

# **Practical Aspects of Evolutionary Medicine**

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## **Introduction**

Since Randy Nesse's and George Williams' (1991) seminal article developing a paradigm for Evolutionary Medicine (EM) the field has been expanding rapidly, although the number of books focused on the general topic still number less than ten. One of the earliest problems recognized by Nesse and Williams was the need to convince clinicians that this emerging field was relevant to their sphere of work. As stated in their 1991 article "medicine is a practical enterprise, and it hasn't been immediately obvious how evolutionary explanations might help us prevent or treat disease".<sup>1</sup> Although the number of papers pointing out the utility of EM for clinical applications has been growing, there has been no comprehensive discussion to my knowledge of what makes EM eminently practical or, perhaps, more appropriately "applied", and thus the problem for this field in acquiring recognition from practising doctors will continue.

The purpose of this paper then is to write a short review covering five examples of topics that cut across both clinical medicine and evolutionary theory and that demonstrate the practical benefits of EM. The paper differs from others in this book since it draws not only on published research but also on the first author's (practical) experience in teaching a class called "Evolutionary Medicine" at University College London (UCL) from 2002 through 2006. The class differed from the usual format of university lectures in that a series of guests were actually interviewed in class on their topics of speciality relevant to EM (Table 1). For some of the classes two guests were invited (often from different disciplines or different perspectives) in order to generate debate. Students were encouraged to ask questions at any point during the interview in order to increase their active participation in learning. Most of the interviews from 2003 onwards were videotaped by Media Resources at UCL.<sup>2</sup>

The purpose of designing the class as a series of interviews and the teaching and learning benefits of this format will not be dealt with in this paper. Instead, it will focus on one of the questions that were consistently presented to the guests, namely whether they thought their own particular speciality had practical benefits for EM, or whether they considered evolutionary explanations for a particular pathology, or set of pathologies, might have practical applications. In a sense then, these interviews represent an informal survey of clinicians, evolutionary biologists, anthropologists, and others of their opinions concerning the practical aspects of EM. This paper will also attempt to cover some newer areas that have not, to our knowledge, been previously discussed in other books specifically about EM (such as emergency

medicine and racial medicine) but will also cover topics that have been dealt with in other books (obstetrics, public health and various aspects of epigenetics). Given the limited space in the chapter, this is intended as a summary rather than an exhaustive review of the topic.

### **Racial Medicine**

This topic is a contentious and relatively new area that embraces genetics, pharmacology, social and environmental issues. The guest for the class at UCL was Dr. Mark Thomas, a geneticist in the Biology Department at UCL (see Table 1) who, when asked about the practical relevance of Racial Medicine for EM, replied with the following:

*This is the most practical application in evolutionary medicine without a shadow of a doubt. It's absolutely clear cut . . . it's not teleological . . . evolutionary studies . . . are impacting medicine in a real and profound way, and it's all from evolution; it's all from understanding molecular evolution that our ability to construct models or appropriate statistical tests comes from, and then it's been applied to medicine. So, it is the least teleological and the most applicable of all areas, I think, in evolutionary medicine.*

Racial Medicine primarily concerns pharmaceutical applications that might be more efficacious for specific ethnic groups either because they differ in their susceptibility to specific diseases (up until 2004, 29 medicines and possibly more were indeed claimed to have different effects in different human groups, depending on the ethnic population targeted <sup>3</sup>, or because they differ in their response to particular medicines (the study of genetic variation in drug response is known as pharmacogenomics). Susceptibility to pathologies may depend on genetic polymorphisms that have been selected for over long periods of time, as in sickle cell anaemia, thalassemia, or lactose intolerance, conditions that have well-known associations with geographical areas, and particular ethnic groups. These pathologies are relatively easy to diagnose and their genetic and evolutionary origins are fairly clear.

Increasingly, however, researchers are uncovering more subtle genetic variation both within and between human populations that have epidemiological implications. For example, Jonathan Cohen and colleagues <sup>4</sup> have recently analyzed allelic variation in the proprotein convertase subtilisin/kexin type 9 serine protease gene or PCSK9 among both US blacks and whites. Out of 3,363 self-reported African Americans, 0.8% carried PCSK9<sup>142x</sup> compared to only 0.02% of whites, while 1.8% of blacks had the allele PCSK9<sup>679x</sup> compared to 0.04% of whites. In contrast, 3.2% of white subjects carried PCSK9<sup>46L</sup> compared to 0.7% of blacks. Carriers of these alleles benefited from substantial reductions in low-density lipoprotein (LDL) cholesterol and risk for coronary heart disease (CHD). The origin of these allelic variations is unclear.

Studies like the above example offer the potential to tailor medicines along individual lines. There are, in fact, other specific examples where this has happened <sup>5</sup>. Indeed, the idea of individualising medicine is gaining increasing acceptance as the optimal form of clinical care. The time and expense involved in such an endeavour, however,

so far outweigh any other considerations in most circumstances. However for many diseases, genetic susceptibilities may be dwarfed by environmental issues. Even in the Cohen study, cited above, one black carrier of the beneficial allele did have CHD, but was described as obese with a body mass index of 34, with hypertension and smoked. As stated by Francis Collins “in many instances, the causes of health disparities ... have little to do with genetics, but rather derive from differences in culture, diet, socioeconomic status, access to health care, education, environmental exposures, social marginalization, discrimination, stress and other factors”<sup>6</sup> Collins went on to espouse a list of objectives in the search for those factors that underlie health risks, to include adequate consideration of these other factors quoted here, and is supported by many other advocates<sup>3,7</sup>.

One of the major problems, in fact, with “Racial Medicine” is that the focus has been on precisely those pathologies with very clear environmental components. Two notable examples are CHD and kidney disease, pathologies more common in individuals with a history of poor diets, low rates of exercise, and smoking<sup>8</sup>. Many of these characteristics also tend to be associated with low socioeconomic status, at least in Europe and the USA. Social issues like poverty are often difficult to separate from ethnicity in certain groups depending on their immigration history to northern and western countries, reinforcing the concerns expressed by Collins and others outlined above.

There is already a vast literature in anthropology and genetics that deals with the issue of “race” itself, and whether this is an artificial construct<sup>9,10,11</sup> (cf. Ch ? in this volume) as well as an equally large literature dealing with inequalities in health resulting from social factors correlated with ethnicity<sup>3,6,7,13</sup>. Suffice it say here that our species appears to have evolved from a very small founding population<sup>14,15</sup>, but it is arguable from a statistical perspective whether genetic diversity between individuals is indeed as great as that between populations as originally claimed by Richard Lewontin<sup>16</sup> (cf. Edwards 2003 for critical comments on Lewontin’s statistics and intent), despite the repetition of this claim in many other articles. Recent work shows that it may indeed be possible to separate populations statistically using genetic data, and that these clusters correspond to geographical areas that may offer some epidemiological insight<sup>17,18</sup>, although this claim has also been subject to criticism and reanalysis<sup>19</sup>.

In addition, there is the added social problem of identifying racial origins of individuals who may, for example, look “black” but have mixed genetic ancestry. In any discussion of racial medicine, then, the genetic make-up of individuals targeted for particular drug treatments should be clearly evaluated. This is, however, often impossible for the same reasons why individually tailored medical treatments are visionary but impractical.

A second major problem is that some drugs have been approved for use with specific ethnic groups following *retrospective* analyses of data from completed clinical trials that happened to have participants that could be identified by self-report as either “black” or “white”<sup>8</sup>, or have originated from small-scale trials without adequate cross-group comparisons. The progress of the drug *BiDil* (a combination of two generic drugs called hydralazine and isosorbide dinitrate, a vasodilator and nitric acid donor respectively) which was approved by the US Food and Drug Administration

(FDA) in 2005 specifically to treat heart disease in US blacks, has been described recently by Jonathan Kahn (2007) as a “tangled tale of inconclusive studies, regulatory hurdles and commercial motives” thus darkening a complicated picture of genome-targeted drugs.<sup>20</sup>

Here, the retrospective analysis of the Vasodilator Heart Failure Trial that led originally to the patenting of *Bidil* as a racial medicine, focused on only 49 self-reported black participants who used this drug combination. A more specific trial, however, known as the African-American Heart Failure Trial (A-HeFT) was initiated in 2001 and prematurely stopped in 2004 following findings of significantly more deaths in participants from the placebo arm of the study. A-HeFT enrolled 1,050 self-reported African Americans to examine more closely the effects of *Bidil* on this ethnic group. Two striking facts about this trial were that, first, most of the patients on the trial continued to take their normally prescribed heart medications, while no comparative group of whites were enrolled in the trial. It is thus entirely possible, as suggested by Kahn (2007) that *Bidil* is just as effective in white patients as in blacks and that the subsequent A-HeFT trial in blacks only may have been motivated by commercial interests related to the length of patents filed for the drug as a racially targeted one.

But are all racially targeted clinical trials suspect? There are a number of other completed and ongoing clinical trials focusing on specific ethnic groups, or including larger cohorts of different ethnic groups, including the African-American Study of Kidney Disease and Hypertension (AASK), the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and the Losartan Intervention for Endpoint Reduction in Hypertension Trial (LIFE). These include much larger groups for study (for example >15,100 participants of African descent for ALLHAT and an additional 8,000 Hispanic participants for comparison). Many clinicians (e.g., Taylor and Wright, p. 3658)<sup>8</sup> are of the opinion that “inclusion of subjects by race/ethnicity in clinical trials is essential to define the reasons for differences in health outcomes, *whether environmental or biological*” (my emphasis). That being the case, what needs to happen is a better consideration of those genetic and environmental contributors to disease profiles.

Human populations do appear to cluster by geographical area. There is also no question that individuals have different susceptibilities to diseases depending on their genetic legacy. But the question remains open whether grouping individuals together on the basis of diseases that have strong environmental components is an effective way of targeting specific drug applications. While this area remains contentious, the implications of how EM can become actively engaged in this debate remain clear, particularly given the history of involvement by anthropologists in the race debate.

### **Epigenetics**

Again, this is a relatively new field that has emerged in recent years. While treated initially with scepticism (see<sup>21</sup> for comments on early resistance to this field), epigenetics is gaining increasing recognition for its importance in determining phenotypes. The term (meaning literally “outside the genome”) was coined about 50 years ago by the late Conrad Waddington – a geneticist at the University of Edinburgh

-- and refers to the expression of traits that do not involve actual changes in the genome. Epigenetics as a topic is perhaps the perfect complement to the discussion of Racial Medicine, because it clarifies that one's genetic heritage is not deterministic. Rather particular features of one's environment, or even one's parents and grandparents' can alter the molecular switches that may either turn on, or off, gene expression. Such mechanisms often involve a process known as DNA methylation where a methyl group (one carbon and three hydrogen atoms) is added to particular sections of DNA, or by alterations to the chromatic packaging of DNA.

Numerous animal models have illustrated epigenetic effects *in utero* on offspring. For example, several researchers have experimented with dietary and other supplements given to agouti mice (mice with a specific gene that makes them susceptible to diabetes and cancer; they are also phenotypically obese and yellow in colour)<sup>22,23,24</sup>. In one such experiment, pregnant agouti mice fed the phytoestrogenic compound, genistein –commonly found in soy products and thought to be protective against at least breast cancer – gave birth to offspring with a different coat colour and with a lowered predisposition towards obesity. Analysis of the genome of these offsprings revealed six sites located near the Agouti gene (normally responsible for the specific phenotypic characteristics of the agouti mice) that had been methylated, with additional evidence that this methylation had occurred early in embryonic development<sup>23</sup>.

### *Foetal Programming*

Subsumed under the banner of epigenetics is the topic of foetal programming that has been covered previously in other books on EM<sup>25</sup>. Although earlier work in the field of foetal programming did not use the word epigenetic per se, there are now a number of articles suggesting epigenetic mechanisms can explain the link between poor nutrition *in utero* and health in later life<sup>26,27,28,29</sup>, although specific identification of genomic mechanisms remains elusive in studies of humans.

Despite the lack of an early link between those researchers studying epigenetics and those involved in foetal programming, the latter field has overtly embraced evolutionary theory such that researchers in this field, despite coming from clinical backgrounds, have themselves embarked on writing introductory and popularized texts about the field of EM<sup>30,31,32</sup>. Although early researchers such as Elsie Widdowson had discussed foetal development in relation to later health, it was David Barker and his colleagues at Southampton University who fuelled research in this area with their analyses and publications. Initial data derived from a careful search by the Medical Research Council in the UK for any historical records of maternal and infant health that could be linked to surviving adults. They found a series of very detailed records begun by the Chief Health Visitor, Miss Ethel Margaret Burnside, for children born in Hertfordshire between 1911 and 1945. These records ran from birth through to the fifth year of these children's lives. The MRC team were able to locate many of these now adult individuals using various national databases and to compile health information for them; more men were successfully located than women who tended to change their name on marriage<sup>30</sup>. When these data were analyzed, there appeared to be a relationship between low birth weight and an increased risk for CVD and other metabolic diseases, results that have been replicated in many other studies elsewhere. These articles spawned a plethora of research on the association between foetal

development and adult health, and led to an increasing interest by medical doctors involved in this field with evolutionary concepts.

One of the guests in class who came to discuss foetal programming at UCL was Keith Godfrey a medical doctor located in Southampton in the DOHaD Centre (Developmental Origins of Health and Disease). When asked about the perceived current synergy between those people studying foetal programming and an interest in evolutionary theory, Godfrey replied:

*Absolutely right! We're not as medical docs gonna solve this, certainly in isolation we're not gonna solve it, because the timescales, the perspectives of it have to encompass evolutionary theory, and they have to encompass life history and life course perspectives, and the complexities are great here. There are developmental effects on maturational processes -- that's, for example, things like the timing of puberty -- and these have evolutionary implications, and we'll only understand them by going backwards as well as trying to predict, going forwards, and what we think might be beneficial in the short-term – feeding kits, it's the mission of UNICEF – actually if you take account of evolutionary perspectives, you might start to see that it might be disadvantageous. So, we've a lot to learn. I think the epigenetic aspect is starting to provide the mechanism by which many aspects of evolutionary theory might have to change actually. This is not just about natural selection, probably, this is about a whole new range of processes coupled with natural selection. So, we've a lot to learn and both camps have got things to learn from each other.*

Since the early work by Barker, there has also been increasing recognition that the period of early life when phenotypic traits can be modified probably extends beyond the foetal period to encompass at least critical phases during childhood. In particular, researchers in foetal programming and health across the life course are discovering that the combination of low birth weight together with rapid growth in early childhood increases the risk of diseases associated with metabolic disorders including obesity, hypertension, CVD and type 2 diabetes <sup>33,34,35</sup>

There are other areas of growth, development and health that might also be affected by epigenetic modifications that occur during childhood. Recently, Nunez and colleagues <sup>36</sup> have shown that Bangladeshi women who grow up in the UK as migrants have significantly higher levels of salivary progesterone and higher rates of ovulation compared to Bangladeshi women who grow up in their home country where they are exposed to a greater number of infectious and parasitic diseases. These hormonal levels also appear to be “set” in women between birth and eight years of age with little modification until puberty, and no modifications during adulthood regardless of environmental changes that might occur during this time. Higher levels of progesterone are associated with an increased risk for breast cancer in later life suggesting there might be a trade-off between early fertility and later health risks. This study contributes to a growing recognition of the importance of plasticity during development in predicting and adjusting the phenotype appropriately to an

individual's environment <sup>37</sup>. Thus epigenetic modifications can occur far more rapidly than modification to the DNA.

There is also a growing body of research in both animal models and humans demonstrating a transgenerational effect of environmental conditions that goes beyond one generation. For example, Michael Skinner and colleagues <sup>38</sup> have shown that female rats exposed during early pregnancy to endocrine disruptors produced male offspring with lower sperm counts and higher infertility than normal unexposed male rats. Furthermore, the effects lasted through at least four generations. The effects were believed to be caused by altered methylation in the germline. Despite the importance and publicity that the study of endocrine disruptors has generated, there are as yet no studies showing similar effects in humans.

Other studies, however, examining nutritional status in one generation have been able to point to effects among grand children. For example, Bygren and colleagues <sup>39</sup> used a historical rural Swedish cohort to look at the transgenerational effect of fluctuations in food supplies on grandchildren. They found that excess food documented in the environment of paternal grandfathers when they were aged 9-12 years old (referred to as the slow growth period) resulted in a shorter lifespan in their male grandchildren, and an increase in risk of CVD <sup>40</sup>. This article, however, suffers from low sample sizes and an inability to link general information concerning food availability to actual consumption patterns of individuals or families raising the possibility of spurious results.

### *Genomic Imprinting*

Another topic that sits squarely within epigenetics is genomic imprinting also covered in earlier volumes on EM <sup>41</sup>. This sub-field first developed during the 1980s with the first "imprinted" gene -- insulin-like growth factor 2(IGF-2), also known as somatomedin A -- discovered in 1990, and primarily responsible for embryonic growth. At least 100 imprinted genes have been discovered up until 2005. It is believed, however, that imprinted genes represent less than 1% of the total genome. Imprinting of genes appears to violate the normal rules of Mendelian inheritance since expression of the genes is determined by only one allele from either the father or mother which can either switch on or off gene function, much as environmental factors now appear to be able to do this in some circumstances as described above, depending on the particular stimulus <sup>42,43,44</sup>. Imprinting is perceived as a kind of genetic arms race between maternal and paternal genes and may have evolved in eutherian and marsupial mammals because of the potential to manipulate the provision of resources to internally gestated offspring; egg-laying species such as birds do not imprint genes since resources in an egg are finite once it is laid <sup>45,46</sup>.

The importance of imprinted genes was demonstrated early in murine studies of IGF-2. If the normally paternally expressed allele was switched off, then offspring experienced a 40% reduction in growth, whereas if there were mutations in the maternal allele for IGF2r, then the resulting offspring were oversized, unviable phenotypes <sup>47</sup>. Other early experiments by Azim Surani in Cambridge were conducted to see if mammals could produce parthenogenetically (from one sex only). In these experiments, maternally derived DNA was removed from mouse oocytes and replaced with two sets of paternally derived DNA, and conversely paternally derived

DNA was removed from oocytes and replaced with two sets of maternally derived DNA. In neither set of experiments were the offspring viable <sup>48</sup>.

Other work suggests that imprinted genes influence various areas of neurological development. For example, Keverne and colleagues <sup>49</sup> used mouse chimeras to explore the influence of maternal versus paternally derived alleles on the development of intelligence and emotion. They found that maternally derived genes clustered in the cortex of the brain a region associated with intelligence and planning, whereas the paternally derived genes clustered in the hypothalamic region associated with primitive emotions. Such findings reverse the common male/female cultural stereotypes.

The role of imprinted genes in affecting intelligence is confirmed by specific human disorders that are known to derive from dysfunctions in normally imprinted genes. Two such syndromes are known as Prader-Willi Syndrome and Angelman's Syndrome. In the former Syndrome, problems in the expression of paternally imprinted genes (locus 15q11-q13) on Chromosome 15 leads to dysfunction associated with activities controlled by the hypothalamus such as hyperphagia (overeating) and obesity, placidity in temperament, and an under-developed adult sex drive. In Angelman's Syndrome, problems in the expression of the maternally imprinted gene (UBE3A) on Chromosome 15 results in physical defects related to activities controlled by the cortex and striatum including mental retardation, spasmodic movements and difficulties with speech <sup>50,51</sup>.

David Haig <sup>41,45,52</sup> has contributed significantly to the literature outlining the evolutionary significance of genomic imprinting by explaining its origin in terms of parental conflict as well as maternal-foetal conflict. A good example of this kind of conflict is illustrated in the respective roles of imprinting genes in foetal development. Paternally expressed alleles in the genome are responsible for factors such as placental development (where it is argued it is in the father's interests to acquire resources for his offspring at the potential expense of the mother), whereas maternally expressed alleles control embryonic growth, therefore potentially conserving maternally-derived resources. Haig <sup>45,53</sup> has argued that such conflict can explain maternal prenatal conditions such as pre-eclampsia as well as calcium metabolism. Finally, the two areas of foetal programming and genomic imprinting are beginning to converge. Some researchers have recently suggested that low birth weight, which we know is associated with health problems in later life, might originate from dysregulation of imprinted genes that control foetal development and that this dysregulation might itself have environmental origins such as differential nutrition <sup>54,47</sup>. The potential marriage of these two areas at present originates from those studying genomic imprinting, but it will probably not be long before those scholars engaged in studying foetal programming begin to look more closely at the kinds of mechanisms that might be responsible for programming the foetus in utero as suggested by one of Godfrey's recent articles <sup>26</sup>.

Epigenetics is an exciting and growing area of research which has the potential to explain many current aspects of disease and epidemiology with very clear practical applications to medicine. There is even the growing potential to develop "epigenetic drugs" that could be used to inhibit or enhance DNA methylation or to alter chromatin structure <sup>55</sup>.

## Emergency Medicine

In a fascinating and much publicised lunch-hour lecture at UCL in 2004, Melvyn Singer, a Professor of Intensive Care Medicine and Centre Director of the Bloomsbury Institute of Intensive Care Medicine at UCL who has published widely in the field of emergency medicine, delivered a provocative talk entitled “Are We Ignoring the Lessons of Waterloo at our (Patients’) Peril?”<sup>56</sup> Drawing on historical records during this stimulating hour, Singer discussed the remarkably low mortality rates for severely wounded men in battles such as Waterloo where most appeared to have survived. For example, of 52 men from the 13<sup>th</sup> Light Dragoons wounded by cannon, sabre or gunfire during the Battle of Waterloo, only three died, while only six men died among 102 wounded survivors on board the ship *Victory* during the Battle of Trafalgar; this latter number including men with amputations or gangrene.

By pointing out these apparent medical anomalies, Singer speculated whether the absence of contemporary emergency room (ER) procedures might have helped to save the lives of these wounded soldiers. From a contemporary clinical perspective, this kind of speculation might sound very strange. But, in his academic publications, Singer and colleagues have suggested that multi-organ failure as a sequela of trauma (as in battles), systemic infection, or other life-threatening illnesses might be an *adaptive*, functional response to physiological injury that could protect the body against death.

In one relevant publication, Singer et al<sup>57</sup> (p. 545) have written that

*multiorgan failure is an attempt by the body to ensure cell survival in the face of sustained critical illness with affected cells entering a dormant state analogous to hibernation or aestivation. This response enhances the recovery of organ function should the patient survive . . . and might have evolved as a mechanism that increases the chances of survival in animals in which an external insult is potentially overwhelming (my italics)..*

For the field of EM, it is encouraging to see clinical doctors at the front-line of treatment using unprompted Darwinian terms such as “evolved.” On the more practical level are the implications of Singer and colleagues’ work for medical treatments. For they go on to suggest that many interventions hitherto used fairly routinely in ER contexts such as mechanical ventilation, blood transfusions, intravenous administration of exogenous hormones, supplementation of nutritional status or with other medications may have adverse effects because they interfere with natural physiological defence processes.

These assertions are substantiated by a growing literature in the field of intensive care and emergency medicine that is examining the pros and cons of such interventions. For example, many recent studies have called into question the previously prevailing liberal strategies surrounding the use of red blood cell transfusions<sup>58,59,60,61</sup>. A number of clinical trials have, in fact, found increased rates of mortality or morbidity

among critically ill patients who have been given transfusions, while others have found either no effect, or increased benefits, from lowering the haemoglobin concentration in transfusions. Patients in intensive care appear able to tolerate and survive severe anaemia, contrary to previous prevailing wisdom<sup>59</sup>. Reductions in transfusion rates could also lead to lowering of potential disease transmission caused by contaminated blood supplies as well as lowering immune-related responses to transfusions, and other reactions such as iron overload or electrolyte toxicity<sup>59</sup>.

Similarly, Moloney and Griffiths<sup>62</sup> have suggested from the results of meta-analyses that tidal volumes used in mechanical ventilation could be reduced without affecting patient survival and, in some cases, might significantly improve survivorship by reducing conditions such as pulmonary overdistension, oedema and infection. They also discuss the possibility that mechanical ventilation might contribute to multiple organ failure due to the release of proinflammatory cytokines that affect cell function, a suggestion confirmed in at least one mouse model<sup>63</sup>.

Similarly, there is growing recognition that the re- introduction of oxygen to patients that have, for example, experienced cardiac arrest may actually induce cell death rather than improve the chances of patient recovery. It is in fact this process of reperfusion that actively kills body cells that have already initiated the protective response of lowering cellular activity<sup>64</sup>. Recent experiments have shown that somatic cells can, in fact, survive for long periods following oxygen deprivation<sup>65</sup>. These findings are revolutionizing the study of intensive care medicine and leading to new research into how to reintroduce oxygen more safely into cells that have effectively moved into a dormant state<sup>66,67</sup>.

These articles also tie in with emerging methods in triage where doctors are experimenting with ways of inducing suspended animation to preserve body function through cooling, aortic flushing, and even administration of toxic gases such as hydrogen sulphide – in a sense mimicking the body's own natural defences when multiple organ failure occurs<sup>68,69,70,71,72</sup>. In one aspect, these artificial methods replicate many of the physiological defences described as adaptive by Singer and colleagues, but they are also in response to an increase in the number of studies that are examining the adverse impact of many interventions used routinely in emergency medicine, and the key role of cellular mitochondria in producing these responses.

Linking both Singer's work and those of intensive care physicians and their teams, such as Lance Becker, Mark Roth and Patrick Kochanek, is a focus on oxidative phosphorylation by the cell's mitochondria that provide energy and consume the bulk of oxygen. Singer suggested that multiple organ failure resulting from trauma or sepsis results from a decrease in oxidative phosphorylation and thereby a reduction in cellular metabolism by the mitochondria. Similar reactions are in fact produced by the clinical interventions described above that also aim to produce a state of suspended animation. For example, the normally toxic gas, hydrogen sulphide, interferes with oxidative phosphorylation by binding to cytochrome c oxidase which normally binds to oxygen to produce adenosine triphosphate or ATP, the primary cellular fuel.

Findings such as these and their link to innovative research investigating evolved physiological responses to trauma, make Emergency Medicine an exciting clinical

area that can be added to the growing corpus of topics in EM that have practical significance.

## **Public Health**

Public health professionals study problems that have group-level consequences in terms of significantly increased morbidity or mortality for some population of interest. Within EM, articles dealing with public health have mostly focused on the topic of the apparent mismatch between the environment in which humans evolved relative to more recent environments where conditions are vastly removed from ancestral ones<sup>1</sup>. Hence there has been a focus on pathologies connected with contemporary lifestyles such as CVDs, obesity, hypertension and so forth<sup>37, 73</sup>. Many of these conditions have behavioural causes. For example, obesity is associated with over-eating and lack of exercise, CVDs with a sedentary lifestyle, smoking, and an unbalanced diet rich in polysaturated fats; hypertension with stressful lifestyles and atherosclerosis which is again linked to poor diet and lack of exercise over the lifecourse.

The standard approach in public health to change such “irrational” behaviour has been to appeal to ‘good reasons’ for engaging in an alternative, desirable ones, based on the notion that the irrational behaviours stem from a lack of relevant information: provide the information and people will change their behaviour. Health education professionals have thus attempted to get large numbers of people to come to rational decisions about themselves with respect to often fundamental types of behaviour – how they have sex, what they eat, or how they spend their leisure time. For example, anti-smoking campaigns have long been based on the notion that ‘smoking kills’ by causing lung cancer – that is, trying to persuade people to preserve their health with explicit warnings about the disease risk of their behaviour. Such appeals to cognitive-level processes have not been particularly successful, probably because cognitive level control is relatively weak, while the behaviours themselves have ancient roots. The appeal of foods rich in sugar and fats lies in evolved preferences for these kinds of substances that were once in short supply in the ancestral environment, but where they offered an important nutritional component of the ancient diet. Hence humans evolved to have high preferences for these kinds of foods with negative consequences in environments with supermarkets.

Evolutionary psychology – particularly the notion that the brain is an evolved organ – suggests a different kind of approach to that of most public health perspectives. It argues that most of the reasons for widespread, persistently maladaptive behaviours are in fact either habitual or motivated by emotional causes. Further, these motivations – due to ancient mechanisms of control over behaviour – made good sense in the environment in which they evolved. Using this evolutionary perspective, a few public health workers have therefore begun to put forward hypotheses about behaviour change based on recognition of potential mismatches.

For example, a particular health problem which has been well-studied from an evolutionary perspective is sun-tanning<sup>74</sup>. The mismatch in this case is between contemporary cultural values which induce people with fair skin to become tanned in order to look beautiful, and the consequence of excessive exposure to the ultraviolet radiation: skin cancer<sup>75</sup>. The standard approach to studying sun-tanning is based on psychosocial models, which examine the relationships between beliefs, attitudes,

intentions, personality traits, or normative factors to shed light on an individual's decision to sunbathe. For example, recognition that in one's social group, there is a norm to protect oneself against excessive sunlight can predict an individual's expressed intention to use tanning protection<sup>76</sup>. However, public health campaigns designed to reduce sunbathing based on the standard health education approach of trying to change beliefs and attitudes have not proven effective<sup>77,78</sup>. Neither has increasing people's knowledge led to significant changes in the desired behaviour<sup>79,80</sup>. Most sunbathers seem to know that ultraviolet radiation is not good for their skin, but nevertheless persist in the practice.

An evolutionary approach, on the other hand, leads to an understanding of empirical patterns associated with sunbathing – in particular the fact that women are more likely than men to sunbathe, singles more than married people, and younger people more than older people. Women, despite being more aware than men that sunbathing is unhealthy for the skin, sunbathe more than men<sup>81</sup>. “That so many should engage in behavior so seemingly self-destructive can only suggest that powerful motivating psychological forces are at work”<sup>82</sup> (p. 421). The reason appears to be that, for cultural reasons, in northern societies, cultural values currently associate tanned skin with beautiful, healthy condition. Health and beauty are, of course, important surrogates for reproductive potential, and so getting a tanned skin should be an important goal, particularly for young women in the mating game. As an evolutionary approach would suggest, an intervention focused on a message that emphasized the damaging effects of indoor tanning on appearance (rather than an education message) was effective in changing attitudes, intentions and behaviours, as well as being more effective on younger respondents<sup>83</sup>. Presumably, an approach designed to counter the evolved causes of sunbathing would be even more effective at getting people to protect themselves from the harmful rays of the sun – perhaps by providing alternative means of appearing tanned (e.g., chemical solutions).

In a similar vein, Valerie Curtis, Director of the Hygiene Centre at the London School of Hygiene and Tropical Medicine, was a guest in the UCL EM class one year and ran a workshop for the students. She was able to demonstrate graphically, using a variety of plastic props of disgusting items (such as faeces) that people usually have innate responses to such objects even where they know they are not real. She pointed out that an important problem, especially in developing countries, is childhood infection, largely associated with contact with excreta. In fact, diarrhoea and respiratory tract infections are the biggest killers of children worldwide. Such contact has become endemic due to urban crowding, coupled with a lack of sanitation facilities that can separate people from their waste products. In such situations, hand washing with soap has been shown to reduce the probability of infection by up to half, and respiratory infections by a similar amount<sup>84</sup>.

As a result of these findings, a public-private partnership composed of international funders (such as the Bill and Melinda Gates Foundation), non-governmental organisations, soap-producing multinational corporations and academic institutions has been set up by Curtis and others to design hand washing campaigns in the developing world ([www.globalhandwashing.org](http://www.globalhandwashing.org)). This partnership supervises the implementation of public health programmes at national levels designed to make more people wash their hands with soap, particularly at the junctures which will have the greatest impact on disease reduction, such as after using toilet facilities.

Obviously, such campaigns could follow the health education model by telling people about the dangers of diarrhoea for their children. However, as in other cases, basing campaigns on fear and information about disease risks have not proven generally persuasive. Inspired by evolutionary psychology, Curtis, together with colleagues, has shown that there is an appropriate emotion to target in such cases: disgust.

Although a wide variety of objects in the environment inspire disgust – faeces, rotten meat, dead bodies, insects, unwanted sexual intercourse – what all of them share is their capacity to serve as habitats for pathogens or as agents of disease. Disgust is an evolved response to avoid environmental disease agents.<sup>85</sup> Contact with infectious agents – and thus diarrhoea and respiratory infections – can therefore potentially be reduced by inducing disgust reactions, rather than appealing to the need to ‘avoid germs’, which a rational health education approach would suggest. Mass media campaigns designed to induce disgust reactions at the important junctures of the day have proven effective at increasing the awareness of the need to hand wash in several countries<sup>86</sup>. Presumably, using such inspirations to develop programmes for other kinds of public health problems with a behavioural foundation would also improve their effectiveness.

Curtis and colleagues<sup>87</sup> have summarized the situation this way, claiming that hand washing promotion:

*‘offers one of the few effective preventive interventions against the two biggest, and most neglected, child killers; the diarrhoeal diseases and the respiratory infections (causing almost 2 million deaths each per year, according to WHO). Rates of handwashing with soap at key junctures around the world are low; typically only 5-15% of mothers do so after cleaning up a child, or after using a toilet, but can be substantially improved if programmes are built on a solid foundation of understanding target audiences and their handwash motivation’.*

The practical benefits of such public health campaigns rooted in evolutionary principles are thus clear. There is a real ability to save not just thousands but potentially millions of lives around the world, if only health promoters take more seriously the insights to be gained from adopting a perspective from evolutionary medicine. The stakes are high and the rewards potentially enormous.

### **Evolutionary Obstetrics**

This is a topic that has been covered in other books on EM, but is worth including here because of the many radical clinical changes that have arisen in obstetrics partly in response to findings that birth companions can significantly improve the outcome of the birth experience for both mother and baby. One guest that was interviewed in class at UCL was a practising obstetrician generally unexposed to evolutionary theory, but cognizant of anthropology, namely Yehudi Gordon.

Yehudi Gordon has become well-known in the UK as a kind of celebrity obstetrician because he is sought out by many well-known individuals in the entertainment industry (such as Cate Blanchett, Gwyneth Paltrow, and Heather Mills McCartney) to

deliver their babies. He now runs a private natural childbirth clinic at the Hospital of St. John and St. Elizabeth in London but has also worked in other hospitals in London such as the Royal Free. Dr. Gordon is distinguished from other obstetricians by his very early incorporation of childbirth practices that are advocated by many anthropologists, and particularly the use of birthing companions to assist in the psychological and physical process of childbirth. He introduced the use of water births for labouring women and other innovations to relax mothers during parturition. The increasingly difficult process of birthing for human females that accompanied the evolution of bipedality and encephalization may have led to the need for a birthing companion who could assist a woman in this process<sup>88,89</sup>. Ellison<sup>88</sup> has suggested that the slowing of labour that arises in contexts where women lack a birth companion may represent an evolved mechanism to delay parturition until help can be obtained. Evidence for this assertion comes from studies of doulas, either lay or professional birth attendants, who provide emotional support during the birthing process even if they are previously unknown to the woman in labour. Statistics from such studies show significantly fewer perinatal and postnatal complications including oxytocin administration, emergency Caesarean sections, and meconium discharge, and that doulas are also associated with faster labour times and better breastfeeding success in women<sup>90,91,92,93</sup>.

In his twenty or so years of work, obstetricians such as Gordon have moved obstetric practice back to the acceptance of birth as a natural process as opposed to an illness<sup>94,95</sup>. Gordon has shunned practices such as shaving of the pubic hairs, enemas, episiotomies, use of the lithotomy (or prone) position during childbirth which are practices still used in many countries including the UK and USA and which have been shown, in many cases by the Cochrane Collaboration (a group that studies the results of clinical trials) to have either adverse or neutral impacts on the childbirth process<sup>96,97,98,99,100</sup>. But, at the same time, Yehudi Gordon was explicit in class about the still appropriate clinical aspect of obstetrics, its role in reducing maternal morbidity and mortality, and the concept of “natural” childbirth in all its meanings:

*Natural versus unnatural? I mean it depends on your perspective? Is it natural to give birth in a tribal hut in Kenya . . . the active birth pictures from our hospital – they’re definitely not natural cos you’re in a concrete building which has got central heating, it’s got fans . . . it’s got facilities downstairs so that if anything goes wrong for mother or baby we can perform a Caesarean or deliver the baby with forceps, so there are degrees of natural . . . In that context, even on the Birth Centre, almost nothing is natural, but it’s a little bit closer to nature than in some other places. If you look at the natural maternal mortality when I worked in South Africa . . . (it) was one in 500, and the maternal mortality in the UK is under one in 10,000, so it’s 20 times at least as safe to have a baby in the UK. So, actually, we’re better than nature, but what’s the cost, the cost is a lot of intervention . . .*

*Now you can achieve massive reductions in maternal mortality and perinatal mortality with very simple things like hygiene, and a few instruments that you cut the cord safely, and don't introduce infection, and women better nourished in pregnancy, and then you'll get most of that, probably about 85%, but then to get the other 15%, you've got this massive resource, a massive amount of money being spent . . .*

Whether or not the field of Obstetrics generally recognizes the role that evolutionary anthropology has played in contributing to the literature about more natural methods of childbirth is unclear, but it is undisputed that in recent years, the practical benefits of these realizations are being applied in at least some clinical settings.

### **Conclusion**

In order to counter early criticisms of the field that it had little relevance to medical practitioners, this paper has attempted to cover some areas in EM which have very clear and practical applications to clinical medicine and that have received less coverage in earlier volumes. Clearly there are many areas in EM that are successfully merging with evolutionary biology while retaining relevance for improving treatment and health for patients, as well as enhancing our understanding of the origins of specific conditions. Increasing attention to such areas in EM will potentially deflect criticisms of this field that it has little relevance to medical doctors, and raise awareness of the practical nature of many sub-fields within this emerging discipline.

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