J Acupunct Meridian Stud 2010;3(4):221–231

REVIEW ARTICLE

Human Ultraweak Photon Emission and the *Yin Yang* Concept of Chinese Medicine

Roeland van Wijk[1]*, Jan van der Greef[2,3], Eduard van Wijk[1,2]

[1]*Meluna Research, Amersfoort, The Netherlands*
[2]*Sino Dutch Center for Preventive and Personalized Medicine, Leiden University, The Netherlands*
[3]*TNO Netherlands Organization for Applied Scientific Research, Zeist, The Netherlands*

Received: Jul 8, 2010
Accepted: Jul 20, 2010

KEY WORDS:
Chinese medicine;
connective tissue;
radical oxygen species;
triboluminescence;
ultraweak photon emission;
yin yang

Abstract
The relationship between connective tissue and meridian function is discussed in terms of energy transmission. The network of hydrogen-bonded water molecules interspersed within the collagen fibrillar matrix is especially significant for both the sensitivity of connective tissue to weak signals of mechanical pressure, heat, or electricity and the electrical intercommunication that may correlate with the meridian acupuncture system. Special electromagnetic properties of connective tissue have similar collective properties of ultraweak photon emission. A relationship between ultraweak photon emission and *yin yang* dynamics is based on three types of ultraweak photon emission studies, focusing on diurnal and annual dynamics, diseased states, and acupuncture points. A novel concept explains the functional (health) integrity of physiologic systems in relation to the left-right balance in ultraweak photon emission by pointing to, (1) balanced corticoneuromusculoskeletal activities and triboluminescent aspects of ultraweak photon emission by skeletal structures, and (2) local fine-tuning in oxygen supply and the formation of radical oxygen species. This approach offers testable hypotheses for further validation utilizing a combination of human photon recording techniques and specialized metabolomics for the estimation of organ-specific oxidative states.

1. Introduction

The revival of Chinese medicine as a system functioning in parallel to Western medicine was already under way by the time of Mao's declaration. Today, *zhong yi* (Traditional Chinese Medicine, TCM) integrates biomedical information with the traditional concepts of TCM. The fundamental concepts of TCM begin with *yin* and *yang*, which represent opposing and complementary phenomena existing in a state of dynamic equilibrium and give a tangible expression to the Dao of ancient Chinese thoughts. The Yellow Emperor's Inner Classic, the oldest text to comprehensively discuss the medical application of *yin* and *yang*, tells us that *yin* and *yang* are the way of heaven and earth [1], and express ideas about normal physiology and pathological processes. The text also explains how *yin* and *yang* could be utilized to correlate the living system experience with health and disease [2]:

As to the yin and yang of the human body, the outer part is yang and the inner part is yin. As to the trunk, the back is yang and the abdomen is yin. As to the organs, the viscera are yin whereas the bowels

*Corresponding author. Meluna Research, Hoefseweg 1, 3821 AE Amersfoort, The Netherlands.
E-mail: rvanwijk@melunaresearch.nl

are yang. The liver, heart, spleen, lung, and kidney yin; the gallbladder, stomach, intestines, bladder, and triple burner are yang.

In addition to the concepts of yin and *yang*, *Qi* is crucial to TCM, representing the idea that the body is impacted by subtle material and mobile influences which initiate most physiologic functions that maintain the health and vitality of the individual. *Qi* is often used synonymously with the term energy, but this conceals its distinct material attributes. Energy is defined as the capacity of a system to do work, while the concept of *Qi* embraces much more; there are many different types of *Qi* in the body. In general, the features that characterize each type of *Qi* derive from its source, location and function, including the functions of activation, warming, defense, transformation and containment. Ultimately, all illness (as defined by TCM) is an imbalance of *Qi* within the body, and signs and symptoms reflect the anatomic location of the disturbance or obstruction of *Qi*. Acupuncture and moxibustion, therapeutic tools utilized to assist in the regulation of *Qi*, are deeply wedded in TCM and are used to provide a specific stimulus to body points that lie along channel pathways and to remove an obstruction. When the flow of *Qi* is unimpeded, the body is in a state of health.

According to classical Chinese theory, acupuncture meridians are "channels" with "meridian *Qi*" flowing through them [3]. These meridians run longitudinally along the surface of the body linking acupuncture points (APs); charts portraying APs and meridians date as far back as 300 BC [4]. Modern acupuncture charts highlight 12 principal meridians serving as "links" between the extremities, trunk and head. "Accessory" meridians include deep internal "branches" originating at specific points along the principal meridians and extending to internal organs. A characteristic feature of acupuncture treatment is the sensation of feeling the *Qi*, which has been compared with capturing the wind. Although we cannot see the wind, we can infer its presence from a boat's filled sails. Biomechanical evidence has been documented regarding the body's response to needle manipulation [5]. Rotation and/or pistoning of a needle by an acupuncturist typically causes an ache in the patient [6], while simultaneously the acupuncturist feels a "tug" on the needle (referred to as "needle grasp") as the needle is manipulated [5]. In both *in vivo* and *in vitro* experiments, acupuncture needle rotation initiated connective tissue winding around the needle, creating a tight mechanical coupling between the needle and tissue, compared with control locations [7,8].

Contemporary Western medical science, based almost exclusively on the concept of cell pathology, generally ignores the concepts of meridian pathways and energy exchange [9], which may be due to the different approaches in Western and Chinese medicine. In Chinese medicine, the emphasis has been on health promotion (salutogenesis) and strengthening the resilience of the system, while in the Western world the emphasis has been on disease management. Over the past 40 years, Western culture has introduced integrative educational healing programs that emphasize acupuncture in particular in fulfilling the need for new prevention and diagnostic principles. In addition, many research studies have focused on understanding the concepts of meridian pathways and energy exchange from a "Western" biological perspective.

This review will address the scientific evidence for an energy/information system in the body that is a property of connective tissue and has distinct electromagnetic and light communication properties related to TCM perspectives.

2. Connective Tissue and Meridians

It has been postulated that the interplay between APs and meridians reflects a network formed by interstitial connective tissue [10]. Histological and biomechanical features have been used to differentiate APs from surrounding tissue [11–13], and this has demonstrated that 82% of all classical APs consist of a composite that includes a blood vessel and a nerve within a sheet of loose connective (mesenchyme) tissue perforating superficial fascia separating subcutaneous from muscle tissue [14]. Analysis of gross anatomic sections of a human arm [5] revealed that more than 50% of meridian intersections are present at intermuscular or intramuscular connective tissue planes, with the probability of such a correlation at $p<0.001$ [5].

Speculation about an interplay between connective tissue and meridian functioning (i.e., energy transmission) would, most likely, emphasize special connective tissue structural features, which might be accomplished by comparing epithelium and connective tissue with respect to the relative contribution of cells and extracellular matrix. Cells in connective tissue are plentiful, but sparsely distributed within the extracellular matrix, and direct attachments between cells are relatively rare. Generally, the extracellular matrix is composed of a variety of proteins and polysaccharides secreted locally and assembled into an organized network. Variations in the relative amounts of these macromolecules and their organization give rise to a diversity of forms, each adapted to a particular tissue's functional requirements; a matrix may calcify to form the hard structures of bone or teeth [15], comprise the transparent matrix of the cornea, or develop into the ropelike assembly that gives tendons their tensile strength [16].

Collagens, the major proteins of the extracellular matrix [17], are a family of fibrous proteins whose fibrillar matrix significantly contains an interspersed and ordered network of hydrogen-bonded water molecules. The hypothesis that such a network supports the rapid jump conduction of protons, a form of semiconduction in condensed matter, has been confirmed by dielectric measurements which demonstrate that collagen conductivity is a function of the collagen fibrillar structure [18]. This conductivity increases significantly with increased water absorption (in accordance with power law relationships) [13]. The conductivity along the length of a fiber has been estimated to be at least 100 times greater than across a fiber's diameter [19]. Dielectric and electrical conductivity properties in connective tissue facilitate greater sensitivity to mechanical pressures, pH, and ionic composition [20,21], and weak signals of mechanical pressure, heat, or electricity may be readily amplified and propagated by a modulation of proton currents or coherent polarization waves [22]. Data also suggest that these special structures (i.e., the oriented nature of collagen liquid crystalline mesophases in connective tissues) may provide channels for electrical intercommunication that may correlate with the meridian acupuncture system. By contrast, APs may correspond to singularities, as gaps between collagen fibers or where collagen fibers are oriented perpendicular to the dermal layer.

The special electromagnetic properties of connective tissue have led to speculation that this highly structured tissue has similar collective properties related to photon emission dynamics. Evidence of such properties has been derived from a fundamental study regarding photoinduced delayed luminescence characteristics of bovine Achilles' tendon [23]. This tendon is a quasi-unidimensional, hierarchically ordered system formed by aggregates of collagen triple helices. The observed delayed reflecting luminescence of the tendon cannot be simply described in terms of excitation and de-excitation of single molecule electronic levels. Instead, it is dependent on the order parameters of the system and, for a description of delayed luminescence, it is necessary to consider the existence of collective electronic states [24,25]. Special photon emission properties have been confirmed using collagen gels and collagen fibrils isolated from rat tails and it was concluded that these collagen structures both conduct and modify photon pulses coming from biological sources [26].

Additional arguments for special optical properties of meridians originate from studies of primo-vessels. These newly described types of microconduits are assumed to be the mechanistic underpinning of acupuncture meridians. In the early 1960s, Bong-Han Kim of North Korea claimed to have discovered such vessels, which appear to exist as a novel circulatory system throughout a living being [27]. These vessels are specially characterized by their high *in vivo* affinity for staining by trypan blue, which distinguishes them from background tissue (dermis, muscles, and similar-looking lymphatic vessels) [28]. The optical properties of primo-vessels have been compared with those of the surrounding tissues, such as dermis and muscles. Application and rapid removal of the stain can prevent generalized spreading of the stain, and the observed high infiltration and staining by trypan blue is histologically understood to be due to its multilumen structure (compared with other tissues), involving loose collagenous openings and pores at the outer boundary.

Light transmittance and reflectance of the primo-vessels have been measured in the 400–700 nm range [29,30], showing lower absorption and scattering coefficients than surrounding tissues (dermis and muscles with Mie scattering dominant in the vessels). Thus the primo-vessels appear more transparent, and able to transport light with high efficiency and act as an optical channel [31].

Since the macrostructure of collagen fibers (but not of cells or organelles) constitutes the transparency of collagenous tissue, it was of special interest to study the light transparency of artificially prepared collagen gels, in particular the phenomenon of ultraweak photon emission (UPE). A preliminary study of collagen gel transparency for enzyme-dependent UPE, produced by the xanthine oxidase/xanthine enzyme system in combination with the enhancer methylated Cypridina luciferin analog, demonstrated that collagen gels increase photon emission, suggesting that the collagen fibril in the connective tissue macrostructure may play a role in light-piping within connective tissue.

3. Biophotons and Their Possible Relationship to the *Yin Yang* Dynamics

Is there a relationship between the *Qi* and the biophoton concept? Intact whole organisms and individual tissues spontaneously emit photons in the visible electromagnetic spectrum. However, does this correlate with TCM suppositions? If this is the case, such correlations should enable researchers to develop objective methods of diagnosis and this could corroborate TCM concepts such as the "eight principles" (*yin*/*yang*, interior/exterior, cold/heat, and deficiency/excess). Balance is one of the essential concepts in TCM (i.e., balances within the function of the body, such as left/right, upper body/lower body, and the dorsal *yang*/ventral *yin*). Evaluation or diagnosis of a patient's physical state is a dichotomic classification according to the "eight principles" and is based upon a practitioner's subjective inspection by listening, inquiring, and palpation. Biophoton emission has been hypothesized to be an effective signal that could be quantified in terms of the "balance" concept [38]. UPE dynamics during diurnal and annual cycles might assist the study and understanding of the "balance" concept. According to TCM, the palms and dorsum of hands provide different diagnostic information. The palm corresponds to the *yin* side, having a passive nature and three meridians providing information regarding the lung, pericardium, and heart, and the hand dorsum corresponds to the *yang* side, reflecting the active nature of body functions related to the large intestine, triple warmer, and small intestine. In addition, the left hand corresponds to the *yin* side and the right hand the *yang* side.

Cifra et al [32] and Van Wijk et al [33] examined the diurnal pattern of UPE from left to right and the palm/dorsal sides of the hands and found that emission intensity is low during the day, rises in the evening, and is high at night for both dorsal and palmer sides. No large differences were found between palm and dorsal side of the hands, but of interest was the shift in emission rate between the left and right hands; there was an intensity increase on the left (*yin*) hand starting around 8 PM, and from 12 PM until 5 AM the left hand emits more than the right. Subsequently, the left side emission decreases and right side (*yang*) increases, being higher between 10 AM and 3 PM [32,33].

The diurnal rhythm of emission was estimated during August to September and showed that, during this period, the dorsal emission rate is lower than the palm (see below). Kobayashi et al [34] demonstrated, using a sensitive charge-coupled-device (CCD) camera, that the photon emission intensity on the face and upper body appeared to display time-dependent changes, with photon emission being weak in the morning, increased in the afternoon, and at a peak in the late afternoon. This diurnal photon emission rhythm of the human body is not a consequence of a change of temperature or microcirculation, and a clear negative correlation of temporal changes of photon emission and cortisol concentrations suggests that this diurnal rhythm reflects changes in cellular metabolic processes under the control of a circadian clock.

Cohen and Popp [35,36] considered long-term periodicity in a systematic study of photon emission from hands and forehead, examining the palms of the hand and the forehead daily for a 9-month period. Recordings demonstrated the preference of left and right hand correlation and a deviating pattern for the forehead. Bilateral hand emission was higher in summer than in other seasons of the year but, unfortunately, the authors did not present data regarding a left/right ratio [35,36]. Jung et al [37] studied human hand photon emission from three healthy subjects for 1 year with weekly measurements of the subjects' left and right palm and dorsum. During the year, average photon emission values depended on the month of the year, with the seasonal fluctuations on the dorsal sides being twice that of the palmar sides [37]. These features could not be explained simply by external conditions, such as sunlight exposure or changes of hand position, and the authors speculated that the *yang* sides of the hands are more active, according to TCM; such activity is reflected in the instability of photon emission rates. It would be very interesting to further explore the relationship between the dynamics of diurnal and annual rhythms in photon emission as well as possible correlations with *yin yang* dynamics according to TCM and Korean Medicine. This hypothetical interpretation should be tested in future studies with a larger number of subjects.

Another approach to studying the "balance" concept could be the study of disease states. The fundamental thought that diseases are caused by an imbalance between the vital forces of *yin* and *yang* is important to consider [38]. It is expected that *yin yang* imbalances will be reflected by biophoton studies and several research groups have already presented data regarding photon emission intensity changes during disease. Cohen and Popp studied a multiple sclerosis patient who exhibited both increased biophoton emission and left-right asymmetry compared with ordinary healthy subjects and suggested that in other diseases, left-right UPE symmetry also may be broken [35,36,39]. Jung et al [39] studied left-right photon emission symmetry from the palm and dorsum of the hands of seven Korean hemiparetic patients and compared that data to data obtained from the hands of 20 self-reportedly healthy participants. They reported that left and right differences of photon emission rates from the hands of the hemiparetic patients were very large in four of the seven patients compared with the healthy subjects. They also reported that, after acupuncture treatment, the biophoton emission differences between the left and right was dramatically reduced; in each case, the lateral difference was normalized after treatment [40]. Lee et al [41] measured biophotons from the palm and dorsum of both hands of 10 common cold sufferers; the common cold is known as one of the diseases originating from a *yin yang* imbalance. Their results demonstrated quantitatively that the left-right photon emission of the palm and dorsal sides were not balanced and changed according to the patients' symptoms. After the recovery from their cold, the biophoton rates of the left-right and palmar-dorsal sides in these patients became balanced once again [41].

A third possibility regarding a relationship between biophoton emission and *yin yang* dynamics arises from research focusing more directly on APs. In early studies by Inaba [42—44], attention was focused on photon emission from APs distributed on the hand and fingers, with emission intensity compared with that from non-APs. The author reported that photon emission tended to gradually decrease from the Shang-yang point to Ho-ku, including the Chuchih points, and that their intensities differed between the right and left [42]. Insertion of a needle or laser beam into an AP enhanced photon emission from other APs [43,44]. Yanagawa et al [45] reported the effect of thermal stimulation using moxa, applied with an adjustable moxa height container to avoid a local painful burn, and reported observation of photon emission from the moxa point. As a control, moxa treatment was carried out on a special cowhide mat that demonstrated no effect on photon emission [45].

In a recent study, UPE intensity was studied during electrostimulation of the JG4 acupuncture active point, using chemiluminescent and fluorescent hydrophilic, hydrophobic, and amphiphilic molecular probes overlaid on the skin and an ultrasensitive CCD camera (Night Owl; EG&G Berthold, Wildbad, Germany). The results showed that electrostimulation of this AP produced weaker biophoton emission (1805 photons/mm^2) than the stimulation of neighboring inactive areas (2744 photons/mm^2) [46]. These data support the view that light producing processes are channeled within acupuncture active points whereas less light is produced or transmitted outside.

Another recent study focused on the light-storage capacity of APs utilizing delayed luminescent (DL) properties of APs and non-APs, with DL measurements performed in combination with impedance spectroscopy. Both techniques are designed to provide useful information regarding possible collective modes of biological systems. Four points of the pericardium meridian were measured on 10 volunteers, with control points chosen at a distance about 2.0 cm from the AP, and DL was registered from an area of about 2 mm^2. Impedance spectroscopy was able to successfully discriminate APs from non-APs, and it was also evident that the impedance of APs varied considerably [47]. DL measurements exhibited variations both in terms of total counts and the time trend, reflecting light storage capacity, and it appeared more difficult for DL measurements to distinguish between APs and non-APs. However, the data, once again, confirmed the validity of the relationship between the dielectric constant of biological tissues and their DL [48].

These facts are promising and could serve to open more perspectives for the investigation of the physiologic foundation and action mechanisms of acupuncture and electroacupuncture. Indirectly, the opportunity arises to better understand the regulatory processes of biological systems and the energy and information exchanges that regulate the possible coherent states influenced by these processes. It is interesting to examine the potential of reactive oxygen species (ROS)/UPE measurements (section 4) within the framework of our current thinking in healthcare. Figure 1 illustrates an oversimplified view of health and disease because the border between health and disease depends on the individual and the environment. Health is not a fixed entity; it is a multidimensional state and varies for every

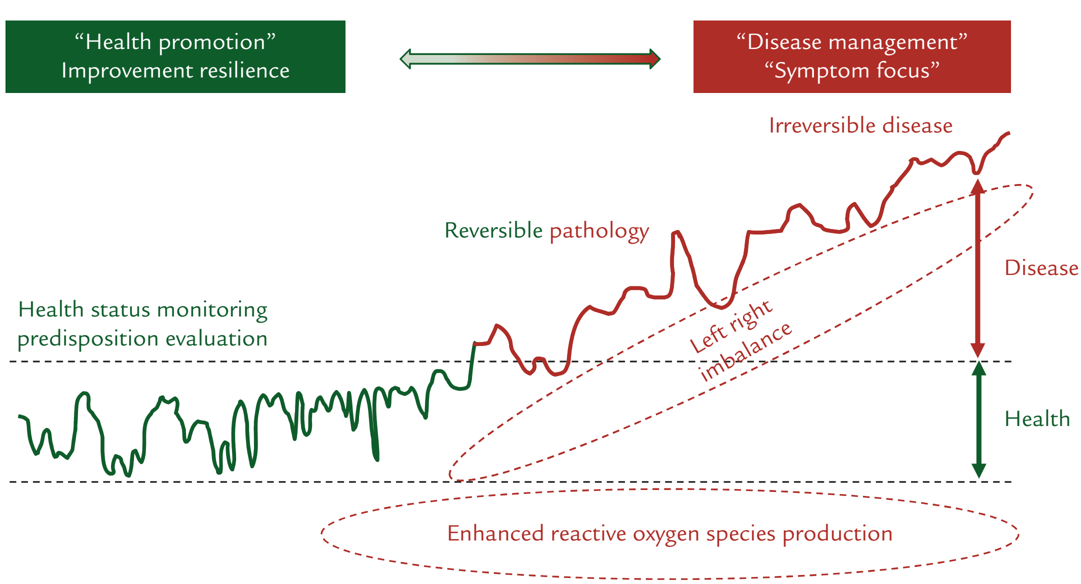

Figure 1 A simplified view of health and disease.

individual, depending on the individual's circumstances. The dotted lines illustrate the boundaries of the situation that is experienced as healthy, with the balanced situation different for each person. When a dynamic situation loses its control capability (homeostasis), it will develop into a disease state. In TCM, the emphasis has been on health promotion (Figure 1, left side), while in the Western world the emphasis has been on disease management (right side). New diagnostic principles should be able to detect subtle changes in the system, presenting a clear opportunity here for utilizing UPE measurement of left-right balance shifts in the system.

4. Anatomy of Human UPE

Over the last several years, considerable research has been done into building knowledge of the anatomic pattern of human photon emission. A study of spontaneous human UPE, by gathering imaging data, began with a systematic multisite recording of 29 anatomic sites. Site selection was designed to obtain quantitative UPE distribution for right-left and dorsal-ventral symmetries, the ratio between central anatomic locations and extremities, and flat versus highly structured anatomy. Recording with a highly sensitive photomultiplier of the 300–650 nm range demonstrated that variation in photon count over the body depended on the subject and on time of day. Recording of emissions in the morning and afternoon demonstrated that emission increase had different patterns and, in many cases, a location with high-emission in the morning exhibited further increase in the afternoon. Although the body emission patterns was highly idiosyncratic, they shared some general features, e.g., the emissions from the hands and head were commonly higher than from other body locations. In subjects with large fluctuations over the body, higher values were also recorded for elbows, knees, and feet and, in such cases, left-right symmetry remained but dorsal-ventral symmetry could not be observed. The latter observation was particularly evident for knees, hands, and elbows. Body parts that were more shaped and structured (elbows, knees, and hands) emitted more than the relatively unstructured, flat body parts and the former structures revealed characteristic differences between anterior and posterior parts. The authors suggest that there might be a correlation with lack of homogeneity of the electrical field of the body surface (a "spike" effect) [49,50]. Overall, the data suggested that a "common anatomic human photon percentage distribution emission pattern" exists corresponding to the above described levels of emission.

Another system utilized to characterize anatomic distribution of spontaneous human photon emission was a two-dimensional imaging technology using a cryogenically cooled CCD camera system operating at −100°C with a dark signal (electronic noise) of $0.65e^-$/pixel/hour and spectral range of 400–900 nm. This system was used in various studies to measure photon emission from the upper frontal torso, head, neck, and upper extremities of subjects and showed that emission intensity around the face and neck was highest and gradually decreased first over the torso and subsequently over the abdomen. There was also a gradual decrease in intensity from the superior central torso to its lateral dimensions. Dorsally, the highest intensity was emitted from the neck and the facial emission was higher than the body. Moreover, photon emission intensity from the face was not homogeneous, with the central areas around the mouth and cheeks, probably teeth, being higher than the orbits. While the hands (both dorsal and ventral) demonstrated relatively high emissions, the nails produced higher emissions than the anterior ventral (fingerprint) sides [34,51–53].

The CCD data above facilitated the selection of 12 anatomic locations from the frontal torso, head, and hands to be used to define a human pattern. Subsequent studies with a larger population of 60 healthy male participants utilizing a moveable photomultiplier system confirmed the existence of a "common" human male body emission pattern and illustrated that photon emission from the abdomen was the lowest, with increased emission along the central axis rostrally to the throat, and the highest values observed over the cheeks [34,51–53].

However, in the above study, the subjects differed in overall emission intensities, with photon counts varying by a factor of four to five. Spectral analysis, using cutoff filters on the photomultiplier and repetitive measurements in the 200–650 nm range, documented major spontaneous emission from 470–570 nm [50].

The etiology of the "common" pattern of emission, the differences in overall emission intensities between participants, and the diurnal and annual fluctuations within a participant are presently under investigation as two major lines of research: the relation of these phenomena to ROS and the mechanical origin of photon emission. Following early research in Eastern Europe, many scientists have used photomultipliers to measure light emitted by ROS-generating systems, such as peroxidizing lipids *in vitro*, and studies have been extended to tissue and whole organisms, with low-level chemiluminescence sometimes called ultraweak chemiluminescence or dark chemiluminescence. This UPE is related to the direct utilization of molecular oxygen and the production of electronically-excited states in biological systems (in particular, oxygen dependent chain reactions involving biological lipids)

[54–59]. In mitochondrial and microsomal fractions [60,61], singlet molecular oxygen appears mainly responsible for the observed UPE, and experimental evidence for singlet oxygen generation has been obtained mainly through the effect of specific quenchers or spectral analysis [61–63]. Both the differences in overall intensities between participants and the diurnal and annual fluctuations within participants may be traced back to physiological conditions. One such situation is the effect of ischemia-reperfusion of ROS. Cell functioning is dependent on the availability of oxygen and the functioning of respiration, a cell-based process in which mitochondrial proteins play a role in energy formation as adenosine triphosphate. As respiration enzyme processes are not perfectly tuned, a small percentage (2–4%) of oxygen ends up as ROS, a proportion that can increase considerably with tuning between metabolic reactions decreases. Tissues made hypoxic or ischemic may survive for various times, depending on the tissue, and respond to ischemia in a number of ways. If the ischemic period is insufficiently long to cause tissue cell death, much of the tissue can be salvaged by reperfusion of the tissue with blood and reintroducing oxygen and nutrients. However, it was shown in the early 1980s that oxygen reintroduction to ischemic or hypoxic tissue could cause additional insult to the tissue (reoxygenation injury) that is, in part, mediated by ROS. The relative importance of reoxygenation (often called "reperfusion") injury depends on the duration of ischemia or hypoxia. If sufficiently long, the reoxygenation injury component may become more important and the amount of tissue remaining undamaged be significantly increased by including ROS scavengers in the reoxygenation fluid. If the reactive oxygen is able to react, it does so with many types of molecules, including DNA, lipids, and proteins and it is clear that such damage can impact mitochondrial function. Free radicals and other "reactive species" play important roles in living systems and have been implicated in the pathology of many human diseases. However, a problem in ascertaining the true importance of ROS and reactive nitrogen species has been that these evanescent species are difficult to measure *in vivo* [59].

For the etiology of the "common" pattern of emission, it was evident that body parts that were shaped and highly structured (and/or mineralized) emitted more than relatively unstructured, flat body parts, which suggests a special role for highly structured connective tissues in UPE. In a few studies, attention has been paid to the photon emission of mineralized connective tissues, particularly from human dentin, bone, and enamel, which display the property of phosphorescence, a long-term luminescence, at a relatively high intensity. This photon emission has been specifically related to the semiconductor properties of these tissues; bone is a specialized connective tissue composed of an organic matrix of type I collagen that is subsequently mineralized with an inorganic phase of calcium hydroxyapatite crystals. The organic matrix provides flexibility while the added mineral confers increasing degrees of material stiffness [64–68]. The main components of teeth include the enamel, dentin, pulp, and the periodontal ligaments. Enamel, the most visible part of a tooth, is highly mineralized to provide strength to withstand the forces of mastication and to protect the dentin. Dentin consists of mostly collagen and forms a structure, termed "a dentinal tubule," that radiates from the dental pulp to the enamel and cementum; dental pulp is at the tooth center where blood vessels and nerves are located. The periodontal ligaments are collagen fibers that hold a tooth in place by connecting the cementum to the jawbone.

Comparing the bone, dentin, and enamel, it has been observed that, at optimum concentration, dentin and bone contain phosphorescent intensities nearly four times that of enamel [69]. The phosphorescence of calcified tissues arises principally from the organic moiety and the diminished phosphorescence of enamel has been explained by qualitative differences in the organic moiety of different calcified tissues [70]. Collagen may exert this control over the apatite structure through surface contact, which would be compatible with the knowledge of bone semiconducting properties in which apatite serves as a P-type carrier and the collagen as an N-type carrier. Apatite belongs to the halophosphates, which are phosphors characterized by their use of two activating elements: one, the sensitizer, introduces an absorption band at the desired location and some of its absorbed energy is transferred to the other element, the activator, which has no absorption band in that region and alone would produce no luminescence.

The phosphorescence in calcified tissues has been suggested to be generated by some of the same luminophores involved in fluorescence. In early searches for these chromophores, fluorescence had been reported under excitation by ultraviolet radiation of 365 nm. The spectral curves of calcified tissue emissions have demonstrated a common pattern consisting of a major peak at approximately 440 nm and the observed fluorescence confirmed the role of apatite and collagen [71]. The separation of collagen and apatite revealed that both decollagenation and demineralization initiated a reduction in fluorescence compared with original, whole bone. This suggests that the role of collagen in the matrix may be to enhance the luminescence of internally bound apatite crystals.

Nails are another example of highly structured hard tissue, with keratin the major protein and its mechanical strength determined, in part, by the content of sulfur-containing amino acid content forming disulphide linkages within its tertiary structure [72]. Phosphorescence studies from nails, however, has not been reported, but it is evident that the relation of the human "common" pattern of UPE related to bone, tooth, and nail phosphorescence, specifically in relation to flexibility and concomitant changes in the organic matrix structure and semiconductor tissue properties, require further research. Such research may also confirm the complexity of connective tissue that results in both its light-piping properties and light storage capacity, discussed earlier.

5. Functional Integrity of Physiologic Systems in Relation to Balanced Corticoneuromusculoskeletal Activities

Discussions of connective tissues and meridians, the photon emission and storage capacities of different connective tissue types, and UPE and *yin yang* dynamics offer intriguing perspectives for developing a more holistic approach to health and disease. In this section, an attempt is made to outline this perspective, which is based on the role of skeletal structures in body integrity and, concomitantly, on the role of the musculoskeletal system in health and disease. Body functions are not dependent on sharply compartmentalized anatomic or self-limiting physiologic systems. Instead, the body functions as a unit and, to understand health and disease, one must consider the total body, and body unity cannot be understood without the musculoskeletal system, which comprises 60% of the body mass.

In evaluating the body as an integral unit, somatic dysfunctions are closely related to, and even diagnosed by, local asymmetry, restriction of motion, and textural changes reflecting fixed skeletal and postural tensions. Literally, this indicates impaired or altered function of related components of the somatic (body frame work) system, comprising skeletal, arthrodial and myofascial structures plus related vascular and neural elements. This notion is well developed in manual therapies such as osteopathy, chiropractic therapy and massage techniques among others, and it has resulted in manipulative techniques facilitating natural symmetry and leading to effective treatment of "somatic dysfunction." Skeletal and joint dysfunction may mimic the symptomology of disease in more remote body systems, and normalization of both the body mechanics and neuromusculoskeletal system is capable of defending against pathologic conditions. Emotional tension, infection, physical training, and immobilization all contribute to irritation, pain, and, in particular, muscle tension, which itself can result in internal tissue ischemia, retained metabolites, edema, and inflammation. These cause-and-effect processes are similar to those seen with the effects of aging on the musculoskeletal system; postural changes and attitude often lead to joint strain, periarticular change, and increased fascial tension. Muscular contraction can result in restricted motion, bone resorption, and alterations in forces of gravity that disturb balance and reduce height.

When considering an organism in its functioning entirety and dynamic movements, a key concept is the distribution of forces that are exerted at the skeletal (bone) structures and dependent on skeletal muscle coordination under the control of sympathetic nerves. The real challenge within the organism is that every movement requires the adaptation of its local supply of oxygen and nutrients. Intriguingly, the brain cortex may be able to coordinate muscle movements in correlation with visual and other sensory information, leading to a key concept of coherence in the motor system which, as a whole, extends from intention to behavior (including brain cortical activity). This extended system is comprised of sympathetic nerve activity and the muscles for motor activity and often named "the corticoneuromuscular network." The documentation of these highly interrelated physiologic activities includes studies of synchronization or cross coherence [73].

The role of coherency has been studied extensively with respect to rhythmic muscular activity. Muscular or motor force is modulated by the combined activity of groups of motor units that produce individual contractions in numerous synergistic and antagonistic muscles. The functional role of motor unit synchronization is to increase the force (e.g., capacity to lift a weight) during rapid contractions of multiple muscles operating in synergy. There is also a remarkable synchronization between human sympathetic activities that have been recorded simultaneously from nerves in both legs or from both arm and leg; observed synchrony was different during certain maneuvers. Corticomuscular coherence has been studied with a focus on task-dependent variation, producing results showing that, in several disorders, abnormal features were observed [74]. Research on sympathetic coherence has been further extended to the synchronization of somatic motor outflow and sympathetic efferent activity during exercise. This coupling represents an exquisite mechanism of fine-tuning, in which, for example, a certain degree of sympathetic vasoconstriction to active muscle vascular beds may be required to prevent an excessive decrease in vascular resistance during intense dynamic exercise involving a large, skeletal, muscle mass. A comprehensive review has been presented by Bischof [73].

In consideration of the supply of oxygen and nutrients to tissues, the essentials of the oxygen supply system, including the heart and respiration system, must include a second major condition. As alluded to previously, connective tissue forms a structural, functional, and energetic continuum extending into all of the body's nooks and crannies, excluding no part of the organism from this matrix. In this loose connective tissue structure, the supply of oxygen and nutrients is regulated by arterioles and very fine capillaries that ultimately penetrate as close as possible to the tissue cells. In almost all tissues, no direct contact occurs between tissue cells and capillaries, yielding a "transit area" where substances, such as oxygen, nutrients, and excretion products, are exchanged between the capillaries and nearby cells.

It can be concluded that the corticoneuromusculoskeletal network involves considerable intrinsic tuning, possibly regulating local fine-tuning of specific motor tasks requiring oxygen and nutrient supplies to yield optimal metabolic processes. The consequences of the above perspective regarding the role of photon emission *in vivo* may be tremendous, as it becomes evident that disturbances in the symmetries of skeletal forces can result in enhanced phosphorescence, as a consequence of skeletal mechanically-induced luminescence (or triboluminescence). Simultaneously, it is evident that disturbances in the skeletal pattern symmetry can become linked to ischemic-reperfusion complications of certain compromised physiologic states; this condition may thus result in additional photon emission.

6. Discussion and Conclusion

This review has addressed scientific evidence for an energy/information system in the body which is a property of connective tissue and that also contains distinct electromagnetic and light communication properties which seem, at this time, related to TCM perspectives. The idea that the body is impacted by subtle material and mobile influences, which initiate most physiologic functions and maintain an individual's health and vitality, has been expressed in the concept of *Qi*. Therefore, as defined by TCM, a diseased state is an imbalance of *Qi* within the body.

The question discussed above was if there is a relationship between *Qi* and the biophoton concept? In particular, is biophoton emission an effective biomarker that can be used to scientifically quantify the existence of the "balance" concept? This paper describes two major possibilities for the study of the "balance concept": (1) the dynamics of UPE during diurnal and annual cycles and (2) UPE in diseased states. Some evidence suggests that *yin yang* imbalances might also be reflected by biophoton studies, but more research is required for definitive answers for these questions.

The origin of UPE was discussed according to two principles that are related to energy shifting in disease. The first is the principle of triboluminescence, a mechanically-induced luminescence, particularly in bone tissue (skeletal structures), that may explain the initiation of an anatomical emission pattern, as well as left-right (im)balances or (a)symmetries in disease states. It is evident that shaped and highly structured (and/or mineralized) body parts produce more UPE than relatively unstructured flat body parts, and related data suggest a special role of highly structured (and mineralized) connective tissues regarding UPE. Mineralized tissues display a relatively high intensity of phosphorescence, a long duration luminescence. Research suggests that the role of collagen in the matrix may be to enhance the luminescence of internally bound apatite crystals and may exert this control over apatite structure through crystal surface contact. The relationship of human UPE to bone phosphorescence, specifically in relation to flexibility and concomitant changes in organic matrix structure and semiconductor properties of tissues, requires further study.

The second principle is enhanced photon emission under conditions of local (organ) ischemic-reperfusion fluctuations when tuning in the corticoneuromusculoskeletal unity is disturbed. Considering an organism's functioning entirety, the most remarkable feature is its dynamic movements; movements based on highly organized changes in the muscles of arms, legs, hands, or fingers and which draw upon and challenge the local supplies of oxygen and nutrients. The basic bioregulatory role of connective tissue then becomes evident, as this tissue forms a structural, functional, and energetic continuum extending to the every part of the body. The supply of both oxygen and nutrients is regulated in this loose connective tissue structure by arterioles and very fine capillaries that penetrate the tissues to close proximity to peripheral cells. As respiratory enzyme processes are not perfectly tuned, a small percentage of oxygen forms ROS, such that in the presence of ischemia, the clinical timing of providing additional oxygen is a critical decision. Oxygen provided prematurely and/or excessively is clinically precarious.

These two basic biophotonic principles related to energy shifting with disease are strongly connected and may follow each other over time during the course of growing imbalance (Figure 1). It can be hypothesized that imbalance is expressed first in enhanced ROS production and without a left-right imbalance which, later, may become dominant. A link of this phenomenon to organ specific imbalances has not been revealed by biophotonics research techniques. Research here requires additional techniques and, in particular, metabolomics, the comprehensive quantitative and qualitative analysis of all small molecules in a system (in cells, body fluids, and tissues) [75]. With the help of metabolomic techniques, it is possible to characterize the oxidative state of a variety of metabolites, but additionally, it allows the estimation of imbalances in the blood levels of tissue and organ specific metabolites. The current situation in healthcare with ever increasing costs and little gain in quality of life, emphasizes the need for prevention. New diagnostic principles and techniques which are able to detect subtle changes in a biologic system are needed. Metabolomics is an excellent technique for revealing biochemical changes, such as ROS production. However, a clear opportunity exists here for utilization of UPE measurement in detecting left-right balance shifts in a system. Linkage of UPE observations with metabolomic biochemical information and correlation with organ-specific dynamics has great potential. It is hoped that this overview will stimulate well conceived and designed scientific inquiry into energetic imbalances in health and disease to meet the major unmet medical needs in today's society.

Acknowledgments

This work was supported by an independent research grant from the Samueli Institute of Information Biology and the Rockefeller-Samueli Center for Research in Mind-Body Energy. The authors thank Jan Schroën and Herman van Wietmarschen for their valuable suggestions. The authors also thank Dr John Ackerman for his helpful ideas and his assistance in editing the text.

References

1. Wiseman N, Ellis A, Zmiewski P, Li C. *Fundamentals of Chinese Medicine*. Taipei, Taiwan: Southern Materials Center, 1993.
2. Wong CK, Wu TL. *History of Chinese Medicine: Being a Chronicle of Medical Happenings in China From Ancient Times to the Present Periods*. Taipei, Taiwan: Southern Materials Center, 1985.
3. Kaptchuk TJ. *The Web That Has No Weaver. Understanding Chinese Medicine*. Chicago: Contemporary Publishing, 2000.
4. Veith I. *The Yellow Emperor's Classic of Internal Medicine*. Berkeley: University of California Press, 1949.
5. Langevin HM, Yandow JA. Relationship of acupuncture points and meridians to connective tissue planes. *Anat Rec* 2002;269:257–65.
6. O'Connor J, Bensky D. *Acupuncture, A Comprehensive Text (Shanghai College of Traditional Medicine)*. Seattle, Washington: Eastland Press, 1981.
7. Langevin HM, Churchill DL, Fox JR, Badger GJ, Garra BS, Krag MH. Biomechanical response to acupuncture needling in humans. *J Appl Physiol* 2001;91:2471–8.
8. Langevin HM, Churchill DL, Cipolla MJ. Mechanical signaling through connective tissue: a mechanism for the therapeutic effect of acupuncture. *FASEB J* 2002;16:2275–82.
9. NIH. *Consensus Statement. Acupuncture*. Bethesda, Maryland: National Institue of Health, 1997.
10. Pischinger A. *Das System der Grundregulation*. Heidelberg: Haug Verlag, 1975. [In German]
11. Matsumoto K, Birch S. *Hara Diagnosis: Reflections on the Sea*. Brookline, Massachusetts: Paradigm, 1988.
12. Oschman JL. *A Biophysical Basis for Acupuncture*. Proceedings of the First Symposium of the Society for Acupuncture Research, January 23–24, 1993, Rockville, Maryland.
13. Ho MW, Knight DP. The acupuncture system and the liquid crystalline collagen fibers of the connective tissues. *Am J Chin Med* 1998;26:251–63.
14. Heine H. Der Akupunkturpunkt-ein Meridianorgan. *Dtsch Zschr Akup* 1996;39:75–80. [In German]
15. Anthony CP, Kolthoff NJ. *Textbook of Anatomy and Physiology*. St. Louis, Missouri: Mosby, 1975.
16. Asimov I. *The Human Body*. Boston: Houghton Mifflin, 1963.
17. Fleischmajer R, Olsen BR, Kühn K. *Biology, Chemistry, and Pathology of Collagen, Vol. 460*. New York: The New York Academy of Sciences, 1985.
18. Sasaki N. Dielectric properties of slightly hydrated collagen: time-water content superposition analysis. *Biopolymers* 1984; 23:1724–34.
19. Pethig R. Dielectrophoresis. Using inhomogeneous AC electrical fields to separate and manipulate cells. *Crit Rev Biotechnol* 1996;16:331–48.
20. Van Wijk R, Souren JEM, Ovelgonne H. The extracellular matrix, fibroblast activity and effect of Echinacea purpurea. In: Heine H, Anastasiadis G, eds. *Normal Matrix and Pathological Conditions*. Stuttgart, Germany: Fisher Verlag, 1992.
21. Leikin S, Rau DC, Parsegian VA. Temperature-favoured assembly of collagen is driven by hydrophilic not hydrophobic interactions. *Nat Struct Biol* 1995;2:205–10.
22. Mikhailov AS, Ertl G. Nonequilibrium Structures in Condensed Systems. *Science* 1996;272:1596–7.
23. Ho MW, Musumeci F, Scordino A, Triglia A, Privitera G. Delayed luminescence from bovine Achilles' tendon and its dependence on collagen structure. *J Photochem Photobiol B* 2002; 66:165–70.
24. Brizhik L, Musumeci F, Scordino A, Triglia A. The soliton mechanism of the delayed luminescence of biological systems. *Europhys Lett* 2000;52:238–44.
25. Brizhik L, Scordino A, Triglia A, Musumeci F. Delayed luminescence of biological systems arising from correlated many-soliton states. *Phys Rev E* 2001;64:031902.
26. Troshina TG, Loochinskaia NN, Van Wijk E, Van Wijk R, Beloussov LV. Absorption and emission of photons by collagen samples. In: Beloussov LV, Voeikov VL, Martynyuk VS, eds. *Biophotonics and Coherent Systems in Biology*. New York: Springer, 2006.
27. Kim BH. On the kyungrak system. *J Acad Med Sci* 1963;10: 1–41.
28. Lee BC, Kim KW, Soh KS. Visualizing the network of bonghan ducts in the omentumand peritoneumby using trypan blue. *J Acupunct Meridian Stud* 2009;2:66–70.
29. Saidi IS, Jacques SL, Tittel FK. Mie and Rayleigh modeling of visible-light scattering in neonatal skin. *Appl Opt* 1995; 34:7410–8.
30. Mourant JR, Freyer JP, Hielscher AH, Eick AA, Shen D, Johnson TM. Mechanisms of light scattering from biological cells relevant to noninvasive optical-tissue diagnostics. *Appl Opt* 1998;37:3586–93.

31. Han YH, Yang JM, Yoo JS, Ogay V, Kim JD, Kim MS, et al. Measurement of the optical properties of in-vitro organ-surface Bonghan corpuscles of rats. *J Korean Phys Soc* 2007; 49:2239–46.
32. Cifra M, Van Wijk EPA, Koch H, Bosman S, Van Wijk R. Spontaneous ultraweak photon emission from human hands is time dependent. *Radioengineering* 2007;16:15–9.
33. Van Wijk E, Van Wijk R, Cifra M. Spontaneous ultra-weak photon emission from human hands varies diurnally. In: Popp J, Von Bally G, eds. *Proc Spie* 2007;6633:66331J1–9.
34. Kobayashi M, Kikuchi D, Okamura H. Imaging of Ultraweak Spontaneous Photon Emission from Human Body Displaying Diurnal Rhythm. *PLoS One* 2009;4:e6256.
35. Cohen S, Popp FA. Biophoton emission of the human body. *J Photochem Photobiol B* 1997;40:187–9.
36. Cohen S, Popp FA. Low-level luminescence of the human skin. *Skin Res Technol* 1997;3:177–80.
37. Jung HH, Yang JM, Woo WM, Choi C, Yang JS, Soh KS. Year-long biophoton measurements: normalized frequency count analysis and seasonal dependency. *J Photochem Photobiol B*, 2005;78:149–54.
38. Yang JM, Choi C, Yu JH, Soh KS. Yin/Yang polarization: diagnostic evaluation using biophoton measurement from human hands and feet. *J Altern Complement Med* 2006; 12:603–6.
39. Cohen S, Popp FA. Biophoton emission of human body. *Indian J Exp Biol* 2003;41:440–5.
40. Jung HH, Woo WM, Yang JM, Choi C, Lee J, Yoon G, et al. Left-right asymmetry of biophoton emission from hemiparesis patients. *Indian J Exp Biol* 2003;41:452–6.
41. Lee C, Yang JM, Yi SH, Cho HJ, Kang MJ, Yang JS, et al. Biophoton emission from patients with a cold. *J Int Soc Life Inf Sci* 2004;22:362–5.
42. Inaba H. Measurement of biophoton from human body. *J Int Soc Life Inf Sci* 2000;18:448–52.
43. Inaba H. Measurement of ultra-weak biophotonic information. *Proc Inst Electrostat Japan* 1998;22:245–52.
44. Inaba H. Human sensing based on ultimate technology of optical measurement. *Opt Electroopt Eng Contact* 1999; 37:251–67.
45. Yanagawa T, Sakaguchi H, Ueno M, Nitta K. Sustaining faculty of living functions and its biophoton observation. *J Int Soc Life Inf Sci* 2000;18:423–37.
46. Slawinski J, Gorski Z. Imaging of biophoton emission from electrostimulated skin acupuncture point jg4: effect of light enhancers. *Indian J Exp Biol* 2008;46:340–4.
47. Lanzano L, Grasso R, Gulino M, Bellia P, Falciglia F, Scordino A, et al. Corresponding measurements of delayed luminescence and impedance spectroscopy on acupuncture points. *Indian J Exp Biol* 2008;46:364–70.
48. Gulino M, Bellia P, Falciglia F, Musumeci F, Pappalardo A, Scordino A, et al. Role of water content in dielectric properties and delayed luminescence of bovine Achilles' tendon. *FEBS Lett* 2005;579:6101–4.
49. Van Wijk R, Van Wijk EPA. Human photon emission. Recent research developments in photochemistry and photobiology. *J Photochem Photobiol* 2004;7:139–73.
50. Van Wijk EPA, Van Wijk R. Multi-site recording and spectral analysis of spontaneous emission from human body. Research in complimentary and classical natural medicine. *Forsch Komplementärmed Klass Naturheilkd* 2005;12:96–106.
51. Kobayashi M. Modern technology on physical analysis of biophoton emission and its potential extracting the physiological information. In: Musumeci F, Brizhik LS, Ho MW, eds. *Energy and Information Transfer in Biological Systems*. London: World Scientific, 2003.
52. Van Wijk R, Kobayashi M, Van Wijk EPA. Spatial characterization of human ultra-weak photon emission. *J Photochem Photobiol B* 2006;83:69–76.
53. Van Wijk E, Kobayashi M, Van Wijk R. Spatial characterization of human ultra-weak photon emission. In: Beloussov L, Voeikov VL, Martynyuk VS, eds. *Biophotons and Coherent Systems in Biology, Biophysics and Biotechnology*. New York: Springer, 2006.
54. McElroy WD, Seliger HH. The chemistry of light emission. *Adv Enzymol Relat Areas Mol Biol* 1963;25:119–66.
55. Seliger HH, McElroy WD. Spectral emission and quantum yield of firefly bioluminescence. *Arch Biochem Biophys* 1960; 88:136–41.
56. Tarusov BN, Polidova AI, Zhuravlev AI. Study on ultraweak spontaneous luminescence of animal cells. *Biofizika* 1961; 6:490–2. [In Russian]
57. Tarusov BN, Polidova NAI, Zhuralev AI, Sekamova EN. Ultraweak spontaneous luminescence in animal tissue. *Tsitologiya* 1962;4:696–9. [In Russian]
58. Baremboim GM, Domannski AN, Taroverov KK. *Luminescence of Biopolymers and Cells*. New York: Plenum, 1969.
59. Van Wijk R, Van Wijk EPA, Wiegant F, Ives J. Free radicals and low-level photon emission in human pathogenesis: state of the art. *Indian J Exp Biol* 2008;46:273–309.
60. Scarpa A, Dutton PL, Leigh JS. *Frontiers of Biological Energetics: From Electron to Tissues*. New York: Academic Press, 1978.
61. Cadenas E, Boveris A, Chance B. Low-level chemiluminescence of bovine heart submitochondrial particles. *Biochem J* 1980;186:659–67.
62. Nakano M, Noguchi T, Sugioka K, Fukuyama H, Sato M, Shimizu Y, et al. Spectroscopic evidence for the generation of singlet oxygen in the reduced nicotinamide adenine dinucleotide phosphate-dependent microsomal lipid peroxidation system. *J Biol Chem* 1975;250:2404–6.
63. King MM, Lai EK, McCay PB. Singlet oxygen production associated with enzyme-catalyzed lipid peroxidation in liver microsomes. *J Biochem* 1975;250:6496–502.
64. Currey JD. Tensile yield in compact bone is determined by strain, post-yield behaviour by mineral content. *J Biomech* 2004;37:549–56.
65. Follet H, Boivin G, Rumelhart C, Meunier PJ. The degree of mineralization is a determinant of bone strength: a study of human calcanei. *Bone* 2004;34:783–9.
66. Handschin RG, Stern WB. Crystallographic and chemical analysis of human bone apatite (crista iliaca). *Clin Rheum* 1994;13(Suppl 1):75–90.
67. Roy ME, Rho JY, Tsui TY, Evans ND, Pharr GM. Mechanical and morphological variation of the human lumbar vertebral cortical and trabecular bone. *J Biomed Mater Res* 1999;44:191–7.
68. Boskey A. Bone mineral and crystal size. *Osteoporos Int* 2004;14(Suppl 5):S16–21.
69. Hoerman KC, Mancewics SA. Phosphorescence of calcified tissues. *Arch Oral Biol* 1964;9:517–34.
70. Mancewics SA, Hoerman KC. Characteristics of insoluble protein of tooth and bone. I. Fluorescence of some acidic hydrolytic fragments. *Arch Oral Biol* 1964;9:535–44.
71. Bachman CH, Ellis EH. Fluorescence of bone. *Nature* 1965; 206:1328–31.
72. Parry DA, North AC. Hard alpha-keratin intermediate filament chains: substructure of the N- and C-terminal domains and the predicted structure and function of the C-terminal domains of type I and type II chains. *J Struct Biol* 1998;122:67–75.
73. Bischof M. Synchronization and coherence as an organizing principle in the organism, social interaction, and consciousness. *Neuroquantology* 2008;6:440–51.
74. Brown P, Salenius S, Rothwell JC, Hari R. Cortical correlate of the Piper rhythm in humans. *J Neurophysiol* 1998;80:2911–7.
75. Van der Greef J, Hankemeier T, McBurney RN. Metabolomics-based systems biology and personalized medicine: moving towards $n=1$ clinical trials? *Pharmacogenomics* 2006;7: 1087–94.