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Conditioning of the body as healthy medicine

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Abstract

At this time, heart conditioning, which is hormetic stress on the cardiovascular system, is utilized as a healthy strategy, compatible to the heterochronic parabiotic model, in the reversion of disease and aging! The other body systems such as lung and gut conditioning can be utilized as healthy strategies as well. Thus, conditioning of the whole body is a possible healthy medicine, which can oppose, tolerate, treat and reverse disease and aging.

Keywords: heart conditioning; heterochronic parabiosis; healthy medicine hormetic stress; healthy medicine

Heterochronic parabiosis

150 years ago, parabiotic experiments proved that there is reversion of disease and aging (healthy regimen) !

Claude Bernard first pointed out in 1878 that the survival structure of living organisms exists in the fluids bathing them (internal environment or extracellular fluid), and that all physiologically important mechanisms depend on stability such as a stable internal environment or homeostasis[1].

The use of two animal parabiosis to explore their interactions in vivo or circulating factors (extracellular fluid) has been scientifically studied for at least 150 years. Another variant technique, heterochronic parabiosis (Figure 1), is conjoined young and old animals to explore systemic factors of aspects of aging or aging-related diseases, also has a scientific history.

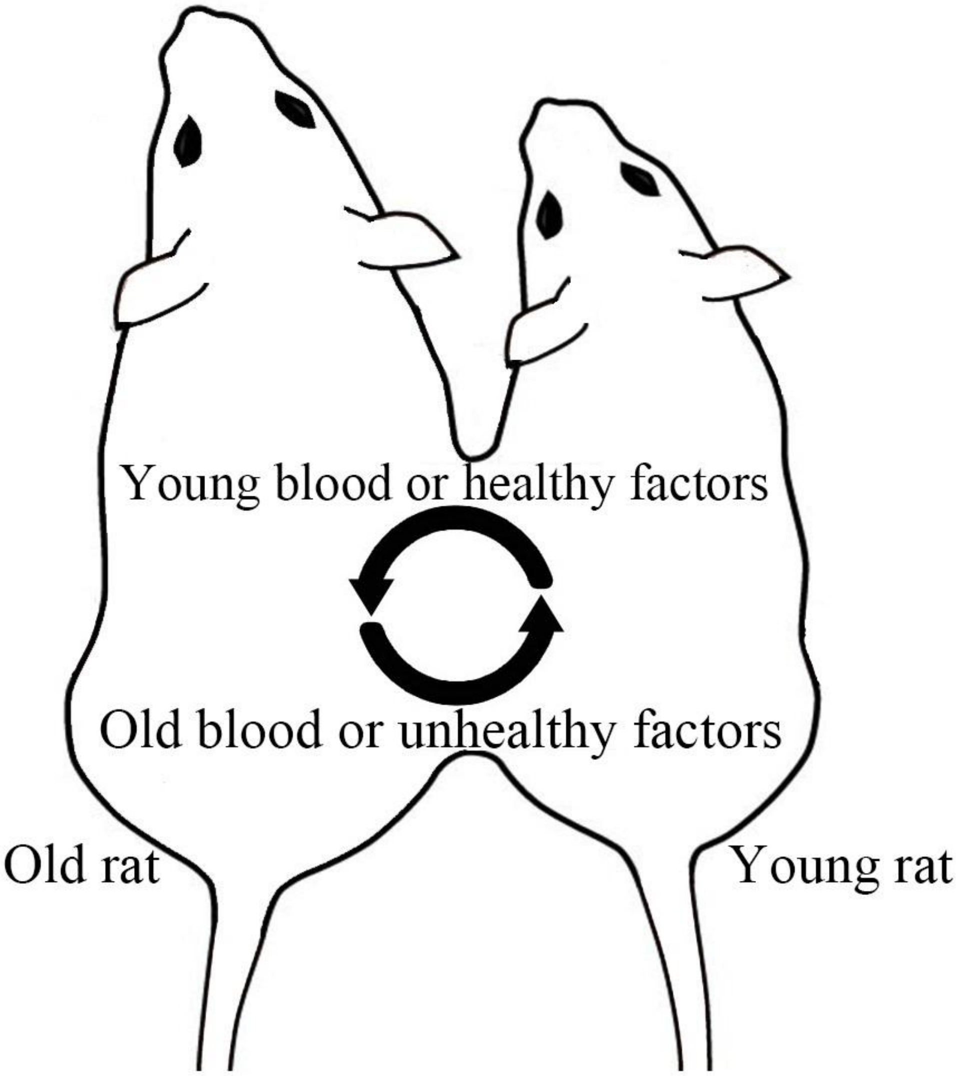

Figure 1: Heterochronic parabiosis: Young rat giving young or healthy blood or factors to the old rat, whereas old rat giving old or unhealthy blood or factors to the young rat. In the old parabiont, therefore, there is provision of healthy factors, at the same time removal of unhealthy factors.

Parabiosis refers to the surgical connection of two living animals to live together and create a single, shared circulatory system. With this technique, two animal conjoins, usually adjacent to the loin on both sides, creating a shared blood circulation. It has been reported that conjoined with healthy animals can extend the lifespan of laboratory animals with fatal diseases or lethal treatments such as radiation[2]. Conjoined with healthy animals, rats with primary muscular dystrophy can extend their lifespan[3].

In the heterochronic parabiotic experimental model, when two animal circulatory systems are connected, the old animal regains its youth[4]. When exposed to a young environment, older stem cells acquire younger potential, whereas when exposed to an older environment, younger stem cells lose their ability to regenerate[5]. Conjoined experiments have also shown that the function of stem cells in liver, spinal cord, and brain in the elderly conjoined animalsis improved[5,6]. In contact with the aging environment, the formation of muscle and nerve cells in young animals is inhibited[5,6]. Ruckn et al. report that a young systemic environment can enhance the brain's recovery from experimentally induced demyelination[6]. Loffredo et al. used the old and young conjoined animal model to point out that the heart hypertrophy and loss of normal heart function in old conjoined animals are reversed by the young internal environment[7]. Huang et al. report that the young systemic environment not only enhances the autophagy function of the elderly kidneys, but also reduces inflammation in the old kidneys, thereby reducing kidney tissue damage and improving kidney aging[8].

In the heterochronic parabiotic model, the old parabiont receives young blood or healthy factors from the young parabiont, at the same time gives old or unhealthy blood to the young parabiont, thus removing the old or unhealthy factors relatively. We propose that this advantageous cycle with implementation of healthy factors and removal of unhealthy factors simultaneously (Figure 2), may modulate the unhealthy or old cell and give rise to a healthy or young cell, leading to reversion of disease and aging, as shown by the above findings[9].

But humans cannot be conjoined. Therefore, this only effective healthy regimen in the world at this time was set aside.

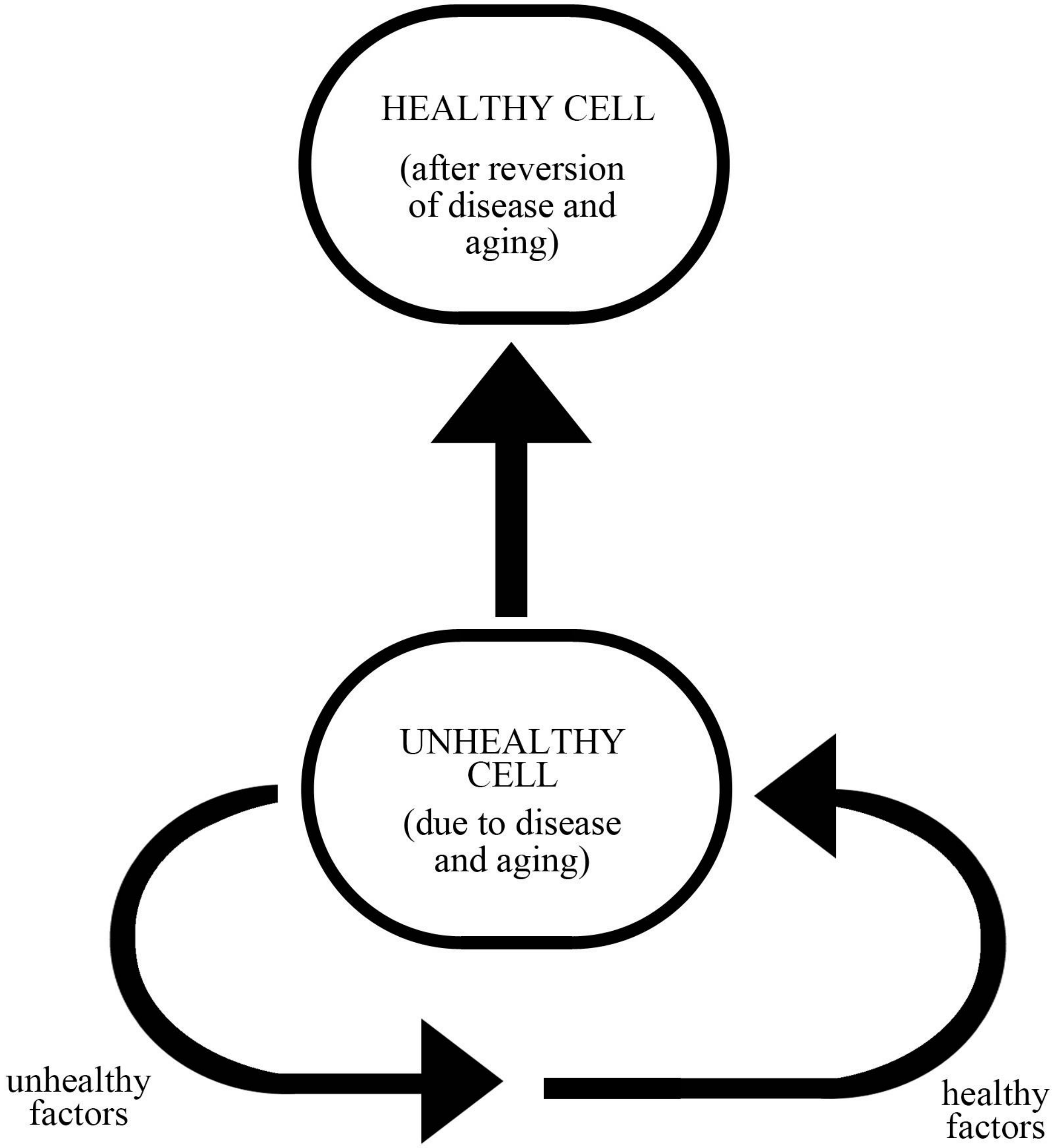

Figure 2: Healthy regimen for reversion of disease and aging: An advantageous cycle with provision of healthy factors (such as conditioning of whole body, healthy diet, regular exercise etc.) and removal of unhealthy factors (such as stop smoking, alcohol, drug abuse, stress etc.) simultaneously.

Heart Conditioning

As yet, heart conditioning, which is hormetic stress on the cardiovascular system, is utilized as a healthy strategy, compatible to the heterochronic parabiotic model, in the reversion of disease and aging![9] The common relation or mechanism of heart conditioning and heterochronic parabiosis is “the extracellular fluid”. Heart conditioning is a stress, eliciting the release of factors in the extracellular fluid. The pairing of old and young animals (heterochronic parabiosis) is the interchange of factors in the extracellular fluid. Both involve the extracellular fluid[9].

Ischemic preconditioning was discovered by Murry et al. in 1986. A brief (five-minute) repeated occlusions of the coronary artery before the subsequent sustained occlusion reduces the extent of myocardial infarction[10]. Ischemic preconditioning has been demonstrated in many animal and clinical trials. Heart conditioning can protect against postischemic contractile dysfunction, ischemia- and reperfusion- induced arrhythmia, apoptosisand infarct injury[11]. This conditioning role of mild, short, physiological myocardial ischemia is recognized as a significant area of heart protection.

Ischemic conditioning has been successfully applied in patients with coronary heart disease. In patients undergoing cardiac catheterization[12] or cardiac surgery[13], heart conditioning improves clinical outcomes. Remote ischemic preconditioning with brief ischemia and reperfusion of a distant organ also guards the heart. It often uses intermittent inflation of a blood pressure cuff to 200 mmHg, with three to four 5-minute inflation separated by 5-minute reperfusion periods[14]. In patients undergoing cardiac catheterization or heart surgery, remote heart conditioning can reduce infarct injury and major cardiac and cerebrovascular adverse events[14]. In addition, it can also effectively reduce the severity of stroke[14].

With mild transient and physiological myocardial ischemia, heart conditioning produces adaptive or compensatory mechanisms, including activation of the neuroendocrine system, cardiac remodeling and other events such as: oxidative stress, vasoconstrictor secreted by endothelial cells, nitric oxide, inflammatory mediators, growth factors, etc. These mechanisms supplement normal factors such as: activation of sympathetic nervous and rennin-angiotensin-aldosterone system, activation of inflammatory mediators required for heart repair and cardiac remodeling, influence heart cell biology, production of protective proteins, activate intracellular enzymes, inhibit mitochondrial death signaling, nitric oxide, etc. At the same time, these mechanisms also remove abnormal factors such as free radicals, cardiac ischemia-reperfusion damage, reduce infarct size, apoptosis, and improve autophagy. Heart conditioning is therefore compatible to the advantageous cycle of the heterochronic parabiotic model (Figure 2), in the reversion of disease and aging.

To briefly recap, mild, transient and physiological myocardial ischemia is a stimulus on the heart that produces compensatory adaptations to maintain the homeostasis and normal functioning of the cardiovascular system, and at the molecular, cellular, structural, tissue, and organ levels. Through this, the heart can be conditioned and protected, as evidenced by the advantageous effects observed following the subsequent ischemia. Therefore, heart conditioning is the most important healthy regimen. Because it can prevent the most common and deadliest sudden death, myocardial infarction and stroke, it can at least reduce its morbidity and mortality. Furthermore, a healthy cardiovascular system interacts and crosstalk with all systems throughout the body. Heart conditioning not only protects the heart, but also protects other organs such as the brain, lungs, kidneys, intestines, against hypoxia and otherinsults such as toxicants, hemorrhagic shock, iodinated radiocontrast media etc.[15]Moreover, it is contemplated that, similar to heart conditioning, the other body systems may in like manner be stressed, conditioned and protected. Hence, evidence that conditioning exists in humans may provide a major impetus to the development of strategies or measures for keeping the heart and the other body systems in a continuously conditioned and protected state, preferably regularly and indefinitely. The human body can recruit a variety of adaptive, compensatory mechanisms to maintain homeostasis and normal functions in response to various stimulus and aggressions. It is becoming increasingly clear that conditioning of the heart and other body system initiate compensatory adaptations to maintain homeostasis, which is the main point of a successful healthy strategy.

Lung Conditioning

In contrast, for the lungs, equivalent or similar to coronary artery, coronary occlusion, and myocardial ischemia are airway, airway obstruction (bronchial contraction or spasms), and ventilation impairment.

Asthma is a lung disease characterized by intermittent and temporary contraction of the airway muscles, narrowing and obstruction of the airway, which significantly increases the resistance of the airflow. Airway contraction (bronchospasm) includes contractions that cause narrowing of the airway such as leukotrienes, histamine, endothelin 1, bradykinin, etc., inflammatory reactions such as edema, inflammatory mediators, mucus secretion and airway remodeling such as wall thickening, fibrosis, decreased flexibility of the lungs, changes in the structure of the airway[16].

Exercise-induced bronchospasm involves narrowing of the airway during or after exercise, resulting in respiratory symptoms such as chest tightness, coughing, dyspnea and wheezing. Exercise-induced bronchospasm can occur in normal people or in asthmatic patients. Exercise-induced bronchospasm has been well described, including that its physiological changes that depend on the intensity of exercise and duration. Exercise of less than 4 minutes does not produce exercise-induced bronchospasm, whereas sustained exercise for 8, 12, or 16 minutes produces the typical exercise-induced bronchospasm response and slowly recovers after 30 to 60 minutes[17]. In addition, repeated exercise within 60 minutes after the initial exercise-induced bronchospasm reaction will produce a milder and shorter bronchospasm than the initial response. This refractoriness is a "warm-up" or "running through" phenomenon, which is beneficial and protective for the airway. This lung conditioning is similar to cardiac ischemic preconditioning, where mild and brief pre-event exercise for about 16 minutes stress, condition and guard the airway, so that subsequent sustained exercise sooner than 60 minutes reduce the latter bronchospasm responses. So although exercise can induce bronchospasm, much evidence suggests that regular exercise and aerobic exercise conditioning can reduce the frequency and severity of exercise-induced bronchospasm. Animal experiments have confirmed that aerobic exercise training can effectively reduce airway inflammation, inflammatory cell infiltration, oxidative stress and airway remodeling, and peribronchial edema and so on, compared with animals not exercised. Human experiments have also confirmed that aerobic exercise training can effectively improve the frequency and severity of asthma symptoms, cardiopulmonary health and normal lung function[18]. Therefore, exercise protocol that can induce bronchospasm response to refractory period are beneficial to the airway and can lead to lung conditioning and protection.

Using a mild brief period of pre-event exercise, lung conditioning produces a "warm-up" or "running through" phenomenon, which can reduce the subsequent exercise-induced bronchospasm response. This refractoriness provides healthy factors such as airway remodeling, improves cardiopulmonary function, and releases protective mediators such as prostaglandin. At the same time, this "warm-up" phenomenon removes abnormal factors such as free radicals, inflammation, peribronchial edema, reduces mast cell mediators, reduces the release of neuropeptides, reduces airway muscle responses, etc.[15]. Lung conditioning is therefore compatible to the advantageous cycle of the heterochronic parabiotic model, in the reversion of disease and aging.

Ischemic and pharmacological conditioning have shown that it can reduce lung damage[19]. Limb ischemic preconditioning can also reduce lung injury due to hemorrhagic shock[20].

Ischemic postconditioning improves pathological changes during ischemia and reperfusion of the lungs and improves oxygenation in the lungs[21]. After remote ischemic preconditioning, hypoxic exercise in healthy adults reduces pulmonary arterial pressure and improves ventilation efficiency and air exchange[22].

Many surgical procedures such as heart surgery, orthopedic surgery, pneumonectomy, lung transplantation, etc., can cause acute lung injury and abnormal lung function. These are the main causes of morbidity and mortality. Remote ischemic conditioning can reduce these adverse events[23].

In summary, regular exercise and aerobic conditioning, as well as remote conditioning, can condition and protect the airway and lungs. It has a beneficial and protective effect during subsequent sustained exercise. This conditioning phenomenon may drive the development of models or methods that can maintain the continuous conditioning and protection of the lungs, preferably regularly and indefinitely.

Gut Conditioning

Calorie restriction is a diet that reduces caloric intake but is nutritionally nourished and can extend the health and lifespan of animals and humans[24]. Fasting improves disease biomarkers, reduces oxidative stress and maintains learning and memory functions. During fasting, cells are subjected to mild stress, and cells adapt to these minor stress to suppress disease[24].

Calorie restriction is typically a 10% to 30% daily reduction in calories from a diet. Intermittent fasting is a considerable amount of calorie restriction (75%-90% of dietary intake) one to two days a week[24]. Calorie restriction and intermittent fasting are equally effective. Calorie restriction combined with intermittent fasting is often applied to produce greater results[24].

To date, there have been no randomized clinical trials to determine the effects of calorie restriction and intermittent fasting, but Muslims who fasted for one month during Ramadan improved insulin sensitivity, blood sugar, and lipid control[25].

Calorie restriction can effectively reduce weight, blood lipids, blood pressure, blood sugar and blood cell volume[25]. Calorie restriction combined with intermittent fasting is associated with weight loss, body fat, and risk of ischemic heart disease[25].

Intermittent fasting increases lifespan, reduces cancer and cardiovascular mortality, improves insulin sensitivity, reduces oxidative stress, inflammation, and reduces the risk of diseases such as diabetes and cardiovascular disease[26].

Clinical trials have shown that calorie restriction can reduce atherosclerosis and improve kidney function. Intermittent fasting reduces weight and metabolic risk factors, reduces insulin resistance, and reduces cardiovascular disease and cancer risk factors[26].

The gut is an organ system whose physiological goal is to absorb nutrients. Calorie restriction and intermittent fasting are nutrient-stimulating stress on the gut that can create cellular defenses or compensatory mechanisms and autophagy, so it plays an important role in the homeostasis and normal function of cells, thereby conditioning and protecting health and organ systems such as muscles, liver, gallbladder, kidneys, heart, nervous system, etc.[27].

With calorie restriction and intermittent fasting, gut conditioning produces compensatory mechanisms including improving cellular adaptation or defense mechanisms, gut remodeling and reduction of oxidative stress, mitochondrial dysfunction and inflammation, and adjustment of gut apoptosis and autophagy[27]. These mechanisms provide healthy factors such as improved disease mediators, improved insulin sensitivity, effects on the endocrine system, improved mitochondrial function, gut remodeling, adjustment of apoptosis and autophagy function[25-27]. These mechanisms also remove unhealthy factors such as reducing blood sugar and fat, reducing oxidatve stress and inflammation, reducing heart infarct injury, and reducing atherosclerosis[25-27]. Gut conditioning is therefore consistent with the advantageous cycle of the heterochronic parabiotic model, in the reversion of disease and aging.

On the other hand, previous studies have shown that preconditioning can have a protective effect on many organ systems such as the nerves, heart, liver, biliary, gut, kidneys, and muscles[15]. Mild ischemia of the gastric mucosa protects against subsequent gastric mucosal damage from continued ischemia-reperfusion. This indicates that the gut also has a preconditioning effect[28]. Using the patient's blood after preconditioning, Zitta et al. report that it protects the human's intestinal cells from damage to hypoxia[29]. In addition, intestinal injury following cardiovascular surgery is believed secondary to intestinal hypoperfusion due to surgery-related factors. Li et al. noted that in patients undergoing abdominal aortic aneurysm repair, cardiac preconditioning protects the function of the intestines[30].

To recap: after calorie restriction/intermittent fasting and ischemic preconditioning, the gut can be stressed, conditioned and protected, resulting in many beneficial effects. This gut conditioning phenomenon may drive the development of models or methods to maintain the continuous conditioning and protection of the gut, preferably regular and indefinitely.

Conditioning of the whole body as healthy medicine

There are 10 organ systems in the body, viz, nervous, cardiovascular, respiratory, digestive, urinary, musculoskeletal, immune, endocrine, reproductive and integumentary systems.

Similar to the heart, lung, and gut conditioning, we can also stimulate, condition, and protect all ten organ systems in the human body. This conditioning phenomenon may drive the development of models or methods that maintain the continuous conditioning and protection of the whole body, preferably regularly and indefinitely.

Therefore, conditioning of the whole body system can produce adaptation, defense and compensation mechanism, which can simultaneously replenish healthy factors and remove unhealthy factors, resulting in conditioning, protecting health and function of many organs and tissues such as nervous system, heart, lungs, intestines and stomach, kidneys, muscles. It is therefore in agreement to the advantageous cycle of the heterochronic parabiotic model, in the reversion of disease and aging.

The performance of conditioning of body systems is a physiological effect, not a drug or therapeutic response. So, conditioning of the whole body can restore or reverse the disease and aging process to maintain the homeostasis and normal function of the body, and then achieve the reversal of disease and aging.

As hormetic stress, heart conditioning can be utilized as healthy strategy.[9]

In the same token, conditioning of the whole body can be utilized as healthy medicine, to oppose, tolerate, treat and reverse disease and aging.

Dr. Zhang Zhongjing of Eastern Han Dynasty 2000 years ago defined the roles of medicine as: 1. to cure disease; 2. to save live and 3. to strengthen vitality so as to keep healthy without disease and aging. In Chinese saying, life is the course of birth, aging, disease and death. By hormetic stress, heart conditioning and conditioning of the body lead to reversion of disease and aging, and is therefore an outstanding healthy medicine.

Author contribution: All authors contributed in the research, data collection and manuscript preparation

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