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Lifetime experiences, the brain and personalized medicine: An integrative perspective

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ABSTRACT

The aim of personalized medicine is to base medical prevention and therapy on the unique health and disease susceptibility profile of each individual. Starting from this idea, we briefly discuss the meaning of the word 'personalized' before analyzing the practical content of personalized healthcare. From a medical perspective, knowledge of a person encompasses both biological and biographical perspectives. The latter includes significant events and experiences throughout the person's lifespan, from conception to the present, in which epigenetic influences play an important role. In practice, we believe personalized medicine should emphasize the development and maintenance of a healthy nervous system. The neurobiological processes involved here depend heavily on the psychosocial environment, in particular the presence of responsible, caring adults and integration in a reasonably fair society. A healthy brain subsequently promotes good health throughout life, both through direct, favorable influences on the body's intrinsic biological pathways, and indirectly by enabling the person to engage in supportive relationships, make wise decisions and take good care of him/herself. From a public health perspective, we conclude that hi-tech personalized medicine based on detailed bio-molecular mapping, monitoring and tailored drug interventions holds promise only as part of a wider, socio-culturally informed approach to the person.

1. Introduction

The goal of 'personalized medicine' to base clinical decisions on the unique health profile of each individual is currently being fuelled by a rapidly increasing scientific insight into the enormous individual differences that exist among people, and a corresponding ambition to build this new knowledge into medical thought and practice for the benefit of patients and society [1]. Once one looks closer at the notion 'personalized' from a medical perspective, however, semantic uncertainties emerge. What types of individual differences are to be taken into consideration? Some definitions of personalized medicine are far more open-ended than others. Consider the following two definitions; (http://www.genomichealthcarestrategies.com/personalized_medicine.html):

The Nature glossary: "The use of genetic susceptibility or pharmacogenetic testing to tailor an individual's preventive care or drug therapy"; The Duke Institute for Genome Sciences & Policy, glossary: "The use of a person's clinical, genetic, genomic, and environmental information to select a medication, its dose, or to choose a therapy, or recommend preventive health measures."

The difference between these two definitions contains more than one might think at first glance. The former is restricted to the individual's bio-molecular profile, while the latter opens for an unlimited range of "clinical and environ-

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mental" information and thereby also explicitly indicates that therapeutic/ preventative intervention can involve more than drug interventions. It is the contention of this article that personalized medicine (both for preventative and therapeutic purposes) should emphasize the fundamental, biomedical significance of a person's lifetime experiences, defined in a wide sense [2].

2. 'Personalized' implies integrating biology and biography

By definition, knowing a person encompasses both naturalistic and humanistic perspectives [3]. Rather than personalized, the term individualized seems appropriate to denote the tailoring of medical interventions to match the patient's biological profile, including genetic and epigenetic traits. Individualized healthcare becomes personalized only when the clinician responsible for a particular patient has also familiarized her/himself with this patient's life-world (See BOX 1). In the following, we argue that personalized medicine needs to encompass the significance of major lifetime events and experiences, because human experience becomes "inscribed" in the developing organism, from conception into the present [2,4]. Such a biological–biographical approach is in concordance with the spirit of Integrative Medicine (http://www.iom.edu/Reports/2009/Integrative-Medicine-Health-Public.aspx). Importantly, the idea of biological–biographical integration also includes exposure to physical stressors, such as pollutants and toxins, noise, radiation, and climatic extremes [5].

Several closely intertwined topics need to be considered as we try to conceptualize how the human brain and body interact with experiences over the life course. These include epigenetics, the nature of the stress response, and the fundamental impact of experiences on a person's brain development and health. In the following, we will review these topics before summing up their implications for a truly personalized, preventive medicine.

3. The molecular starting point: genes, environment and epigenetics

The term "epigenetics", coined by Waddington [6], refers to characteristics of an organism acquired during differentiation and development. It refers to all influences on phenotype "above the genome". A favorite model for visualizing such changes in gene expression was the "puffing" of genes in the polytene chromosomes of Drosophila salivary glands (see [7]). We now know that proteins play a key role, along with other factors, in the folding and unfolding of DNA and in DNA methyation. This knowledge has galvanized a new view of epigenetics in which identical twins are found to differ in gene expression because of changes in methylation caused by factors such as diet, chemicals in the environment and relational experiences during early development, including caregiver–infant interactions [8,9].

Finally, with the sequencing of the human genome and recognition of allelic variants in genes that alter phenotype, including risk for disease, a new concept has emerged, that of "reactive alleles" — the concept that some gene variants increase, while others decrease, the potential for environmental influences [10]. This can be exemplified by the serotonin transporter gene alleles and other gene alleles that have been linked to anxiety, substance abuse and mood disorders [11,12]. However, a "reactive allele" may, in fact, give rise to better outcomes in a nurturing environment, and individuals with those alleles have been termed "orchid children" whereas those with the less reactive allele are "dandelion children" and can do reasonably well in any environment.

4. How humans adapt to challenges: the stress response

Protection and damage are two contrasting sides of the physiological systems involved in helping the human body adapt to the challenges of daily life, whether or not we call them "stressors". Systems promoting adaptation include the hypothalamic–pituitary–adrenal (HPA) axis; the autonomic nervous system; the metabolic system (including the thyroid axis, insulin, other metabolic hormones); the gut; the kidneys; and the immune system (including the regulated network of cytokine producing cells throughout the body). Importantly, the activity of these mediating systems and biochemicals is closely coupled to the psychological and genetic make-up, developmental history, and behavioral state of the individual [13,14].

The term "allostasis" was introduced by Sterling and Eyer [15] to refer to the active process by which the body responds to daily events and maintains homeostasis (allostasis literally means "achieving stability through change"). The term "allostatic load or overload" was introduced to refer to the wear and tear that results from either too much stress or from inefficient management of allostasis, such as not turning off the response when it is no longer needed [16–18]. Other forms of allostatic load/overload involve not shutting off the response efficiently, or not turning on an adequate response in the first place, or not habituating to the recurrence of the same stressor and thus dampening the allostatic response. These differ among individuals, both as a result of genetic endowment and life experiences.

The body's stress response involves release of various biochemicals that can both protect and damage the human body [17]. They enable us to tackle numerous challenges, stressors and activities even in everyday life, such as getting out of bed in the early morning, pushing ourselves to tackle a deadline, or working out in the gym. In the presence of adequate recovery and relational support, such challenges and stressors can evidently be health-promoting. In contrast, a chronic state of unbuffered stress is pathogenetic and associated with many complex and prevalent diseases [12]. Chronic stress may for instance lead to elevated blood pressure and low-grade inflammation. These can over time contribute to the development of atherosclerosis, strokes and myocardial infarctions [17]. Both protection and damage involve a network of non-linear, interacting mediators that work concurrently on all organs of the body, including the brain — the key organ involved in stress and adaptation [19].

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5. The keystone of prevention: growth and maintenance of a healthy brain

Human lifetime experiences have a profound impact on the brain, both as a target of stress and allostatic load/overload and as a determinant of physiological and behavioral response to stressors. The interaction of genes and experience shapes the architecture of the developing young brain, and the active agent is the "serve and return" nature of children's relationships with the important adults in a child's lives. (www.developingchild.harvard.edu) The mutual interrelatedness of brain and experience can be regarded from different angles:

- A well-developed brain lays out a fundamental premise for good health throughout life, both through a direct, favorable influence on the body's intrinsic biological pathways (including the physiological stress responses), and indirectly by enabling the person to engage in supportive relationships, make wise decisions and take good care of him/herself. The brain stores the memories that come to constitute the unique person and thereby plays a central role when the person determines what is threatening and how to respond to a challenge.
- The brain is, like other essential organs in the human body, a primary target of physiological stress responses, for better or worse. The hippocampus, a particular brain system supporting memory and mood, was the first area besides the hypothalamus to be recognized specifically as a target of stress hormones [20]. Importantly, stressful experiences and associated changes in the release of stress hormones produce both adaptive and maladaptive effects on the hippocampus, hypothalamus, and other brain regions throughout life [21]. For example, the amygdala (important for detecting and responding to threats in the environment) and areas of the prefrontal cortex (important for decision making and regulating emotions, impulsivity, and autonomic and neuroendocrine function) are also targets of stress processes [13].

6. Brain plasticity throughout the lifespan

It is important to understand that the human brain possesses a life-long and clinically significant capacity for reversible, structural plasticity. In the hippocampus and medial prefrontal cortex, chronic stress causes dendrites of neurons to shrink and become shorter and less branched, with an accompanying reduction in synaptic input [21]. This reduces the person's capabilities for nuanced cognitive function, memory and self-regulation. Glucocorticoids of the adrenal cortex and excitatory amino acid transmitters in those brain regions participate in the depolymerization of the cytoskeleton and shrinkage of dendrites, by a process that is largely reversible at the end of stress, at least in the young adult brain [21]. With aging, there is some loss of resilience — that is shrinkage of dendrites occurs but recovery is impaired. In contrast to hippocampus and the medial prefrontal cortex, the basolateral amygdala and orbitofrontal cortex respond to the same chronic stress by expanding dendrites and increasing synaptic input, which lead to increased anxiety, vigilance and aggressiveness [21]. Early life events also affect how these brain regions develop, as will be discussed below.

Stress-induced changes in brain regions in the animal models discussed above are mirrored by findings for the human brain that include shrinkage of the hippocampus in prolonged major depression and Cushing's disease, as well as in post-traumatic stress disorder (PTSD) and Type 2 diabetes [13]. In PTSD, a smaller hippocampus, possibly a reflection of low self esteem [22], is recognized as both a risk factor for PTSD, as well as a target of chronic stress associated with PTSD [23]. There is also a smaller hippocampus reported in chronic jet lag, as well as after a 20 year history of chronic perceived stress and also with increased levels of systemic inflammation as well as a lack of exercise [13]. The amygdala is more active in anxiety disorders and depression, while the prefrontal cortex becomes less efficient with lack of exercise and also with higher levels of perceived stress. Regular moderate exercise has been shown to improve prefrontal cortical blood flow and function in decision making and also enlarge the hippocampus within a time frame of 6–12 months [13,24].

The human brain appears not only receptive to favorable physical stimuli, but also to supportive relations and work with meaning throughout life. Structural brain changes have been associated with successful psychotherapy (see ref [4]). It is claimed that psychotherapy can be considered an 'epigenetic intervention', alongside with drug therapy [25].

The health of a person's brain is not only important for effective processing of inputs from the external environment, it also controls adjustments of the body engendered by behavioral states like waking, sleeping, lying, standing, and exercising. These bodily adjustments promote adaptive activities, such as locomotion, and promote coping with aversive situations and discrete stimuli, such as noise, crowding, hunger, excessive heat or cold, and other threats to the person's integrity and safety. In sum, changes in the neural architecture of key brain regions, will affect how the person handles daily experiences, so as to either increase or moderate how a variety of experiences affect the rest of the body and ultimately, the fate of the individual.

7. Early life experiences become biologically inscribed

Animal models have taught us that prenatal stress of the mother can impair features of normal brain development [26] and that prolonged separation of infant from mother also impairs other aspects of brain development and function [27–29]. On the positive side, good maternal care and consistency of that care are powerful determinants of life-long patterns of reduced anxiety and efficient stress reactivity as well as social and cognitive development [30–32]. Moreover, there are transgenerational effects that appear to be behaviorally transmitted by the mother to the female offspring [33]. In contrast, inconsistent maternal care and maternal anxiety, for example, from food insecurity, produce

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anxiety in offspring and appear to contribute to metabolic syndrome and predisposition to diabetes, which itself has adverse effects on the brain [34,35]. Thus, the behavioral and physiological consequences of early life abuse and neglect are profound, and the epigenetic concept of behavioral transmission of abuse and its effects on human brain function are being explored at the level of epigenetic regulation of gene expression [36].

During the last 10–15 years, a number of studies have documented that stress becomes bodily inscribed also in human fetuses and children, with major implications for health throughout the lifespan (eg, [13,37]). Allostatic overload and epigenetic mechanisms shape the developing brain and body's biological vulnerability to disease, as well as its responsiveness to potential interventions [17]. Of particular relevance for children are experiences of abuse and neglect [38]. On the physiological level, adverse childhood experiences are associated with dysregulated cardiovascular, metabolic and immunological functions, which in turn feed into numerous disease conditions both in the somatic and psychiatric domains, according to current classification systems [38]. Chaos in the home and inconsistent parenting impair brain development. This can lead to disturbed cognitive function, instable mood, low self esteem and numerous unhealthy activities, including overeating, substance abuse, sexual acting-out and other forms of legal or illegal risk-taking [39]. For example, a 10 year history of a child growing up in a home where the mother has chronic depression is associated with the child having a larger amygdala [40]. Furthermore, low self-esteem and locus of control are associated with a smaller hippocampus and a lesser ability to turn off the cortisol stress response [22]. And children growing up without adequate verbal stimulation and in chaotic, unstable home environments are vulnerable to impaired cognitive function, increased systemic inflammation, cardiovascular disease, substance abuse, anti-social behavior and depression [41,42].

8. Social gradients and the biology of disadvantage

Beyond close relationships in childhood, the wider social and physical environment also has a fundamental impact on health. Studies on animals from rodents to infra-human primates have revealed widespread effects of social hierarchies on the brain, as well as on the stress responsive, immune [43] and cardiovascular systems, including the development of atherosclerosis where at least some of these effects are different between males and females [21].

Clear parallels exist in human society. The well-established epidemiological concept "the social gradient in health" can to an increasing extent be seen in light of a recently launched physiological concept; "the biology of disadvantage" [44]. Differences in income, education, and societal standing in a wider sense, collectively referred to as "socioeconomic status" (SES) have significant effects on mortality and morbidity for a number of diseases, with low SES faring worse than middle SES and much worse than high SES individuals in industrialized western societies [45]. The SES differences are also evident, in a linear fashion from low to high SES, for predisease conditions such as obesity and metabolic syndrome and fibrinogen, as well as substance abuse, and anxiety and mood disorders [45]. Subjective SES, that is, where people themselves rate their socio-economic position, is also an effective predictor of health status [46]. Possible links include negative affect over such issues as economic insecurity associated with low SES and sense of control related to socioeconomic position and self-esteem [47]. There is now some initial evidence that subjective SES is related to differences in volume of a key brain structure, the prefrontal cortex [13].

9. From evidence to action: personalized prevention in real life

We currently find ourselves in an environment characterized by rapid advance in hi-tech knowledge about genomics, metabolomics and all the other -omics which pertain to the human organism. At the same time, the costs of conventional healthcare are soaring. It is therefore not surprising that a vision of personalized and preventive healthcare evokes huge interest, both among researchers, healthcare planners and investors. In relation to medical prevention, the aspirations go far beyond any preventative measure known to clinical medicine today: the goal is no longer just to detect and treat individual diseases early, in an asymptomatic stage. The aim is to identify and intervene in pathogenetic biological trajectories even before they develop into specific disease patterns. For this purpose, it has been suggested that the health record of any given individual will soon encompass more than a billion data points, repeatedly monitored over time with the help of advanced computer algorithms [1].

This hi-tech vision of personalized medicine might seem compelling, and some elements of it might prove realizable. Nevertheless, the most radical and cost-effective form of medical prevention does not apply a natural science focus on biological pathways but rather a humanistic focus on relational and societal factors which have a profound and fundamental effect on health and disease development. During the last two decades, natural science research has brought groundbreaking, new insight into the interrelatedness of biology, experience and social arrangements [4]. Sir Michael Marmot refers to the fundamental relational and socio-cultural health determinants as "the causes of the causes" (http://www.bmj.com/content/341/bmj.c3617.short?rss=1); see also [48]. No systematic preventive intervention will ever match the health promoting impact of being brought up by responsible and caring adults and having access to decent education. So, in practice, if it is the ambition of 'personalized medicine' to foster health on the most fundamental and sustainable level, it should direct its focus to the family and the wider society into which new individuals are born. As noted earlier, genetic differences are evidently important [10], but beyond genes, consistent and good parental care is what matters the most to foster biological health. Exposure to novelty and to challenges against a backdrop of stable caregiving is key.

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The recent policy statement from the American Academy of Pediatrics represents a major step:

"As trusted authorities in child health and development, pediatric providers must now complement the early identification of developmental concerns with a greater focus on those interventions and community investments that reduce external threats to healthy brain growth. To this end, AAP endorses a developing leadership role for the entire pediatric community – one that mobilizes the scientific expertise of both basic and clinical researchers, the family-centered care of the pediatric medical home, and the public influence of AAP and its state chapters – to catalyze fundamental change in early childhood policy and services. AAP is committed to leveraging science to inform the development of innovative strategies to reduce the precipitants of toxic stress in young children and to mitigate their negative effects on the course of development and health across the life span." [49]

Programs like Head Start have worked best when the family environment supports the child and the child comes home to a stable and understanding environment. The Perry School Project (http://www.highscope.org/Content.asp?ContentId=219) is an example of this combination and has shown a large return on investment not only in earnings and achievement for the individual but also for society in terms of less crime and less need for special education, welfare and greater income tax revenue. Programs like Nurse–Family Partnership (http://www.nursefamilypartnership.org/) provide social support and education for first time mothers and families, and the Harlem Children's Zone Baby College (http://www.hcz.org/) is an attempt to provide this type of education in a class for expectant mothers and their partners. Yet we must not give up on those who have suffered the effects of adverse childhood experiences; those interventions will help the individual compensate for early life stress. Yet they require considerable time and effort and further underscore the need for prevention.

Throughout adult life, some experiences and activities remain health promoting, no matter the background and biography of the person in question. Social integration and support rank high on this list [50]. But these premises may be more or less beyond the person's control, and then it is important not to dismiss more traditional "lifestyle" factors; physical activity, sufficient sleep, a healthy diet, and abstinence from smoking and abuse of other substances. On a physiological level, these "life-style interventions" all buffer against allostatic load. And they can sometimes represent equally effective or even superior alternatives to drug treatment [21].

10. Closing remarks

The vision of a hi-tech personalized medicine, based on detailed bio-molecular mapping, monitoring and tailored drug interventions is profoundly fascinating and we believe it holds a certain promise. But in our opinion, this path is sustainable and responsible [51] only if seen as one element of a wider socially and culturally sensitive approach. Only then will personalized medicine do justice to the nature of human beings and hopefully be able to live up to expectations.

11. BOX 1

11.1. *Biology and biography — the narrative side of personalized medicine*

An authentic case history, presented with permission from the patient. Elina is a woman in her late 50s, working full-time at a teaching hospital. She comes to see her new primary care physician because of exhaustion and a painful right shoulder. Elina feels unable to work and says she needs a sickness certificate "for a week or so". The doctor asks what is going on in her life, and Elina explains: During the preceding two weeks, she has lost both her parents. First her father passed away, and a couple of days later, her mother died. Two months before all of this, a very dear, male cousin in his 30s died from a slowly growing, destructive brain tumor.

"It feels like I have hit the wall", Elina says. "I have no energy, and my shoulder is killing me". Towards the end of the consultation, she briefly mentions that she feels haunted by memories of the look in her mothers' eyes in the hours before her death at the nursing home. Elina describes it as a look of appeal or desperation. Yet, the healthcare personnel present at the deathbed never thought that her mother explicitly suffered.

The doctor finds it easy to understand Elina's fatigue, but something about the patient still puzzles her. She however finds it best to inquire no further — Elina might think the doctor does not see enough reasons for her to call in sick.

Regarding her painful shoulder, Elina has recently consulted an orthopedic surgeon, who recommends an operation. But she has no energy to tackle an operation right now and wants a second opinion. The primary care doctor feels it is best to wait. She fills in a sickness certificate and suggests that the local priest might help Elina work through the losses and the memories which seek upon her.

Four weeks later, Elina comes to see her doctor for the third time, as agreed. She is still tired, but the look in her eyes has changed now.

Elina tells the doctor that she has been seeing the priest. And the priest has helped her tell a story she has hardly shared with anyone for over 30 years, from the time when the tragedy happened: her first child, a boy, died from a domestic accident when he was only one year old. This experience was, and has remained, so overwhelmingly painful that Elina has never talked about it. She is long since divorced from the father of the dead child, but she sometimes visits the little boy's grave together with her understanding current husband. But beyond this, the death of her little son has been silenced.

As Elina's story becomes a shared story in the consultation room, the atmosphere becomes filled with lightness and awe. Patient and doctor smile at each other in somewhat a bewildered manner, moved by a new and mutual understanding of the situation. Deep down, they both realize that Elina's grief has not only represented a burden on her mind, but also a strain on her body's adaptive physiological systems.

In the weeks following the sharing of the story of the dead child, Elina's shoulder gradually becomes less painful. It is by no means healed, but Elina is confident that an operation is not worth any risk of complications.

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About 10 weeks after her initial visit, Elena feels ready to start work again. The doctor agrees. "But I have been wondering…", the doctor says, "…about your mother's eyes?" Elina is quiet for a few seconds before responding: "It might sound strange to you, what I intend to say now. My mother and I were quite close. Her life was never easy but she always tried to help me, the best she could. I have come to think about the look in her eyes as her way of helping me, even in her final hours. She did manage to push me, to finally seek some help for myself. I realized I could not go on like this any longer… Therefore, I am no longer bothered, I feel grateful."

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