that analysis are in Table 9.

The data in Table 9 shows that *P* values of less than 0.05 that were generated for naturalistic (MI 8) intelligence does show a significant difference, at the 95% confidence level, between the pre-test and post-test scores for the aggregated students following the EEREE course at SISKY between 2013 and 2016.

The statistically tested assessments showed no improvement in the control group pre-test post-test scores. But there were improvements in both the MI 8 score of the MIDAS tests and using the environmental sensitivity questionnaire. The use of these two separate instruments provides sound evidence that students who followed the EEREE course increased their naturalistic intelligence whereas students in the control group did not.

Trends in IGCSE examinations at SISKY

Table 10. SISKY yearly mean average standardized IGCSE scores in all subjects from 2011 – 2015

Year	Year number	Total number of examination entries	Mean Percentage score for all subjects	Mean Percentage score for sciences
2011	1	73	67.0	56.4
2012	2	58	72.6	65.1
2013	3	27	63.1	41.5
2014	4	42	59.5	58.2
2015	5	139	61.6	63.0

An additional source of evidence to demonstrate measurable changes in intelligence, knowledge and problem solving is the analysis of results from examinations. At SISKY the students complete IGCSE tests from CIE.

The data in Table 10 shows that the sciences consistently scored a lower percentage on average, compared the average score of all subjects combined for

each of the four years prior to the former 2013-14 EEREE students taking their IGCSE exams in June 2015. This trend is verified in two ways.

Firstly, the students in each Year 9 cohort had completed Cognitive Ability Test (CAT) assessments that were used as a predictor for their future performance in IGCSEs examinations that followed two years later. The IGCSEs are reported by CIE both as standardized percentage scores and grades G –A*. The lowest grade, G, given a score of 1 point and an A* is worth 8 points. Table 11 shows that there has been a general upward trend in the value added from the CAT prediction to the actual IGCSE grades obtained in the period 2011 – 2015. The numbers of students sitting examinations in Year 11 has varied substantially and this may have caused a bump in the trend in 2013. The students who participated in the 2013 EEREE course took their IGCSE examinations in 2015 and out-performed any previous cohort by significantly exceeding their expected outcomes showing noticeable value added. Secondly, the trend in underperformance in the sciences goes back even further historically. In the years prior to 2011 the CIE results of IGSCE examinations were not accessible as percentage marks but as grades within set boundaries. Also CAT data from that period was not available from SISKY, so it was not possible to assess value added during the years before 2010. However, in a comparison by the residual analysis of the SISKY IGCSE results in the period 2004 to 2010 do show that the combined science results were consistently below the averaged results of other subjects[3].

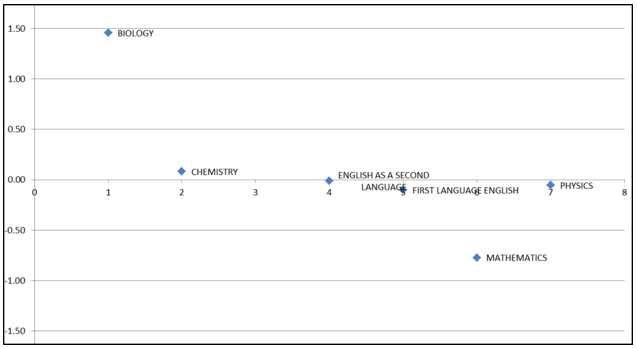

Figure 3. SISKY 2015 core subject IGCSE residual scores.

Residual Value (Y axis) versus Subject Residentials

The results for the science can consistently be seen to be noticeably lower than most if not all other subjects. These residuals for each subject are calculated by subtracting the mean of all IGCSE results for a cohort of students from the mean grade of the results for the same cohort of students in that given subject. It is a simple but useful technique to compare a group of students' performances in different subject relative to other subjects. The IGSCE residual results for the core subjects taken in at SISKY in 2015 from the students who followed the 2013 EEREE course are shown in Figure 3. It is clear that although Physics results are still marginally below average, the overall science residuals are considerably improved on the former years. They also show significantly higher positive values for Biology, which again links to the rise in MI 8 shown in table 8. The significantly higher value for Biology will have made a significant contribution towards the average percentage scores in table 5 and towards the value added scores given in table 6.

Table 11. SISKY Value added for IGCSEs

Year	Number of Y11 candidates	value added factor
2011	8	0.90
2012	6	0.95
2013	3	1.19
2014	4	1.06
2015	18	1.24

Discussion

Collectively the two sources of medical data, BMI records and a log of students seeking medical attention, show that there is a slight and lasting improvement in general health and wellbeing of more senior students at SISKY. Based on these criteria there has been a greater improvement in recent years that happened since the inclusion of EEREE into the curriculum for those senior students.

There is a strong link to show that improvements were observed in naturalistic intelligence. These increases were shown to be statistically significant when assessed using two different assessment tools. The inclusion of many evaluation exercises throughout the EEREE course ensured students exercised and developed higher order thinking skills. The benefit to their academic achievements was determined through the comparison of IGCSE results from former years with those of EEREE students, the value added to IGCSE data relative to CAT score predictors and the residual values when Science subjects were compared to other subjects.

Collectively this is an indicator that students at SISKY, since the introduction of the EEREE course, were indeed living healthier and becoming more successful academically. As education and health are both integral for sustainability it may be argued therefore that students ate SISKY who studied EEREE were able to follow more sustainable lifestyles compared to students in the same classes in former years.

Recommendations for further research

The benefits to health from studying EEREE require greater verification. Both in terms of a longitudinal study and through the use of a wider number of indicators such as blood pressure, blood cholesterol levels and heart rate recovery times. There also is a need to determine whether the students were consciously aware of having an increase in self-confidence or self-esteem. Other activities such as participation in public speaking events, analysis of diaries or records of participation in extracurricular activities from school social media records may prove useful sources of data for determining this.

As for the mechanism that caused the greater increase in naturalistic intelligence and subsequent examination grades it could be possible to analyse past examination papers and determine which skills the students had performed better than in former years or against the international examination cohort for that year as a whole.

[3] These data presented in graphs similar to Figure 3 from 2004 onwards are available upon request.

Finally a longer term study into the potential health benefits of learning bioethics would also be of great value. This longer term study could be achieved through follow-up of students form previous years and from other comparable studies around the world in other institutions.

Implications

From this small case study it does suggest that there are measurable benefits to physical health and academic achievement. The EEREE course sits well within secondary PSHE curriculum and this could be an option for other schools to include into their programmes of study. If further research does verify that there are lasting impacts on health and wellbeing then an economic argument for the inclusion of EEREE would also be possible.

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Stem Cell Tourism: Addressing the Challenge of Regulatory Cosmopolitanism

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Abstract

Stem cell tourism is a serious worldwide problem. This is where acute patients, especially the very ill, who live in countries where stem-cell-based medical treatments are not available, travel to other countries to seek such therapies. There have been reports of baseless claims of cures, charlatans and adverse medical events including deaths. These treatments are at the experimental stage, and most are unregulated. Some of the clinics offering these therapies are even supported by their local government, regulatory agencies and medical associations. Stem cell tourism is vital to the economies of some developing countries, which may thus be resistant to prohibitions by law.

This article evaluates measures, legal as well as non-legal, to control and mitigate it. Different countries have different notions of right and wrong, and state sovereignty dictates that no state can enforce its laws on another. In the international community, a nation cannot enforce its laws on other nations. It is a challenge if a regulatory approach of a country attempts to dictate local standards to another state, that is, where it seeks to steamroller over local culture and difference. Stem cell tourism is a prudential calculation for the individual and, importantly, the state has a moral obligation to inform its citizens of the potential risks of receiving experimental and unregulated stem cell-based treatment in overseas. Also, the ISSCR guidelines could raise awareness effectively of these critical issues in the international community. While stem cell tourism is a challenging area and appears to be irresolvable, local regulators still need to set up an effective national regulatory framework for regulating untested stem cell therapies within the country.

Keywords: Ethics, law, stem cell tourism, guidelines

Introduction

Stem cell therapy is a treatment that uses stem cells to replace or repair a patient's cells or tissues that are damaged. There are patients, primarily the very ill and

desperate, who will seek out unproven stem cell-based medical procedures and are also prepared to travel overseas to obtain these so-called treatments (known as stem cell tourism). There have been reports of claims of miracle cures, charlatans and adverse medical events including deaths (Kiatpongsan and Sipp 2009). The challenge of regulatory cosmopolitanism is the problem of regulating untested stem cell-based medical treatments available in some countries, in both developed and developing countries.

Stem cell tourism is vital to the economies of some countries, especially the developing ones, which may be resistant to prohibitions by law. Also, different countries have differing notions of right and wrong, and state sovereignty dictates that no state can enforce its laws on another. It is a challenge if a regulatory approach of a nation attempts to dictate local standards to another country, that is, where 'it seeks to steamroller over local culture and difference' (Brownsword 2008).

In this article, I will explore the various ways, legal as well as non-legal, to address the problem. The first part of the paper draws on the work of Professor Roger Brownsword (from Kings College London), a bioethicist and a leading scholar on issues of technology, ethics and law. He recognises the need for the exploration of the social, legal, ethical and regulatory matters arising from the emergence of modern technologies and he has written extensively on these challenges.[4] This is followed by an evaluation of the updated Guidelines for the Clinical Translation of Stem Cells (ISSCR Guidelines). The last part of the article explores the non-legal ways to address this severe problem of stem cell tourism.

Experimental and not established stem cell treatments

Many medical discoveries are based on years, even decades (Main 2014), of research conducted by research institutes, universities and private companies (ISSCR patient handbook 2008). It requires a tedious, expensive and lengthy process that progresses from basic research to clinical research and then phase 1,2 and 3 trials. Like the development of a new drug, stem cell therapies must be evaluated and fulfil stringent criteria before receiving the approval from the regulatory bodies to be used to treat humans. An accepted medical treatment is peer-reviewed, its safety proven through large-scale clinical trials and is regulated by government regulatory bodies.

The clinical translation of cell therapy, especially stem-cell based interventions, is still in the embryonic stage (Kimmelman 2016). Presently, almost all stem cell therapies are experimental/ investigational and innovative. The current spectrum of diseases and conditions from which there are established treatments based on stem cells is minimal (Australian stem cell handbook 2015). Disorders of the blood and immune system and loss of bone marrow function could be treated with blood stem cell transplantation. While stem cell research holds the promise for the treatment of a broad range of illnesses, there is still much work necessary to translate this research into safe and effective therapies. In the early stages, these treatments may not be effective and worse; they may even cause adverse effects. Accordingly, it is critical for patients, and their caregivers to know what to look out for and consider before making a firm decision whether to opt for a stem cell therapy.

Not only many stem cell-based treatments are experimental, but they are also not stringently regulated. With regulatory loophole and weak law enforcement, the pressing concern is that stem cell treatments are currently being advertised and sold around the world before they have been proven safe and effective. Stem cell clinics are a global phenomenon and patients went to hospitals in China, with Mexico, Germany, the Dominican Republic, and India the next most common destinations (Stem Cell Therapies 2014). Some patients are prepared to travel overseas and pay a high price to seek these medical treatments. Private clinics/ companies offering these services advertise the procedures on websites, YouTube and blogs. Some of these clinics are even supported by their government, regulatory bodies and medical associations and thus remain in business (Kiatpongsan and Sipp 2009).

There was a research conducted by Timothy Caulfield (University of Alberta, Canada) where he and his team analysed websites advertising so-called stem cell therapies (Lau 2008). The study noted that these direct advertisements made to patients on a plethora of sites were easily and readily accessible. It found that stem-cell-based treatments were offered by privately operated clinics around the world including China, Turkey and Ukraine. The average expenses amounted to US$21,500 excluding travel and accommodation for patients and their carers. The authors assessed whether the claims made on the websites were substantiated by reports published in the medical literature and found that most of these clinics overpromised results and underestimated the potential risks of the medical treatments they offered. A follow-up study found that the marketing practices remain unchanged (Ogbogu 2013).

The common conditions being treated include paralysis, multiple sclerosis, cerebral palsy, visual disorders/ blindness, and brain injuries (Stem Cell Therapies 2014). As there are no registries in which data are compiled, it is not possible to ascertain the number of patients who are receiving stem cell therapies, and it is also a challenge to determine the home countries of these patients. Moreover, there are clinics that offer treatments for an extensive array of illnesses and conditions (Lee 2012).

These stem cell clinics are providing these medical treatments in nations by exploiting their regulatory loopholes. The various types of harm that resulted to patients subsequent to receiving the treatments included brain tumour growth (Amariglio 2009), autoimmune disease (Bohgaki 2008), meningitis (Mendpara 2002)

[4] Professor Roger Brownsword is a founding member of the Centre for Technology, Ethics, Law and Society (TELOS) at the Dickson Poon School which aims to engage in policy-relevant research examining the ethical, social and legal implications of innovative technologies. The interview was held on 18 November 2009 in his office in the law faculty, Kings College London. Brownsword has been associated with the UK's House of Commons Science and Technology Committee. This committee's role is to ensure that the UK Government policy and decision-making are based on good scientific and engineering advice and evidence.

and deaths (Coghan 2010, Tenenbaum 2014). A patient had bone fragments growing in her right eye after a cosmetic stem cell treatment in Beverly Hills three months earlier (Jabr 2012). Moreover, there is economic harm with a therapy costing between US$20,000 and US$50,000, which excludes travel (National Academies 2014). As regards the lack of efficacy, a patient suffering from urinary incontinence sued the hospital administrator as the treatment did not improve his symptoms (Abbott 2008).

Patients are motivated to seek treatments at these clinics since they believe they have no choice (Stem Cell Therapies 2014). For acute patients, they cannot afford to wait for stem cell treatments to be formally authorised through the slow conventional processes. They feel desperate, frustrated and victimised by the system. Whereas clinics abroad connect with the patients by providing some hope and offer the patients some control over their lives so they can choose the medical treatments they desperately need. Patients leapfrog their doctors and go directly to the therapy.

As Alta Charo said, 'Patients are potentially being exposed to treatments that are not proven, not approved, not regulated and possibly dangerous' (Stem Cell Therapies 2014). This issue is becoming even more problematic as untested stem cell therapies are becoming more commonplace in this globalised and connected flat world with speedy internet access and easy travel. The provision of such so-called 'therapy' is scientifically and clinically unacceptable as well as unethical. The harms caused to patients have eroded public confidence and undermined the legitimacy of the stem cell field. In the next sections, I will consider the various possible ways to address the problem of stem cell tourism. I will begin by exploring Professor Roger Brownsword's insights on the challenge of regulatory cosmopolitanism.

Addressing stem cell tourism: Brownsword's regulatory cosmopolitanism

The problem of regulatory cosmopolitanism is that regulation confined within national boundaries cannot be entirely effective in controlling stem cell tourism. Stem cell tourism is a complicated issue, but there are ways, legal and non-legal, to manage and mitigate it.

Professor Roger Brownsword introduces the concept of regulatory prudence. He stresses that one of the concerns with new technologies is whether they are safe. While he concedes there are risks associated with new technologies, the risks are borne only by the person(s) who elects to use the technology. He, therefore, argues that regulators prudently ought to leave that decision to the individual concerned. He gives the example of the various screenings currently available, "If you submit to screening, it can be risky particularly if there are matters you'd rather not know. So long as the risk is only to you and the benefit is only to you, it seems to be only a matter of personal prudential judgment; so regulators need to hand it back to the individual. But where there are risks to the third party, the regulators need to set a regulatory framework". He argues that with stem cell tourism, regulators need to leave the decision to the individual patient. He explains, "what can we do other than alert people to the risk of taking this stand? Unless we can actually stop people at the airport- something that we would not do. We rely on there being local control in places where these experimental treatments are being offered ... that local control is only going to be put in place where there is some external pressure, some overarching control. The stem cell community can exert some external pressure. They could try to isolate those countries which are not properly regulated. In the end, people need to be informed with the question: "should I take the risk with this?"

Brownsword stresses the importance of the moral obligation of the state to inform its patients of the risks associated with the stem–cell-based treatments. He explains, "it's a judgment of what I prefer to do to myself: the calculation of risk and benefit. Regulators should hand the decision back to the individual provided these individuals are properly informed ... in the end, people need to be properly informed. In the individualised prudential calculation, for desperate people, it's a matter of life and death. They are going to use up part of their savings; they are going to die, so there's no good to the money. This is provided they are informed of the risks".

Whether ill patients at the airport can be prevented from departing the country, Brownsword opines that it is not practical in stopping people from leaving the country. Similarly, with suing/ prosecuting the overseas doctor who administers the medical treatment, he says there are also practical difficulties in pursuing that course of action. Besides these challenges, resorting to the traditional law such as tort law and consumer law is reactive, and there are also evidentiary issues.

About the possibility of prosecution of a person who returns home after receiving medical treatment that is not legal in his/her country, Brownsword explains that the current UK prosecution guidelines do not favour the prosecution of terminally ill patients. He adds that even if there is a prosecution, there will be sympathy from the jurors. He continues, "Where regulators are making a prudential calculation, there is prudential pluralism ... different people have very different ideas about the balance of benefits and risks. Regulators sometimes have to make a collective decision".

Brownsword is of the view that it is a challenge to regulate stem cell tourism and it is ultimately a prudential calculation for the individual patient. The next section will critically analyse the comprehensive and aspirational ISSCR guidelines to determine whether it could resolve some if not all of the issues surrounding stem cell tourism.

Addressing stem cell tourism: the Guidelines for the Clinical Translation of Stem Cells 2016 (ISSCR Guidelines)

Recognising the risks to health and welfare posed by stem cell tourism, the scientific community and advocacy groups have begun to respond to the problem by formulating guidelines for doctors and scientists engaged in the clinical translation of stem cell research. The International Society for Stem Cells Research (ISSCR) developed the *Guidelines for the Clinical Translation of Stem Cells* (*ISSCR Guidelines*) in 2008, updated in 2016. The ISSCR is an independent, non-profit organisation established in 2002 to foster the exchange of information on stem cell research. It is the

world's largest international professional organisation engaged with stem cell science.

The 2016 ISSCR guidelines were prepared by the ISSCR Guidelines Updates Task Force, a multidisciplinary group of 25 scientists, ethicists and regulatory officials from nine countries. It is noted that most of these nations are developed countries. Before the guidelines were finalised and published, there was feedback received on the drafts from more than 100 individuals and organisations including regulators, funding bodies, journal editors, patient advocates, researchers and member of the public.

The ISSCR's objective is to provide guidance on the proper and responsible translation of stem cell research into safe and appropriate applications. The guidelines build on a set of widely shared ethical principles in science, research with human subjects, and medicine such as the Nuremberg Code, 1949, Department of Health, and Education and Welfare, 1979, European Science Foundation, 2000, Medical Professionalism Project, 2002, Institute of Medicine, 2009 and the World Medical Association, 2013.

By way of recommendations to institutions, review committees and investigators, best practice standards to be observed in preclinical translational applications of stem cell technology are established. These ISSCR Guidelines provide comprehensive guidance for the future development of responsible stem cell therapies from research to clinic. In the following sections, the various recommendations in the guidelines that deal with the problem of stem cell tourism are explored.

Addressing stem cell tourism: Fundamental ethical principles of ISSCR guidelines

Core ethical tenets of the ISSCR guidelines, found in section 1, include primacy of patient welfare, respect for research subjects and transparency. The guidelines promote an efficient and sustainable research enterprise for stem cell research and medical interventions that will enhance human health. The main objective of biomedical research and its clinical translation is to prevent, reduce or even eliminate the human suffering caused by injury and sickness. Accordingly, it is essential that patients participate in clinical research trusting that the studies are justified and risks are reasonable in relation to the benefits. Also, doctors can be sure that the evidence they rely on to make vital decisions is concrete and rigorous.

Doctors, and doctor-researchers, owe a duty of care to the patient/ research subject, and they must not place their patients at risk. Application of stem cell-based interventions should be evidence-based and subject to independent expert review. Promising novel methods should be assessed early and before use to larger populations. To advertise and offer stem cell-based interventions to a large patient population prior to receiving rigorous and independent expert review of safety and efficacy tantamounts to breach of professional ethics. Also, patients/ research participants should provide informed consent to researchers, clinicians, and clinics. Accurate and comprehensive information about the risks and the state of evidence for stem cell-based interventions should be submitted to the subjects before treatment is offered to them. Moreover, researchers should promote open and timely sharing of ideas, methods, data, and materials on the latest scientific state of the art including uncertainties about the safety, reliability or efficacy of the potential applications. There should be prompt communication with the groups including the patient communities.

Addressing stem cell tourism in ISSCR guidelines: Well designed clinical trials

Like testing new drugs and innovative clinical devices, clinical trials/ interventional studies/ clinical research interventions are crucial in translating cell-based treatments. A clinical trial is a type of research study using human subjects to assess biomedical or health-related outcomes. The clinical trials process is particularly relevant for the development of stem-cell therapies. This rigorous process will determine its efficacy and safety/ lack of serious side-effects.

The private clinics providing unproven stem cell treatments leapfrog this vital stage of conducting clinical trials. The ISSCR condemns the administration of unproven stem cell based-interventions outside of the context of clinical research or medical innovation (for the discussion of medical innovation, see next section). Given the importance of clinical trials, the ISSCR guidelines recommend standards as discussed below.

Well designed clinical trials of stem cell-based intervention will safeguard the welfare of the patients/ research subjects, show respect to them and ensure transparency. Properly and adequately developed trials will incorporate essential matters like the provision of consent including informed consent, adverse event reporting and monitoring of the patient. Members of the research community have the moral responsibility for promoting the ethical conduct of clinical trials including sponsors, investigators, host institutions, oversight bodies, and regulators.

Essential requirements in these clinical trials include having adequate pre-clinical data, informed consent, independent oversight, peer review, research subject monitoring, auditing of study, and trial registration and reporting. Clinical trials of stem cell-based interventions should follow universally recognised principles on ethical conduct of clinical research and the safeguard of research subjects (World Medical Association, 1964, Department of Health, and Education and Welfare, 1979; European Parliament and Council of the European Union, 2001). These steps are examined below, starting with measures that will safeguard the patient's welfare and also show respect to the patient in a clinical trial setting.

First, there must be an identification of risks and benefits. With reference to recommendation 3.3.2.2, 'risks should be identified and minimised, unknown risks acknowledged, and potential benefits to subjects/ and society estimated. Studies must anticipate a favourable balance of risks and benefits.' The potential benefits to the research subjects must be realistically delineated and not overemphasised. Studies should be done to ensure there is maximum data on the safety of the approach being tested. A well-designed clinical trial includes measures that reduce risks and recruit the smallest number of research subjects. The eligibility criteria should consider comorbidities that may increase the risk or change the risk/benefit ratio.

Next, rigorous informed consent must be provided by the patient/ research subject participating in the clinical trial. This is an essential and established aspect of the ethical conduct of clinical research. Its goal is to protect the patients as this process ensures they make an informed decision to participate, entirely out of their free will and they are not pressured to participate in the clinical trial. Recommendation 3.3.2.6 provides that informed consent should be given by the research subjects or by their legally authorised representatives. During the informed consent process, the subjects should be informed that their participation in the trial is entirely voluntary. They should be provided with a written document (reviewed and approved by the review board) containing all vital information, e.g. the risks and potential benefits of the study, in clear and easy to understand language about the study. Moreover, it should be emphasised to the subjects that their participation is not needed for their continued clinical care, and also their non-participation will not affect their ongoing clinical care. These steps will ensure that the subjects are not under duress and their consent to be involved in the clinical trial, based on full information communicated to them, is genuine.

The ability to provide consent by the patient/ research subject should be assessed carefully. Very sick/ acute patients' judgments could be impaired and thus there is diminished capacity. Also, there are young patients (below 18). Just because these people who lack such ability to provide consent are vulnerable does not mean they should not be excluded from potential biomedical advances involving stem cells. According to recommendation 3.3.2.7, before obtaining permission from subjects who have diseases or conditions that could affect their cognition, their capacity to give permission should be evaluated. Appropriate steps should be taken to get the consent from their guardians or surrogates to make judgments on the patient's behalf.

Recommendation 3.3.2.6 provides that re-consent of the research subjects is necessary if there are significant changes in risks or benefits of a study intervention and if alternative therapies arise over the course of the research. Furthermore, the subjects should be allowed to change their minds and withdraw their consent to participate in clinical trials without penalty.

It is essential to conduct follow-up and trial monitoring of the patient/ research subject of the clinical trial. Recommendation 3.3.5.1 of the guidelines provides that 'an independent data-monitoring plan is required for clinical studies. When deemed appropriate, aggregate updates should be provided at predetermined times or on demand. Such updates should include adverse event reporting and ongoing statistical analyses if appropriate. Data monitoring personnel and committees should be independent of the research team.' Recommendation 3.3.5.2 of the guidelines provides for long-term follow-up of the patient/ research subject.

Stem cell-based intervention clinical trials are characterised by dynamic developing science and uncertainties. Thus, it is essential that the patients/ research subjects are observed throughout the stem cell-based clinical trials. Over the course of clinical research, the risk/ benefit balance may change. Long-term follow-up of the subject serves an essential purpose. It enables the researcher to observe the emergence of late adverse events. If the patient/ research subject wishes to withdraw from the research, this should be conducted in an appropriate manner to promote his/ her physical and psychological welfare. As performing long-term monitoring may be challenging, it is vital for researchers to maintain contact with the research subjects. They could adopt mechanisms that facilitate long-term follow-up.

Adverse event reporting of the patient/ research subject is essential. As discussed earlier, there are patients who have reported suffering from adverse medical effects after receiving the untested stem cell based-treatments, some severe (e.g. deaths or life-threatening conditions), others less (e.g. side effects). According to recommendation 3.3.7.2 of the guidelines, adverse events should be reported. The report should include the severity of the event and the causal connection with the experimental stem cell intervention**.** Adverse events associated with cells, procedures, and all other aspects of the intervention should be reported. Moreover, the absence of severe or fatal adverse events should be stated in the report. Understanding the safety profile of these interventions is critical for effective translation. Timely evaluation of safety information can minimise the uncertainties surrounding stem cell-based interventions.

A well-designed clinical trial promotes transparency. As provided in recommendation 3.3.7.3, researchers should promptly publish results of their research. This is irrespective of whether the results are positive, negative or inconclusive. Studies should be released in full, timely, accurate and should follow the international reporting guidelines. To ensure the development of clinically effective stem cell-based treatments, publication of findings is encouraged. Not only this will promote transparency in the clinical translation of stem cell-based therapies, but it will also prevent patients in later clinical trials from being subjected to unnecessary risk. And this will acknowledge the research subjects' contribution to the research. However, it is rare to see publications of negative or inconclusive findings of the study.

Provided there are sufficient privacy protections for the research subjects; researchers should explore different ways to disseminate their research data. The research project can be written according to internationally recognised reporting guidelines. Editors of journals also should include publications of inconclusive and disconfirmatory findings.

Registration of the clinical trials in databases provides openness and transparency regarding stem cell-based interventions. Recommendation 3.3.7.1 provides that clinical trials should be registered in public databases. In this way, patients, regulators and the scientific community can monitor their efforts, reduce risks and maximise benefits of clinical trials. Also, registration in databases enables access to clinical trials for patients who might not otherwise know of them.

As mentioned, some patients spent vast amounts of money on receiving the so-called untested stem cell therapies. In clinical trials, often the question raised is whether the patients/ research subjects should pay for the trials at all. This may pose ethical challenges for

ensuring scientific merit, integrity, and fairness. The patient sponsors may not have the skills to differentiate between meritorious protocols and dubious ones. They may insist on trial designs that eliminate essential features like eligibility criteria and randomisation to a comparator arm which are necessary for promoting scientific validity and patient welfare. Recommendation 3.3.2.9 provides for patient funding for clinical trials and direct payments by patients to participate in clinical trials. Those issues could be managed by requiring that the protocols are subject to independent expert review for scientific rationale and design. Such oversight will ensure the responsible conduct of analysis and reporting.

The last feature of a well designed clinical trial involving stem cells is the use of placebo or sham comparator in the later stage of the trial. According to recommendation 3.3.4.2, 'where there are no proven effective treatments for a medical condition, and stem cell-based interventions involve invasive delivery, it may be appropriate to test them against placebo or sham comparators, assuming early experience has demonstrated feasibility and safety of the intervention'. If initial phase trial demonstrates safety and efficacy, there may be justifications to adopt a placebo or sham arm in later stage trials. Thorough assessments of stem cell-based interventions may involve randomised trials (by chance) where sham procedures are used as comparators.

These procedures may be cumbersome for patients/ research subjects who will not derive a direct benefit. The adoption of sham comparators should be necessary for the study. It is vital that researchers explain the use of placebos/ sham procedures to the patients with clarity so that they are aware and agree that there may be no anticipated clinical benefits. To reduce the subject's burdens, researchers should choose the least invasive option and the choice of arms type should be justified.

The discussion above indicates the various recommendations in the ISSCR guidelines that propose well-designed, elaborate and stringent clinical trials involving stem cells could address the ethical issues that arise from unproven stem cell treatments. Thus, the conduct of a well designed clinical trial is a crucial step in translating cell-based therapies but this vital stage is bypassed by doctors offering untested stem cell therapies to the public. Members of the medical and research community have an ethical responsibility for promoting the ethical conduct of clinical trials. Properly conducted clinical trials of stem cell-based intervention will ensure the welfare of the patients, provide respect to them and encourage transparency as well as accountability. The next section explores stem cell medical innovations.

Addressing stem cell tourism in ISSCR guidelines: Medical innovations

In the absence of clinical trials, medical innovations have been introduced into clinical practice such as surgical techniques. Thus there should be attempts to add legitimate stem cell-based medical innovations. As provided in recommendation 3.4.1, 'clinician-scientists may provide unproven stem cell-based interventions to at most a very small number of patients outside the context of a formal clinical trial and according to the highly restrictive provisions outlined in this section.'

Compared to clinical research, medical innovations have disparate objectives. The goal of clinical research is to create generalised knowledge about new drugs or innovative approaches to surgery or cellular treatments, not the individual patient's benefit (Lindvall 2014). In contrast, a medical innovation is aimed at providing benefits/ improvements to the particular patient's medical condition, and it is not research per se. As a professional imperative, medical innovation will later progress to a more formal clinical trial so that these innovations can benefit society.

Unfortunately not every medical innovation leads to major advancements in clinical care; some have been less effective or even risky to the patient (ISSCR guidelines 2016). Stem cell-based products involve complicated manufacturing procedures require considerable expertise to exploit for clinical benefit. Only in limited circumstances, it could be justified to embark on medically innovative stem cell-based interventions, i.e. in cases where there is a small number of patients, and these patients are seriously ill. Also, there is a distinction between commercial purveyance of unproven stem cell treatments and legitimate attempts at medical innovation.

Stem cell-based medical innovations have to be sensitive to the uniqueness and complexities of stem cell science. Compared to new drugs or innovative surgery techniques, stem cells may behave in much more unpredictable ways due to its novelty. Thus, a medical innovation should be subject to stringent oversight to protect the patients. The provider of the medical innovation should be subject to rigorous independent expert review. Moreover, he/ she should not advertise, promote, recruit or commercialise this practice. The highly restrictive conditions in recommendation 3.4.1 include requirements of peer review approval, informed consent by the patient, an action plan for adverse events, insurance coverage or other forms of financial support to cover complications arising from the procedure and that the personnel have the appropriate skills/ qualifications.

The provisions also include writing a detailed plan which is must be approved by experts through a peer review process. The plan should provide a scientific rationale that justifies why this particular method has a fair chance of success, full characterisation of the kinds of cells being transplanted, description of how the cells will be administered and follow up. Adopting these highly restrictive provisions is critical to building public trust in the conduct of stem cell-based medical innovation.

It is important to reserve space for stem cell-based medical innovation. If conducted with strict oversight, stem cell medical innovation in synergy with the stem cell clinical trials process could be a formidable route for developing future therapeutic treatments.

Addressing stem cell tourism in ISSCR guidelines: Accurate and effective communication

It is easy for the general public to be confused over mixed messages. On the one hand, stem cells are often touted as the next medical breakthrough therapy, on the

other hand, patients are informed that these treatments may not work. Section 4 of the ISSCR Guidelines is about communications and description of the stem cell science. According to recommendation 4.1 of the ISSCR guidelines, 'the stem cell community should promote accurate, balanced, and responsive representations of stem cell research' (ISSCR guidelines 2016). In this increasingly connected world, the public portrayal of the stem cell field puts it in the spotlight in the media and social networks. The high profile of stem cell science is understandable given its clinical potential. The risks to the clinical application are sometimes downplayed whereas the potential benefits are exaggerated (Caulfield 2016). Public forums on stem cell-based medical treatments have been markedly positive, 'lending an air of legitimacy to stem cell therapy that hasn't been validated by research' (Lee 2012). Such hype, misrepresentations and overselling are exploited by for-profit clinics which aggressively promote stem cells for untested clinical uses. Inaccurate, incomplete and half-true claims could profoundly impact society.

Regular engagements with the general public are essential. The research community should be proactive through outreach work. As there is keen interest in the stem cell field, scientists could communicate their work through a number of ways including public talks and social media. Not only these public engagements provide understanding for their exemplary work among lay people/ non-specialists, but the scientists also receive public recognition and respect for their significant contributions to society and subsequent impact. However, it is possible that there could be confusions and distorted perceptions formed about the present state of the science of stem cells such as its potential for application, risks and various uncertainties (Kamenova and Caulfield, 2015).

Aspirational claims on uncertain imminent developments should be restrained. Even good intentioned researchers may prematurely publish their work, for instance, in the 1980s, women with breast cancer were receiving transplants before data demonstrated the lack of efficacy (Stem cell therapies 2014). These claims include forecasts on the clinical application, the likelihood of product approval, or speculation on the future economic impact of currently unrealised technologies. Researchers should be cautious about disclosing research findings that have not passed peer review as premature reporting can undermine public confidence if conclusions are later disproven. And they have a duty to make prompt corrections of errors, inaccuracies or misleading statements in their research.

Media departments exist at large establishments such as universities and scientists could consider working with communications experts at their institutions. They could produce materials that are readable and intelligible without oversimplifying, and do not understate risks and uncertainties. Similarly, research-sponsoring institutions and communications specialists, including editors and journalists, have a responsibility to ensure that the informational materials follow these principles. The scientists in charge of the findings must review the content before release. It may be necessary to seek feedback from independent experts.

Accordingly, scientists, clinicians, science communications professionals at academic and research institutions, and industry spokespersons have a duty to ensure that benefits, risks, and uncertainties of stem cell science are not misrepresented to the public. Adequate care should be practised for the entire communication process. These include the use of social networks, print media, broadcast media and the presentation of results.

Addressing stem cell tourism in ISSCR guidelines: Articulating standards development

Finally, a way to address stem cell tourism is through standards development in stem cell science. According to recommendation 5.1, 'researchers, industry and regulators should work towards developing and implementing standards on design, conduct, interpretation, and reporting of research in stem cell science and medicine'. For instance, to encourage uniform standards for consent and procurement of biomaterials, the ISSCR has created a template donor consent form found in appendix 2 of the guidelines.

Not only standards development will promote the clinical application of stem cells, but it will also promote collaborations among many actors including scientists, clinics, industry, regulators, and patients. There should be the development of standards for matters such as consent and procurement, manufacturing regulations, reference materials for calibrating instruments, minimally acceptable changes during cell culture, a method of delivery and selection of recipients for novel stem cell-based interventions, reporting of animal experiments, the design of trials and reporting of trials. Such efforts limit uncertainties and promote trust among patients.

Moreover, stem cell science is dynamic and rapidly evolving and the ISSCR guidelines 2016 is not intended to be the last word. Recommendation 5.2 provides that the ISSCR guidelines should be periodically reviewed and if necessary, amended, to accommodate scientific innovations, fresh ethical challenges, and evolving social priorities. Thus revisiting the guidelines is required where there are reflection, review, reinterpretation and possibly revision (Daley 2016).

This recommendation does not state how regular the review should be conducted. In some nations, for instance, in Australia, their laws on this area provide that the law review should be performed every 3-5 years. It is debatable whether this time frame is too long as the science is developing rapidly; ideally, there should be reviews earlier. It is noted, however, that conducting a revision of laws/ guidelines is an onerous and time-consuming task which involve many stakeholders.

Ethical problems in the conduct of stem cell research should be addressed promptly. With regular reviews and revisions, stem cell science can progress in a responsible and ethically acceptable manner. This could also increase the probability that the international scientific research community will be governed by a standard set of principles.

The discussions in these sections indicate that the various recommendations in the ISSCR guidelines that propose well-designed clinical trials, accurate communications and standards development could address the serious ethical issues that arise from

unproven stem cell treatments. Nations that are considering adopting a strict regulation to control the problem could follow these commendable recommendations in the guidelines based on bedrock principles.

Legal effect of ISSCR guidelines

While the ISSCR guidelines are exemplary, they are not legally binding. States have no obligation to follow them. These guidelines are merely a set of guidance and principles that direct the conduct of responsible and ethical stem cell research and clinical applications. No guidelines can be the last word (Daley 2016). As stem cell tourism is critical to the economies of some developing nations, their governments may even support or condone it. Likewise, countries which already have well-developed laws and policies may supercede the ISSCR guidelines. Also, societies have different concepts of right and wrong, and no state can enforce its laws on another.

There is scepticism expressed about the effectiveness of the ISSCR Guidelines. Wise Young is of the view that the guidelines would not stop clinics that are already in breach of ethics from giving misleading information (Baker 2008). He adds that the ISSCR guidelines are not likely to influence a patient's decision whether to travel overseas to receive the medical treatment at his/ her risk. I submit that I agree with his opinion and the guidelines are not going to filter all quacks easily and quickly and it is entirely up to the individual patient whether to pursue an untested stem cell therapy. As Jill Lepore said, 'there is a "kind of faith in science that draws" some people to any promise of a cure for disease, no matter how specious' (Stem cell tourism 2013).

Despite doubts expressed as regards the value of the ISSCR Guidelines, I argue that they are nevertheless significant. The guidelines set high global yardsticks and provide robust mechanisms for the conduct of stem cell research and its clinical application. (Daley 2016). Backed by evidence and sound reasoning, they are an essential preliminary step in raising the awareness about the various critical issues in the international community. Nations, institutions, and funders could promote a culture of compliance by incorporating the ISSCR guidelines into their policies (Kimmelman 2016).

While the ISSCR guidelines do not override domestic laws and regulations, they can inform the development and interpretation of local laws and they can guide research practices not covered by legislation (Kimmelman 2016). They set the norms concerning pre-clinical evidence and clinical trial design. Not only the guidelines facilitate a structured basis to resolve disputes, but they can also provide proof of professional standards to the courts of law (Campbell and Glass 2001). While the ISSCR guidelines are highly aspirational, they are intended to provide a benchmark for researchers in clinical trials in less regulated nations, and it is hoped that the guidelines will encourage governments to adopt appropriate regulations (Nelson 2008).

Arguably, guidelines to govern professional conduct may be more effective than the traditional law. The latter is reactive, post hoc and there are challenging evidentiary issues, and the burden of proof is on the plaintiff. Also, the law is 'confined to single jurisdictions, can be blunt regulatory instruments and change too slowly to keep pace with cutting-edge research' (Kimmelman 2016). Also, as in other highly politicised matters, there is a complexity of constant amendments in the laws on stem cells with each change in leadership, creating uncertainties. For instance, in the USA, President Bush was conservative and against embryonic stem cell research whereas President Obama was supportive of the research and had reversed Bush policy. And there are uncertainties with the current Trump administration as to their stance on this controversial area (Khazan 2017).

Recognising the seriousness of the challenge of stem cell tourism and with the professional support offered by ISSCR, it is strongly recommended that regulators in nations with less developed regimes for the regulation of research and clinical trials should, as a matter of urgency, establish effective national regulatory frameworks to oversee all stem cell research and stem cell-based clinical trials conducted within their borders. The ISSCR guidelines provide stem cell scientists with professional standards for the responsible conduct of research.

Addressing stem cell tourism through non-legal means

There are non-legal ways to address stem cell tourism. Brownsword suggests that external pressure, such as peer pressure, might be exerted on the nations that resist prohibitions, by 'isolating those countries'. He further argues that law may not be the answer in every situation. He explains, "On a day to day basis, the things we do are governed by signals for prudential reasons. For the most part, the law is in the background. It must be governed by local etiquette. In the same way, with consensus statements or guidelines, it could be part of the foreground understanding. I think the law is relatively unimportant. What makes the world go round isn't law, it's governed in a much looser sense. Money and peer pressure are two key drivers of how we behave. If we can't afford it, we don't do it. If I'm going to run into criticism by my immediate peers, then again I'm unlikely to do it. So if the consensus statement is incorporated into the workplace environment, then that'll have a real regulatory effect." As such, there are non-legal as well as legal measures that could be taken against these companies that offer such dubious medical treatments such as media reports of such procedures that could create awareness and flag down those unscrupulous companies.

Conclusion

Stem cell tourism is highly complex, challenging and not easily resolvable. With these unproven stem cell therapies, there are serious safety concerns and economic harm. Even if there is no adverse medical event, the treatment may not work. Some patients would rather continue trying until they are proven wrong rather than waiting till it is proven right. As Brownsword said, whether to pursue these therapies is ultimately a prudential calculation for the individual patients.

However, it is critical for nations to acknowledge and address this serious problem. Patients need accurate and

reliable information and they lack the context to understand. Given the present state of scientific knowledge about stem cells, patients should be advised against travel for untested stem cell-based treatments. They need guidance and with sufficient efforts, the comprehensive and highly aspirational ISSCR guidelines will first raise awareness of the critical issues surrounding unproven stem cell therapies in the international community. These guidelines should be widely disseminated to doctors, patient communities, institutions, review committees, regulators, and investigators all around the world. These groups are then urged to collectively inform, caution and better educate the broader community. They could also exercise their influence to discourage the patients from seeking the unproven stem cell therapies. Explicit and strong messages in lay language are necessary.

It is also vital for local regulators set up an appropriate and effective national regulatory framework within their country to regulate unproven stem cell treatments. And scientists should work together with the regulatory bodies to tighten regulation. A mechanism is needed to ensure that unproven stem cell therapies are not marketed to patients. The regulation, coupled with strict enforcement mechanisms, could be in the form of guidelines and or legislation and the exemplary ISSCR guidelines can be referred to as a model. An individual country attempting to address the regulatory challenges is less likely to be effective. The ISSCR and other stem cell professional organisations could proffer their expert assistance to government agencies. Such constructive engagements and collaborations could lead to useful harmonised global strategies and standards to tackle the problem.

This is a continuing dialogue. As Alta Charo said, 'people … need to be informed that stem cell therapies have great potential, that clinical trials are under way and that regenerative medicine bears tremendous promise for the future.' While these steps will not eliminate untested stem cell treatments, they will likely mitigate and control the problem. And there is much work ahead for professional organisations, patient advocates, doctors, researchers, clinicians, institutions and regulators.

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The Struggle unto Death

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Abstract

This article focuses on the legality of euthanasia and assisted suicide in the Netherlands. Euthanasia and assisted suicide are allowed in certain cases, but there is no consensus with respect to the extent of the situations in which physicians should not be prosecuted. I argue that the individual, and, more specifically, his/her suffering, should be the focal point, and that the present legislation falls short in this respect; no solution can as yet be offered to individuals whose suffering cannot be resolved through medical means and which cannot be subsumed under the terms the law specifies.

Keywords: euthanasia; assisted suicide; depression; existential suffering

Introduction

That the interests of the individual should in principle be guiding in medical practice is not seriously questioned by anyone.[5] The way in which psychiatrists and other physicians are to treat the individual and which options should be open to the individual, by contrast, continues to be an important topic of debate. Termination of life on request and assisted suicide are illegal on the basis of articles 293 and 294 of the Dutch Criminal Code, but physicians are not punished as long as they adhere to the following criteria, specified in the Termination of Life on Request and Assisted Suicide Act.

a. The physician must hold the conviction that the request by the patient was voluntary and well-considered;
b. The physician must hold the conviction that the patient's suffering was lasting and unbearable;
c. has informed the patient about the situation he was in and about his prospects;
d. The physician and the patient hold the conviction that there was no other reasonable solution for the situation he was in;
e. The physician has consulted at least one other, independent physician who has seen the patient and has given his written opinion on the requirements of due care, referred to in parts a – d; and
f. The physician has terminated a life or assisted in a suicide with due care.

Similar laws as those which apply in the Netherlands have been adopted in Belgium and Luxembourg. In both countries, just as in the Netherlands, doctors are exclusively allowed to euthanize; in addition, they have to adhere to strict criteria, which do not differ significantly from those that apply in the Netherlands. An important respect in which these three countries differ from others that allow euthanasia is that euthanasia on non-terminally ill patients is legal. With respect to assisted suicide, by contrast, there are important differences between Belgium and the Netherlands. The Belgian law does not provide criteria under which circumstances it would be allowed, from which it may be inferred that it is not allowed, but the issue has raised doubts and debate.[6]

A known proponent of a perspective in which the right of self-determination is not decisive is the Belgian philosopher Herman de Dijn, who states: "The euthanasia act displays a profound opposition in our society, a struggle between conceptions of man and ideas about ethics that cannot be resolved by having everyone act in accordance with his or her own ideas. According to its opponents, the euthanasia act conveys a dangerous message: that certain lives are no longer worthwhile."[7] This is not the proper place to extensively evaluate the arguments for the various positions. I will instead focus on the individual's confrontation with his suffering, in order to ascertain to what extent the current Dutch legislation meets the demand that this suffering should be terminated. What is said here may also be of interest for readers who do not live in the Netherlands, for the theme that is discussed here is not particular to a specific country.

An evaluation of the legislation

The Termination of Life on Request and Assisted Suicide Act, which is based on articles 293 and 294 of the Dutch Criminal Code and specifies under which

[5] I say 'in principle', for in some cases difficult choices must be made. For example, it has recently been debated whether the medication to treat Pompe disease, Fabry disease and Cystic fibrosis, which is relatively costly and used by very few patients, should continue to be paid collectively. Such issues will presumably increasingly be raised as medical progress is made.

[6] H. Nys, "A Discussion of the Legal Rules on Euthanasia in Belgium Briefly Compared with the Rules in Luxembourg and the Netherlands." In: D. Jones, C. Gastmans, C. Mackellar (eds.), *Euthanasia and Assisted Suicide*. Cambridge: Cambridge University Press: pp. 7-25, 10.

[7] This is a translation of the original Dutch text. The original text reads: "De euthanasiewet verraadt een diepe tegenstelling in onze maatschappij, een strijd tussen mensbeelden en opvattingen over ethiek die niet op te lossen is door ieder volgens zijn/haar idee te laten handelen. De euthanasiewet zendt volgens haar tegenstanders een gevaarlijke boodschap uit: dat bepaalde soorten levens niet langer de moeite waard zijn." H. de Dijn, "Euthanasie: een cultuurfilosofische analyse." In: A. Burms and H. de Dijn (eds.), *De sacraliteit van leven en dood voor een brede bio-ethiek*. Kalmthout: Pelckmans/Zoetermeer: Klement, 2011: pp. 71-87, 86.

conditions terminating the life of another person at that other person's express and earnest request or intentionally assisting in the suicide of another person or providing that person with the means thereto is not punishable, has recently been re-evaluated; the problems that individuals whose suffering cannot be medically treated or even diagnosed face was discussed at length. It is this suffering I wish to address here. The crucial criterion in the law is that there must be 'lasting and unbearable' suffering, to be determined by a physician; [8] the exemption itself only applies to physicians.[9] It should be noted that unbearableness is "[…] a highly subjective and difficultly objectifiable factor."[10] This given does not derogate from the fact that the assessment is still *medical*, which serves as a justification for the monopoly of doctors to act when the termination of life is concerned. This monopoly is, however, as I will argue, problematic in a number of cases.

'Unbearable suffering' may be interpreted broadly, covering both pain and (inter alia) "increasing dependence, an ever greater loss of dignity or the prospect of a gruesome death."[11] Yet the government does not go so far as to deem the *prospect* of suffering lasting and unbearable, inter alia as 'lasting' and 'unbearable' are indivisibly linked:[12] "The mere prospect of suffering, irrespective of whether this will result from pain, loss of dignity or fear of an undignified death, cannot, in light of the above, be characterized as lasting and unbearable suffering."[13] It becomes apparent from the evaluation that the fact that precisely that prospect is oftentimes the motive behind requests for euthanasia constitutes an important problem: "If one examines the reasons why people make a request to be euthanized, pain appears to be a factor in only a small number of requests. In actuality, what drives the request is almost always the loss of dignity that is to be expected."[14]

If this is correct, it is justified to say that the present legislation is not adequate to realize the desired goal. The problems will possibly increase with the impending population ageing. Research shows that a growing number of elderly people imagine themselves requesting euthanasia or having a suicide pill available.[15] The introduction of such a pill is, however, at least for the foreseeable future, a politically sensitive issue. In any event, world-weariness is not a recognized criterion to allow euthanasia or medical assistance in ending one's own life,[16] and neither is a 'finished life'.[17]

A reform in this respect is pleaded by, amongst others, those who support the Citizens' Initiative Finished Life ('Burgerinitiatief Voltooid Leven').[18] In the wake of this initiative, political party Democrats 66 has submitted the bill Dignified End of Life ('Waardig Levenseinde'), but this only pertains to people of 75 years or older. If the pill is only made available to the elderly – leaving the issue of what the precise age limit should be[19] –, no solution has been offered to young people who face the same problem. Their position remains outside the purview of the law. This subject matter particularly lends itself to a medical *ethical* reflection, since the questions to which the subject matter gives rise cannot be answered by the medical profession itself.

This became clear in a case in which a general practitioner was found guilty of having assisted the suicide of a patient because the main criteria for medically assisted suicide had not been met, namely, that there has to be (in accordance with was indicated above) 'lasting and unbearable' suffering; he was discharged, however, the act, while principally punishable, not meriting a punishment in this case. As the Dutch Supreme Court expresses it: "The integral care which is to be provided by a general practitioner to patients […] may result in him being assigned with the task to alleviate the suffering of a patient which is not or not predominantly caused by a somatic or mental condition, but which is the consequence of the lack of a life perspective. Given, however, that that physician then enters into a domain that lies beyond his professional competence, he may not, in his capacity of medical professional, form a judgment regarding the unbearableness, lastingness and untreatableness of that suffering."[20]

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[8] Termination of Life on Request and Assisted Suicide Act, art. 2; Parliamentary Documents: House of Representatives, 1993/1994: 23877, no. 1: pp. 4, 5. 'Lasting' is to be understood here in the sense that no prospect of improvement exists.

[9] Articles 293 and 294 of the Dutch Criminal Code.

[10] The original text reads: "[…] een in hoge mate subjectieve, en moeilijk te objectiveren factor." Parliamentary Documents: House of Representatives, 1993/1994: 23877, no. 1, p. 5.

[11] The original text reads: "'[…] toenemende afhankelijkheid, steeds verdere ontluistering of het vooruitzicht van een afschrikwekkende dood […]." Parliamentary Documents: House of Representatives, 1999/2000: 26691, no. 6, p. 70.

[12] Parliamentary Documents: House of Representatives, 1999/2000: 26691, no. 6, p. 60.

[13] The original text reads: "Het enkele vooruitzicht op lijden, ongeacht of dit zal voortvloeien uit pijn, ontluistering of angst voor een onwaardige dood, kan in het licht van het bovenstaande niet als uitzichtloos en ondraaglijk lijden worden aangemerkt […]." Parliamentary Documents: House of Representatives, 1999/2000: 26691, no. 6, p. 60.

[14] The original text reads: "Als je kijkt naar de redenen waarom mensen een euthanasieverzoek doen, is pijn maar een heel klein onderdeel van alle verzoeken. Eigenlijk gaat het bij het verzoek bijna altijd om de te verwachten ontluistering, het verlies van waardigheid." Parliamentary Documents: House of Representatives, 2013/2014: 31036, no. 8, p. 13.

[15] H. Buiting, D. Deeg, D. Knol, J. Ziegelmann, R. Pasman, G. Widdershoven and B. Onwuteaka-Philipsen, "Opvattingen van ouderen over levensbeëindiging." *Huisarts & wetenschap* 56 (3) (2013): pp. 102-105, 104.

[16] Parliamentary Documents: House of Representatives, 2007/2008: 31036, no. 3: pp. 4, 6.

[17] Parliamentary Documents: House of Representatives, 1999/2000: 26691, no. 6: pp. 30, 60.

[18] Parliamentary Documents: House of Representatives, 2013/2014: 31036, no. 8: p. 3.

[19] It is difficult to generalize, and for some people the prospect of having to live until the age of 75 may be dreadful while others may welcome the possibility to live (well) beyond that age.

[20] The original text reads: "De door een huisarts te verlenen integrale zorg aan patiënten […] kan meebrengen dat hij zich voor de taak gesteld ziet om het lijden van een patiënt te verlichten dat niet of niet in overwegende mate zijn oorzaak vindt in een somatische of psychische aandoening, maar het gevolg is van het ontbreken van levensperspectief. Omdat die arts zich dan evenwel begeeft op een terrein dat buiten zijn professionele competentie ligt, zal hij zich niet als medicus een

The question is, then, what, if any, recourse may be available to an individual who is confronted with suffering that cannot be qualified in medical terms, i.e., a case where neither depression nor a physical illness is diagnosed. In cases of 'existential suffering' the Supreme Court commands that a physician "consult others who may be helpful in finding a meaningful fulfillment of one's daily existence."[21] Who these 'others' might be is not elucidated and this may differ from one case to the next, so that a problem of referral will ensue (should a priest, rabbi or humanistic counselor – to mention just a few possibilities – be approached?). More importantly, no solution is provided for someone for whom, in spite of the availability of such possible alternative support, no meaningful fulfillment can be found.[22] This is not to be taken as criticism of the Supreme Court; the possibility to provide adequate support in such cases simply does not exist at the moment. Steven Pleiter, director of the End-of-life Clinic ('Levenseindekliniek'), expresses the problem as follows: "We, too, face patients who 'suffer from life' – that is what we call it – and who have become detached […]. We cannot aid these patients under the present standard, since it is based on the presence of medical suffering. At times, dire situations occur, in which elderly people gravely suffer from life. In my view a proper solution should be available in such cases. The present Euthanasia legislation does not offer such a solution."[23]

Towards a solution

What is the best way to approach this problem? It must, first of all, be acknowledged that removing lasting suffering in some cases is tantamount to ending the life of the individual, namely, in those cases where suffering from life itself is concerned: the suffering permeates life to such a degree that it is no longer acceptable. The only one who is able to determine this highly subjective given is the individual: it is no longer acceptable to him or her.

In order to accommodate people whose suffering is not covered by the Termination of Life on Request and Assisted Suicide Act it is necessary to change article 294, section 2, of the Dutch Penal Code. This article penalizes, as was pointed out above, assisted suicide; only physicians who observe the demands specified in the Termination of Life on Request and Assisted Suicide Act are exempted. In order to confront the problems while acknowledging that some cases do not concern medical issues, non-physicians should also be exempted from punishment.[24] Certain precautions should obviously be in place – crucially, it must be clear that there is a genuine death wish. With this in mind, one may argue that a physician still has a role to play: "If physicians' professional expertise enables them to deal with the existential questions arising in connection with VE [voluntary euthanasia] and PAS [physician-assisted suicide] based on suffering caused by illness or injury – as the conventional view presupposes that it does – it would be inconsistent to deny VE and PAS for persons in purely existential distress by claiming that physicians' professional expertise does not extend to existential questions."[25]

Young's solution, to have both a physician and a non-medical, professional counsellor assess individual cases, may, since he argues that if consulting the latter does not change the outlook of the person requesting assisted suicide this should be allowed,[26] be advisable. In any event, it must be borne in mind that assisted suicide is still *sui*cide (killing one*self*). It would be both peculiar and undesirable to penalize assisted suicide if suicide (or attempted suicide) is not.[27]

Conclusion

The evaluation of the Termination of Life on Request and Assisted Suicide Act makes it clear that no adequate solution may be offered to elderly people who are 'through with life'. If they suffer unbearably and lastingly, euthanasia or assisted suicide may be granted to them on the basis of a medical assessment, but it may be questioned whether these possibilities are sufficient. Perhaps even more pressing are the problems that are not limited to the elderly, where individuals who 'suffer from life' are concerned: their suffering cannot be gauged from a medical point of view, let alone be treated. The physician's role is limited in this respect, which means that individuals have, on the basis of the present legislation, few to no options to have their suffering – and thereby their lives – terminated. By regulating assisted suicide it may become possible to find a solution

oordeel mogen vormen over de ondraaglijkheid, de uitzichtloosheid en onbehandelbaarheid van dat lijden." Dutch Supreme Court, December 24, 2002, *NJ* 2003, 167, par. 8.2.

[21] The original text reads: "[…] het inschakelen van anderen die behulpzaam kunnen zijn bij het zoeken naar een zingevende invulling van het dagelijks bestaan." Dutch Supreme Court, December 24, 2002, *NJ* 2003, 167, par. 5.

[22] Cf. M. Parker, "Words and reasons: psychiatry and assisted suicide." *Australian & New Zealand Journal of Psychiatry* 46 (2) (2012): pp. 80-83, 80: "[…] the person who competently asks for [assisted suicide], in circumstances that we can sympathise with, is not always motivated by psychological pain *for which there is an acceptable alternative*."

[23] The original text reads: "Ook in onze praktijk hebben we te maken met patiënten die "lijden aan het leven" – zo noemen wij dat – en die onthecht zijn […]. Wij kunnen deze patiënten binnen de norm zoals die op dit moment geldt, niet helpen, omdat de norm uitgaat van medisch lijden. Er komen soms heel schrijnende situaties voor waarin ouderen zeer lijden aan het leven. In mijn ogen zou daar een goede oplossing voor moeten zijn. De huidige Euthanasiewet biedt die oplossing niet." Parliamentary Documents: House of Representatives, 2013/2014: 31036, no. 8, p. 9.

[24] The cooperative Coöperatie Laatste Wil ('Last Will Cooperation') has announced that it will communicate the details of an easily obtainable means to end one's life without pain to its members; there is no consensus among lawyers as to whether this is legal.

[25] J. Varelius, "Medical expertise, existential suffering and ending life." *Journal of Medical Ethics* 40 (2) (2012): pp. 104-107, 106.

[26] R. Young, "'Existential suffering' and voluntary medically assisted dying." *Journal of Medical Ethics* 40 (2) (2012): pp. 108-109, 108.

[27] The idea that suicide itself is not illegal may seem, given that the person involved has deceased, evident, but this appears not to have proven to be an impediment to penalize people in the past (see, e.g., M. MacDonald, "The secularization of suicide in England 1660-1800." *The Past and Present Society* 111 (1986): pp. 50-100, 52, 53).

for the dire cases whose suffering must at present last unabated.

The Question of Moral Responsibility and Physician's Practice in Nigeria

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Abstract

Humans are composed of many complex units or organs with diverse functions. Health challenges are bound to arise as a result of our daily interaction with our environment. These necessitate the study of different discipline to help overcome most of these challenges. This paper is concerned with those trained in the field of medicine with the aim of providing solution or treatment to health maladies or challenges. Physicians who swore to an oath of maleficence beneficence, to respect the authority of their clients and adhere to the principle of confidentiality, are equally expected to operate side by side the societal moral demands.

It is the position of this paper that despite man being created as a rational and free moral agent, upon which the physician should be free to make his choice as regards the course of medical treatment to be meted to who in view of the scarce medical resources, saddled him with difficulties in reaching decision. Hence, we appeal to Utilitarian principles, Kant's ethical principles, the Ross ethical principles, Rawls ethical principles and so on, to buttress the argument of the challenge of moral responsibility standing against the physician in his practice of medicine. It is the position of this paper that before subjecting physicians actions to the scrutiny of moral praiseworthiness or blame worthiness, certain questions such as: is the physician really free to act out of his volition, does he have alternative choice to make, is he under any influence, what is his state of mind, is he mentally alert and so on? Must be taken into cognizance to guide our attempts at resolving it. The expository, analytic and critical methods are used to draw the paper to a close.

Keywords: Medical Practice, Moral Responsibility, Utilitarian principles.

Introduction

Well understood, the food we eat, the work we do, and the environment wherein we live do contribute to determining how in good health or otherwise we are as humans. It follows that diseases or sicknesses are likely experiences we have as mankind. Hence, the practice of medicine as attempts at curing man's health maladies becomes very pertinent. Those who study the art of medicine and graduate are known as medical doctors otherwise "physicians". Giving the sacred and all-importance nature of man, those whose studies and practices concern with man (the highest creature), it requires that certain stringent measures be put in place to ensure that much care is taken by healthcare givers. Consequently, it becomes a prerequisite for would be physicians to swear to an oath. Commonly sworn to is the Hippocratic oath, the modern version of which is as follows;

"I solemnly pledge myself to consecrate my life to the service of humanity"

- I will give to my teachers the respect and gratitude which is their due;
- I will practice my profession with conscience and dignity, the health of my patient will be my first consideration.
- I will respect the secrets which are confided in me, even after the patient has died;
- I will maintain by all means in my power; the honour and the noble traditions of the medical profession;
- I will not permit considerations of age, disease or disability, creed, ethnic origin, gender, nationality, party politics, race,, sexual orientation, or social standing to intervene between my duty and my patient;
- I will maintain the utmost respect for human life from its beginning even under threat and I will not use my practical knowledge contrary to the laws of humanity;
- I make those promises solemnly, freely and upon my honour. (Asira and Ogar 2011:3)

It is incontrovertible to say that the claim of rationality-ascribed human necessarily implies morality. It follows that only the rational can be expected to chose the right course of action from alternative courses of actions. Rational quality with morals should guide man to choose good and avoid evil.

Moral Responsibility

Action is moral if said to be intrinsically good and praise worthy (Omoregbe, 1996:14). A person is said to be living a moral life if we are living a good life (Uduigwomen 2003:23). Lacey defines the term moral as that which revolves around habits, customs and indeed an acceptable ways of living within a given society or state. it has to do with assessing a particular action of behaviour as good or bad, right or wrong (1976:138). We assess individuals and gatherings as capable or not, contingent upon how legitimately they take up their responsibilities. Regularly we do this casually, through good judgment. Some of the time we do this formally, for example in legal judgment. The first philosophical use of "responsibility" was political. At the point when John Stuart Mill composes about responsibility his worry isn't with free will, however with the doctrine of representative government. Toward the finish of the nineteenth century, one most striking scholar to talk about responsibility is Max Weber, who propounds an *ethics of responsibility* (Verantwortungsethik) for the government officials. For Weber, the job of politics requests a strong attention for the realities of the

circumstance and consequences of actions– and not to abstract or grandiose principles.

Also, according to *Encyclopedia of Philosophy*, "a person is regarded as morally responsible for some acts or occurrence P if and only if he is believed:

(a) To have done P or to have brought P about and

(b) Done P or to have brought it about freely (1992:184).

Questions of what, when and how as it pertains to good life; when to know a person is living a good life and as well the criterion for making judgment about some basic facts of life as it relates to the performance of our duties, are key to our sense of moral rectitude.

There is no philosophical method for dividing or dissecting the different segments of responsibility, and a few parts are frequently disregarded by thinkers. To adopt a more complete strategy, this article separates the responsibility of people into four zones of enquiry. Modern analytic moral philosophy has had a tendency to ask two questions about responsibility: "What is it to be accountable?" and "What is an individual accountable for?"

The primary inquiry is generally taken as an inquiry regarding moral agency, the second as an inquiry concerning holding individuals responsible for past activities. Idea of moral responsibility therefore concerns things we do within our power and for which we can be held accountable without being forced or coerce to do them. put otherwise, actions based or reached at as a result of the choices an individual makes. Some may have argued that there is no universal ethical code rather in favour of the fact that ethical or moral codes vary from one society to another. This paper is not to occupy itself on ethical discrepancy but upholds that in every society virtuous living like respect for the fundamental human rights; thou shall not kill; steal among others appear to be universally acceptable (Evan, 2004:22-28). Moral responsibility can only be said in a situation to which the agent is at liberty to act without coercion. That is, the absence of all impediments to actions, having his or her intrinsic quality and freedom to perform a particular action or alternatively chooses not to perform a particular action. (Oswald Hamfling cited in Uduigwomen, 2003:24).

Factors that Determines the Limit of Moral Responsibility

Cardinally considered on issues of moral responsibility, is whether the action is voluntary or involuntary.

Voluntary Action: Under this, the agent is said to be very free to act; there must be alternatives of choice; there must be absence of compulsion; there must be knowledge of the subject matter, and there must be mental alertness or sound condition of mind.

Involuntary Action: This is the opposite of voluntary action. In this case, the agent acts under compulsion or in ignorance. That is when other people manipulate the agent to act in their power; where the agent recalls his action regrettably, in pain and wished he/she never acted so. (Macltrye, 1979:69). To lend credence to this, Pascal observes that *"where the 'will' becomes a sort of mechanical reflex, activated by whichever delectation that happens to be the strongest... in such circumstances no moral responsibility can be imputed to it"* (Udugiwomen, 2003:25). It presupposes that for an agent to be morally responsible for his/her action, to include murders, theft and the likes he must have acted without external force or influence acting on him, and ofcourse in good state of mind and that his actions was consciously prosecuted or executed. Also, on this subject, moral responsibility and medical practice may depend on the principles of freedom of the will and causality or determinism (Pellegspring 1981:46-50).

Freedom of the Will/Determinism

Here, holds that human actions are products of their own volition, and as such he/she should be held morally responsible for his actions. While determinism argues that all human actions are products of certain forces transcendental or beyond the control of the human agent. Viewing this work in the light of the above conflicting principles, complicate the challenge of moral responsibility. To explore further, if we subscribe to the principle of determinism then no human being should be blamed or punished for his actions, neither should any be praised since they do not have control of their actions and therefore the entire human society will be chaotic, brutish, short, lawless as captured by Thomas Hobbes' state of nature. If the contrary is the case that determinism is false, then some events or actions are self willed otherwise the acting agent acted out of freewill. On the other way round, we find out that certain events occur by chance. If this is true, it becomes an imposition. Where then lies the freedom of the human agent? (Encyclopedia of Philosophy 1972:184).

Arguing on this, some philosophers support moral responsibility, that a person is morally responsible for his actions, and if determinism is to be brought in, it is the self that may determine action and to which end, the person is to be held morally responsible for his/her actions. According to David Hume, it is only when an action that is determined is also in some sense constrained or compelled, is the actor morally responsible for the act. (Cited in Uduigwomen, 2003:26 – 27). It becomes clear that both freewill and determinism have not been able to strike a compromise as to which actions are products of one's volition, and those that are determined. Except owed to some other moral schools of thought, we are yet to have a generally accepted criterion for judging human actions as praiseworthy or blameworthy. Consequently, many resort to conscience this however is not without contention (Evan, 2004:22-28).

Competing Schools of Thought on Issue of Moral Responsibility

We may have to consider the utilitarian and deontological schools.

Utilitarianism

Utilitarians argue that praise or blame should be apportion accordingly to an active agent in relation to his action. According to Bentham, an agent's action should be directed to maximize good and diminish or minimize evil. It should be the satisfaction of greater minority and dissatisfaction of majority, or negligible few.

Utilitarianism is a Teleological theory. That is an act is judged right or wrong based on its result or consequence.

An act is right depending on the volume of happiness or pleasure it produces, and wrong based on the pain produced rather than avoided. Very key to utilitarianism is the principle of utility. Given this, the moral end that should be sought in all our actions, should insist on the pursuit of the greatest possible good over evil.

This principle cautions that medical practitioners should keenly pursue the attainment of the highest good which is the security of lives by their painstaking attention to patients to save lives above every other promptings (Omoregbe, 1996:172).

Utilitarianism divides into Act and Rule

Utilitarianism: Whereas Act utilitarian principle advances the good and result of actions as the criterion for judging rightness, Rule Utilitarianism encourages the adoption and observation of only those moral rules that would produce happiness for greater majority. He cautions therefore that it is morally responsible for health workers and authorities to see to it as their responsibility to provide medical facilities and services in good number as to promote good health for many.

The enhancement of patient's pleasure should be seen as the key duties of the physicians, who are also supposed to be altruistic as against being egoistic going by the medical code of ethics. However, the challenge of moral responsibility as regards utilitarianism can be discerned when a physician is in a fix as to who of the two or more patients billed for organ transplant should receive the only organ available taking also into cognizance the social and economic status of the said two patients, one the governor, and a peasant fisherman. The physician must following the utilitarian principle, choose the governor at the expense of the peasant farmer.

Kant's Ethical Theory: To Kant, goodwill is the only good thing that cannot be abused. Being the will to act for the sake of duty. Kant's therefore enjoins moral agent in this case, medical practitioners to act freely from his or her volition independent of any eternal force, pressure or influence. He endears the principle of universalization as a yardstick for determining whether an action is good or bad. He adds any action that would not be universally approved is therefore bad. That any person in a similar situation will be willing to allow same action apply to he/she.

Kant holds the view that every human being is a rational worth. Therefore, to treat the president specially while relegating or denying the peasant farmer is morally wrong especially when the peasant-farmer happens to get to the notice of the doctor first before the president. Medical doctors should have goodwill and by implications morally responsible. Hence, their actions should be out of reverence for moral law in a universally valid and acceptable way (Iwe, 1986:235 – 237). He holds the view of equality hence, nobody should be treated partially or in preference of the other. The implication following Kant's ethical theory is that in as much as the peasant (poor) farmer came before the Governor (rich) man the principles of first come first serve should be followed. So medical doctor is morally responsible to do the right thing to gain the praises of the society or do the wrong thing and be blamed (Kant, 1982:236).

William David Ross Ethics: According to William Ross, virtue, knowledge, pleasure and the allocation of pleasure and pain according to desert are the four good things.

Again, he classified duties into three kinds such as: reparation, gratitude and keeping faith. And moral responsibility obligated medical doctor or physician no matter what to insist in doing or carrying right action which is the tendency to promote the general good of his/her client (patient). We should now and always do *prima facie* duties as against less important duties. He concludes by saying medical doctors are morally bound to be faithful to their clients in accordance with the oath they swore to. The obligation to their employer should be less than their obligation to render service according to desert in such a virtuous way as would project them as gratuitous (Kelly, 1990:236 – 238).

Rawls' Ethical Theory: Alternating classical utilitarianism. John Rawls' hypothesis of equity, which is considered as a contemporary refection of egalitarian ethical theories, addresses the issue of reasonable circulation of social products. He enjoins that individuals and associations should advance their rational ends without infringing on the rights of others. To this, it is the moral responsibility of government to arrange medical institutions to achieve the greatest net balance of satisfaction for her citizenry. It is also required that medical doctors adopt the principle of rational choice, be empathetic and as well, impartial in their dealings with the sick ones before them.

Moral Responsibility and Physician's Practice In Nigeria

Today, medical professionals face an unpopular decision between two conflicting moral orders, one situated in the power of our ethical obligations to the sick, the other in the supremacy of self-interest and the marketplace. These two orders are not essentially reconcilable and, similar, and the professional will be compelled to pick between them.

In that decision, ethical theories learnt and ethical code and conducts can play a focal and essential part. Giving health services is a critical moral measure since its significant point is to ensure the welfare of the general population who require treatment and care (1). Ethics not just priorities and the dispersion of healthcare services, but in addition are apprehensive with moral decision making at an interpersonal level (2). Moral sensitivity is the capacity to distinguish the existing moral issue and comprehend the moral results of the choices made on the patient's part (3). Doctors are constantly presented to moral distress because of a few conditions, for example, making a move in spite of one's conscience, not giving full treatment because of the financial limitation of a patient, insufficient treatment, absence of time, and patients on a long waiting list etc. Acting against professional values and interests destructs one's moral integrity and achieves job dissatisfaction, leaving their occupation, and in particular, not giving high quality and safe health care to patients (8). On the off chance that moral decision making is countered with situation that cause moral distress, a therapist won't have the capacity to perceive

situations and moral issues, and make sound judgment. Perceiving distressing and morally problematic circumstances is exceedingly imperative in decision making processes. Satisfying this exceptionally imperative undertaking requires moral knowledge, understanding the ethical theories above, as well as requires moral sensitivity (9, 10). People who have moral sensitivity are fit for solving moral clashes. Besides, they are fit for forming a sensory and scholarly perception of individuals' vulnerable circumstances, and are aware about moral outcomes that are critical in settling on critical decisions for others (11). It is trusted that in clinical settings, reacting to morally distressing circumstances is identified with criteria, for example, moral sensitivity (12). In healthcare, morality is an inter-related and dynamic process that is recommended by moral sensitivity (13).

Over the span of obligation and relationship with patients the doctor must hold fast to specific standards of medical ethics (equity, nonmaleficence, equity and beneficence), rules (confidentiality, fidelity, veracity and privacy) as well as virtues (empathy, respects, kindness, and so on). A doctor might be sanctioned when he breaks the rules and principles of medical ethics; however he may not necessarily be liable or compelled to maintain the virtues involved in his line of duty and practice. It is, in any case, morally upright (yet not compulsory) for a good doctor to be caring, kind and to show regard for his/her patients. Regard for patients and the desires of patients are two distinct issues that must not be confused.

Conclusion

The idea of free moral agency and rationality ascribed to humanity suggests that man is morally responsible for his actions. It follows as has been observed earlier on in the work that, for man to be held morally responsible, there must be alternative of choice, absence of compulsion, knowledge of the subject matter and healthy state of mind or mental alertness. With specific reference to medical practice, the physician has his professional (oath) moral responsibility; and the societal moral responsibility constitute a serious moral challenge to him. it has been rightly observed that sometimes the societal moral responsibility may conflict with his professional moral responsibility. At this point is he expected to act professionally or complies with societal demands for example where the societal demands will compel the physician to divulge information gotten from his client in confidence.

Should physician's oblige them and violate the principle of confidentiality? Again, his professional responsibility and societal moral responsibility which one is superior, and which is less important? Will he be worth the profession by violating his professional responsibility partially or otherwise? Agreed, there may be some exceptions no matter how slightly that maybe to the rules but the work maintains that more attention should be given by the physician working more in conformity with professional moral responsibility of being accountable to his patient, ensures the patient is well treated, and his/her well being is promoted at all times for which reasons the patient came to him; and should there be conflict arising from societal demands, the society should carve any other way to resolving the conflict arising from the patient's action and not through the physician into violating his obligation.

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