

## The suggestions of ancient Chinese philosophy and medicine for contemporary scientific research, and integrative care.

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### ABSTRACT

According to Kelley et al. (2023), BBI Integrative ‘recognises the historical importance of Eastern health practices in the entire field of PNI’ (psychoneuroimmunology). We applaud this editorial innovation and believe that it is an important step in advancing the ability to provide healing to human beings. This article aims to illustrate suggestions for scientific research and integrative care derived from studying the ancient Chinese medicine and philosophy using pathophysiological and clinical examples. It shows how some fundamental categories of ancient Chinese philosophies, such as the yin–yang theory, and healing models, such as yang sheng (nurturing life), can help us understand how the immune system works and where the foundations of health are rooted. It also examines some examples of the yin–yang dialectic in immunology, such as T helper 1 (Th1) circuit control by the same cells that initially produce cytokines (IL-12 and IFN- $\gamma$ ) to activate this circuit and then produce Th2 circuit cytokines (IL-4) to moderate it. In addition, the transformation of regulatory T-cells into inflammatory T-cells (Th17) and the IL-6 dual pro- or anti-inflammatory face, depends on the context. In the first example, yin is present in yang. In the second, the yang is in the yin. Finally, we present an example of the cytokine yin–yang. This article also shows the surprising concordances of ancient Chinese chronobiology with the modern science of circadian rhythms and the unknown connections between organs, such as between the lungs and gut, which has drawn the attention of modern scientific research only recently. Finally, this article highlights the peculiar approach of ancient Chinese medicine to prevention and treatment, called yang sheng, which shows strong concordance with the model proposed by Psychoneuroendocrineimmunology.

### Introduction

The current biomedical paradigm is rooted in the reductionist approach (Engel, 1977; Bottaccioli and Bottaccioli, 2020b), which is primarily based on three ideas: complex medical phenomena have simple determinants, such as genes, single molecules, and receptors, investigated by applying linear cause–effect logic; psyche cannot influence biology and therefore is not a factor of health and therapy; and nutrition, physical activity, and living in a competitive and unequal social environment, although polluted and toxic, are not first magnitude biological factors. Therefore, these ideas entrust research on single genes, molecules, and active ingredients and treatment essentially with

drugs and surgery, virtually dissecting human beings into a myriad of medical specialisations.

The Chinese model (Raphals, 2020), which is historically pre-scientific yet strongly compact and structured, views human beings as a dynamic, unstable organism constantly looking for balance and who is influenced by internal and external factors— primarily psychic factors that, in ancient Eastern medical philosophy, have their roots in the body, even in individual organs.

These characteristics allowed the ancient Eastern medical model to enter the paradigm of psychoneuroendocrine immunology in a congruent and fruitful manner (Bottaccioli and Bottaccioli, 2022). This allows for fruitful dialogue between the Western and Eastern sides of

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science and care. Otherwise, they will remain 'health practices', reduced to the rank of minor therapies, and the mechanisms by which they work will remain unclear.

## Main topics

This section discusses the main topics. For each topic, the traditional Chinese view has been presented, showing its concordance with suggestions for contemporary scientific research.

### Unity–dynamicity: Yin–Yang – The immune system as an example

A text on the 'Harmonic Union of Yin and Yang' was found in 1973 in tombs dating back to the second century BCE at Mawangdui, Hunan (Harper, 1998), one of the cornerstones of ancient Chinese medicine. However, the yin–yang theory predates the second century BCE, as the alternation of the whole sign (yang) and the broken sign (yin) is the foundation of the *Yi Jing*, the *Classic of Changes*, a text of ancient oral tradition (Western Zhou era, 11th–7th century BCE) systematised in writing in the last phase of the 'Warring States' (late fourth century BCE).

One of the fundamental qualities of the yin–yang relationship applied to human physiology is that every phenomenon has both yin and yang aspects. This is not to say that we face indistinctness or ambiguity. There is always a prevalence of one or the other; thus, one can connote the phenomenon as yin or yang. However, one cannot exist without the other because one is the root of the other. 'The yin is located inside, but it is the yang that keeps it there; the yang is located outside, but it is the yin that allows it to act' (the 'Great Treatise on the Correspondence of Yin–Yang Phenomena' in *Su Wen Huangdi Nei Jing*, *The Yellow Emperor's Classic of Medicine*, 1995).

On the contrary, another fundamental characteristic is that one is transmuted into the other. Transmutation is possible because yin is still included in the maximum yang, and vice versa (Fig. 1).

Therefore, we face a dynamic and dialectical vision different from classical Western logic,<sup>1</sup> based on the principle of identity and non-contradiction (A is not B) introduced by Bertrand Russell and Hegelian dialectics. Hegelian dialectics presupposes an ascending order, in which the synthesis transcends and subsumes the datum of thesis and antithesis within itself. In contrast, the yin–yang dialectic is dynamic and adaptive because yang and yin are not in opposition; they are two polarities of the life process whose dominance alternates in cosmology (day and night, summer and winter, sun and moon), physiology (activity and rest), and pathology (illnesses from yang excess and yin deficit, and vice versa).

The yin–yang dialectic is also adaptive because the weight of each polarity can be moderated; thus, excess yang can be moderated by nourishing yin, and vice versa. The yin–yang dialectic, unlike classical Western logic and Hegelian dialectic, allows researchers to understand

<sup>1</sup> It is extremely interesting to note that ancient Greek philosophy was not far from the Chinese dialectical view. The first book of the *Peri Diaites (Regimen)*, in Latin, a medical treatise from 400 BC by an anonymous author (but judged 'worthy of Hippocrates' by Galen), is dedicated to the knowledge of the constituent principles of reality and thus, human nature. In this text, we read, 'Man and all other animals are composed of two, separated by characteristic, united in action, water and fire. Together, they suffice for themselves and for everything else; separated, they suffice neither for themselves nor for everything else. Here is the characteristic of each: fire can move everything, water nourish everything, and each dominates and is dominated, from the highest to the lowest. In fact, neither can dominate completely for the following reason: if fire eliminates even the last particle of water, it lacks nourishment and therefore recoils to find its nourishment. If water, in turn, extinguishes the last particle of fire, it lacks movement; therefore, it stops at this point, loses its superiority and is consumed by nourishing the fire that assails it' (in Hippocrate, 2003, p.4). Thus, in the Chinese philosophy, we could say that water (yin) and fire (yang) are dialectically interdependent.



Fig. 1. Tai Yi, the 'Great One', represents yin–yang relations. The yin (the black part) contains a white point (the yang). The yang (the white part) contains a black point (the yin). The yin is in the yang and the yang is in the yin, which allows for mutual transformation.

biological dynamics, particularly those of the immune system, in a penetrating way. In the recent decades, our view of the immune system has changed (Tauber, 2017, 2022). The traditional meaning of immunity, both in popular and medical imaginations, is protective-privative: one is exempt from something, such as a disease and paying taxes. Therefore, immunity protects the individual such that, in medical circles and everyday language, it is synonymous to 'immune defences'. This concept emerged because of the rise of the microbial paradigm in the late 19th and early 20th centuries, according to which the causes of disease are external to the organism, caused by various microbes, and can be cured with Paul Ehrlich's 'magic bullets'. This paradigm was consolidated in the late 1950s by Frank Macfarlane Burnet's clonal selection theory (Burnet, 1958), which assumes a clear distinction between self and non-self, that is between what the immune cell recognises as its own and foreign (to be defended against), in describing the way a lymphocyte responds to an antigen by cloning itself into many identical copies.

Burnet presented the 'central dogma of immunology' at the same time the 'central dogma of molecular biology' was developed by Francis Crick (1970). According to the central dogma of molecular biology, an individual is a linear and necessary product of the genome contained in the cell nucleus. Thus, the self is genetically cemented to the genetically determined immune mechanisms. The individual is a granitic product; its development is self-centred and driven by necessity and its genome, which was called 'the fundamental invariant, which also contains all the necessary instructions to defend it from the outside' by Jacques Monod, an influential biologist of the 20th century. The immunological self, in this respect, functions as the 'molecular invariant' of the organism, which supports an essentialist model of the individual. The emergence of epigenetics, first reported by Conrad Waddington in the 1940s, radically changed the view of the genome, which is no longer seen as a steering centre that issues instructions to the organism, but rather as an adaptive device that responds to environmental demands by regulating gene expression. Epigenetics is a rapidly expanding field of science that studies the molecular mechanisms by which the environment and individual life affect information contained in the genome.

Adaptation is also a keyword in recent immunology, which questions the concept of a strictly separated immunological self, à la Burnet, starting from the observation that our organisms are colonised by several microbes (bacteria, viruses, and fungi) with their own individual genomes (DNA or RNA), whose number is assumed to exceed that of our cells. The immune system is in constant trade with living beings, whose relative weight is modulated by the environment, diet, stress, and drugs. Therefore, the non-self is internal to the self. The existence of the immunological self depends on the system of relationships established and continually adapts to the non-self that lies within the self. In Niels

Jerne's network theory and some later research (particularly that of Polly Matzinger, 1994), the recognition of the other (antigen) depends on not only its nature, but also the context, that is the system of relations within which it is nested and recognised. Furthermore, recognising the other (antigen) is not as much a molecular fact as a change in the immune network state.

#### Four examples of the yin–yang dialectic in immunology

##### *The brake of Th1: The yin is in the yang*

To respond effectively to a virus, the immune system must activate a lymphocyte circuit known as the type I or T helper 1 (Th1) response. T helper cells differentiate into Th1 cells under the stimulus of the cytokines IL-12 and IFN- $\gamma$ , which are secreted by cells that have encountered the virus. The effector cells, cytotoxic T-cells, and natural killer cells are attracted by the same signals produced by the Th1 cells, which produce a high IL-12 and IFN- $\gamma$  concentration in the first phase; however, within a few days, their concentration decline and IL-4 production increases, which is the Th2 circuit signal that acts as a brake on the excessive inflammation produced by Th1 (O'Garra and Vieira, 2007). In the yang (IL-12 and IFN- $\gamma$ ), there is yin (IL-4), which, as it grows, will act as a brake on the yang.

Furthermore, Guillonneau et al. (2007) documented another mechanism that links IFN- $\gamma$  to successful inflammation resolution. According to this study, IFN- $\gamma$  both activates and inhibits inflammation. According to traditional logic that has governed Western philosophy from Aristotle onwards, we would face a contradiction in terms of whether something is or is not, *tertium non datur*. It is no coincidence that the journal editors assigned the task of commenting on the study to Jingwu Zhang, a Chinese scientist, a member of the Chinese Academy of Sciences, and a neurologist at Baylor College in Houston. To explain this apparent paradox, Zhang (2007) referred to Yin and Yang theory.

When an inflammatory process (yang) is initiated, IFN- $\gamma$  is produced to promote inflammation through multiple genes involved in the immune system (some are indicated). As IFN- $\gamma$  concentration reaches its peak level (the 'hot' point), inflammation intensifies (enlargement of yang area) and compresses its opposite. The dominant IFN- $\gamma$  signal then flows into the opposite area (yin) and activates a regulatory process through various genes and pathways to reach the 'cool' point, thus shifting the to reach the 'cool' point, thus shifting the dividing line toward inflammation reduction (enlargement of yin area, mutually compressing its opposite).

Immunologically, this is one of the main antiviral response regulatory mechanisms, which can be harmful if not controlled (autoimmunity).

##### *From regulatory to inflammatory T-cells: The yang is in the yin*

Recent research has documented that if the main anti-inflammatory lymphocyte cells, regulatory T-cell (Tregs), turn into highly inflammatory Th17 cells when they receive context signalling that changes the epigenetic status and function of *Foxp3* gene from hypomethylation to hypermethylation (Sjaastad et al., 2021). One of the main contextual signals is butyrate, which is produced by the gut microbiota during eubiosis. Butyrate inhibits histone deacetylase; therefore, it increases the acetylation of *Foxp3*, which maintains the hypomethylation of the gene core and, thus, Treg stability. In terms of yin–yang dialectics, this phenomenon can be explained by conceiving that a yin cell has yang potential within it, which can become dominant. If the researcher reasons, in terms of traditional logic, that A is not B, he does not understand the phenomenon.

##### *IL-6: A yin–yang cytokine*

IL-6 has been the focus of ongoing research and clinical trials on COVID-19, as the cytokine concentrations have significantly increased in severe forms of the disease. Cytokines are targets for emergency anti-inflammatory therapy; however, the results are difficult to interpret because the IL-6 function is complex (McElvaney et al., 2021).

Furthermore, IL-6 concentration increases in the blood of individuals after intense aerobic physical activity. In this study, IL-6 was not related to its inflammatory ability. In contrast, it is clearly anti-inflammatory. In the context of aerobics and controlled physical activity, IL-6, instead of activating an inflammatory response, elicits an anti-inflammatory response by reducing TNF- $\alpha$  concentration, which is clearly inflammatory, and stimulates the production of other anti-inflammatory molecules.

This positively affects various biological systems, including the brain and cognitive functions. Therefore, IL-6 can be yin or yang, responding in an inflammatory or anti-inflammatory direction depending on the contextual signals (Borsini et al., 2020).

##### *mregDC: A yin–yang cell*

Although dendritic cells (DC) have an ancient scientific history, significant discoveries have been made only recently. These cells have a unique ability to present antigens to T lymphocytes in the lymph nodes. Even extremely low antigen doses are taken up by DCs and exposed in the lymph nodes after a journey through tissues and lymphatic pathways, which can take up to a few days. Rissoan (1999) have showed that DCs with and without the CD11 marker (CD11 + and CD11 -, respectively) produced IFN- $\gamma$  and IL-4, respectively; the first class was named DC1, and the second, DC2. The selective production of IFN- $\gamma$  and IL-4 by DC1 and DC2, respectively, seemed to have improved the understanding of lymphocyte response regulation: DC1 would activate the Th1 circuit by producing IFN- $\gamma$ , whereas DC2 would activate Th2 by producing IL-4. This phenomenon is yin–yang because DC1s produce less IFN- $\gamma$  and start producing IL-4 after a certain time. This yin–yang condition of DCs has been discovered recently.

Maier et al. (2020) have identified a cluster of DCs that they named 'mature DCs enriched in immunoregulatory molecules (mregDCs)', owing to their co-expression of immunoregulatory and maturation genes. The mregDC programme is expressed by canonical DC1s and DC2s that activate or suppress the antitumour response upon tumour antigen uptake, depending on the tumour signals and the context. The yin–yang function of mregDCs is of great interest for further cancer immunotherapy research (Li et al., 2023).

#### Circadian rhythms: Qi oscillation

Every morning, we wake up after a night of sleep, have breakfast, and start performing activities. We usually eat several times a day, at scheduled times, and then we are ready for another night's sleep. This cycle is called the circadian rhythm (from the Latin *circa diem*, meaning 'about a day') because it relates to the 24 h- cycle of a day and underlies several physiological functions, including the sleep–wake cycle, body temperature, hormone secretion, immune activity, brain activity, and eating habits (Buijs et al., 2016).

Cyclic activity has also been observed in other organisms, including fungi, insects, protists, cyanobacteria, and plants. The reason for the pervasive rhythm observed in living organisms is simple: life has evolved on Earth through the constant alternation of light and dark, which has produced an adaptation in the behaviour of all living things. Every living organism, in organising its activity in the environment, has always had to, and must still, consider the cyclic behaviour of sunlight



Fig. 2. The qi ideogram. The radicals at the top right and bottom left indicate steam swirls and a rice grain, respectively.

transmitted to Earth for more than 4 billion years.

The human being, unlike some other creatures, is a diurnal animal, which organises the variable production of hormones, neurotransmitters, cytokines, and cyclic brain processes, and the function of fundamental organs, such as the pancreas, liver, adrenal glands, intestines, lungs, heart, and ultimately, the cell itself, based on this underlying pattern.

The suprachiasmatic nuclei (the central clock) produce various neuropeptides from 24 prohormones, along with cytokines and neurotransmitters such as  $\gamma$ -aminobutyric acid, glutamate, and nitric oxide. The main neuropeptides include vasoactive intestinal peptides, arginine vasopressin, and gastrin-releasing peptides (Ono et al., 2021). This intricate signal network is further complicated by the discovery that internal organs also have their own clocks (Mure et al., 2018). For example, the heart has its own rhythm that can present extremely vulnerable periods.

Recent research seems to indicate that the fluctuation in heart rhythm is the greatest between 9 and 11 a.m. which makes the organ more vulnerable. According to numerous epidemiological studies, this explains why cardiac events, such as sudden cardiac death, ventricular arrhythmias, angina, and heart attack, mostly occur in the morning (Kanth et al., 2013; Estarlich et al., 2022). Similarly, pulmonary activity also has its own rhythm, particularly because asthma attacks mostly occur at approximately 4 a.m.

According to ancient Chinese medical philosophy, based on the complex chronobiological vision of man and the cosmos, lung energy is at the peak between 3 and 5 a.m.; this observation is quite intriguing. Moreover, the energy of the spleen and heart increases between 9 and 11 a.m. and between 11 a.m. and 1 p.m., respectively. In addition, the spleen and heart share a close relationship. According to ancient Chinese medicine, the spleen helps to produce the blood and ‘keep it in the vessels’.

Therefore, its optimal function is to prevent blood deficiency and bleeding. Therefore, we can say that even according to this ancient medicine, the transition between night and day is a critical moment for respiratory disorders, and by mid-morning, the heart and organs that are perfused by blood, such as the brain, are vulnerable and at risk.

Huang et al. (2016) used a binary pattern to describe the circulation of qi in the human body over 24 h. The ancient ideogram of the word qi (pronounced chi) consists other shows a grain of rice (Fig. 2).

The ideogram represents the fundamental nature of qi: a dense and material reality symbolised by the grain, and an energetic and rarefied reality symbolised by the steam; in short, the earth and sky. Qi, primordial dynamism—neither matter nor spirit—is prior to the world, and

Table 1  
Chinese chronobiology.

VESSEL	TIME (hours)
Lungs	3–5 a.m.
Large intestine	5–7 a.m.
Stomach	7–9 a.m.
Spleen	9–11 a.m.
Heart	11 a.m.–1 p.m.
Small intestine	1–3 p.m.
Bladder	3–5 p.m.
Kidney	5–7 p.m.
Pericardium	7–9 p.m.
Triple burner	9–11 p.m.
Gallbladder	11 p.m.–1 a.m.
Liver	1–3 a.m.

everything is only an aspect and state of its greater or lesser condensation. Condensed is life, rarefied is potentially indefinite; this conception dates to *Zhuangzi* and was used throughout classical China up to neo-Confucianism (Robinet, 1993, p. 12)<sup>2</sup>.

With the development of medicine, qi has become the fundamental life principle of human beings; it constitutes the human body and, at the same time, unifies it.

Therefore, qi must be safeguarded, nurtured, and allowed to flow freely in the channels in accordance with the qi of the sky, represented by seasons. Otherwise, qi and its movements can become pathological due to accumulation, deficit, stasis, or faulty circulation. Therefore, qi causes health problems or diseases<sup>3</sup>.

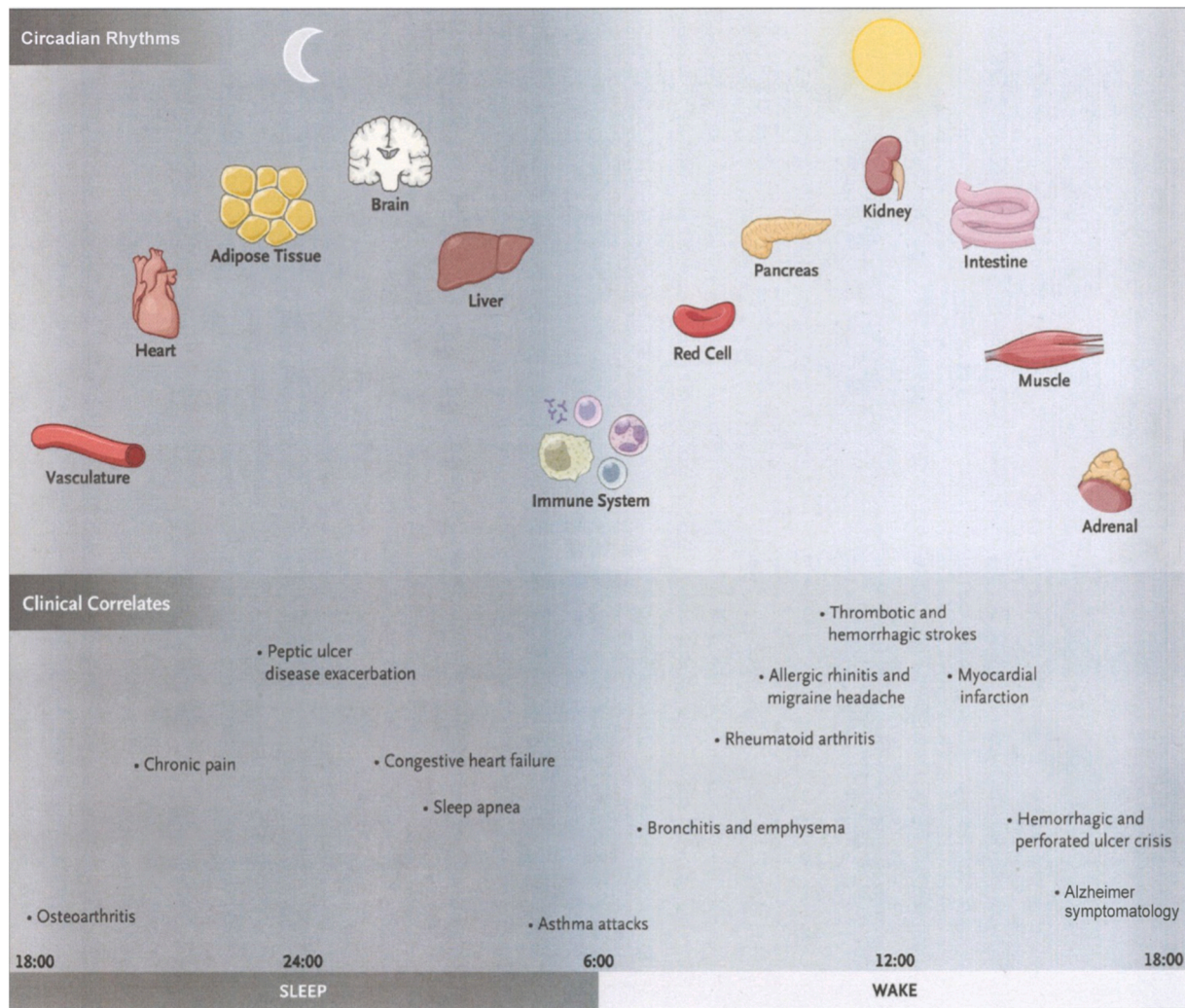
As shown in Table 1, qi activity maximises in the 12 main channels within 2 h. This pattern also has precise applications in diagnostics and therapeutics, as it allows for the formulation of diagnostic hypotheses based on the moment of symptom onset and the preparation of therapies in accordance with the phase of maximum expression of the channels to be treated.

This approach established a scientific foundation for contemporary times in chronobiology (Fig. 3). It is important to synchronise the biological rhythms to be he Therefore, the central clock must be continuously reset using external environmental factors. There are two types of external synchronisers: primary and secondary. The primary factors are evidently environmental: light and dark alternation, season succession, and lunar cycle (which, perhaps not coincidentally, is almost identical to the female menstrual cycle, only a few tens of minutes off). Secondary factors are related to the organisation of our individual and social lives: sleep quantity and quality, work type (day, night, or shift), meal times, travel (jet lag), and overdoing it on the weekend (social jet lag). These individual characteristics draw up what chronobiologists call the chronotype; that is, the characteristics of each individual in terms of their biological rhythm.

Although chronobiology is still quite marginal in scientific research and is largely unknown to doctors, psychologists, and other health workers, knowledge of the biological rhythms of our organisms can be of great help in the care of all human diseases (Allada and Bass, 2021;

<sup>2</sup> Let us note in passing that the primordial dynamism of qi, neither matter nor spirit, regarding which Isabelle Robinet wrote, is very similar to the most accredited theory of the origin of the Universe, which is said to have originated from a ‘quantum foam’ that, with its expansion, gave rise to everything that makes up the Universe, including human beings (Tonelli, 2021). The objects that make up the Universe would then be more or less condensed states of matter, which, in contrast, is an illusion, considering that, according to contemporary physics, approximately 95% of matter is dark matter and dark energy (Tonelli, 2023).

<sup>3</sup> As many scholars have repeatedly noted (e.g., Needham, 2000, pp. 43–44; Bottaccioli and Bottaccioli, 2020), this concept unifies the East and West in that it is present in Greece as *pneuma* and in India as *prana* and, in man, it is closely linked to the breath and thus, to life in its most evident basis and manifestation.



**Fig. 3.** Chronobiology and chronopathology. Top panel: the liver is particularly active after midnight (in Chinese chronobiology, it is active from 1 to 3 a.m.), whereas the pancreas is active in early morning (for the Chinese, the spleen–pancreas meridian functions from 9 to 11 a.m.), and the electrical stability of the heart is sensitive toward the evening, at approximately dinnertime. Bottom panel, asthma attacks are often frequent at 5 a.m. (for the Chinese, the lung meridian runs from 3 to 5 a.m.) while the immune system is physiologically active with cytokine release. Moreover, heart rhythm disorders (arrhythmias) occur frequently between 7 and 8 p.m. (for the Chinese, the pericardium is vulnerable from 7 to 9 p.m.), whereas heart attacks occur at the end of the morning (for the Chinese, heart activity peaks between 11 a.m. and 1. p.m.).

Fishbein et al., 2021).

### Unusual internal physiopathological connections: Lung–gut and liver–brain as examples

According to ancient Chinese doctors, health preserves the harmonic balance between qi and other vital substances such as blood and body fluids. With the development of Chinese medicine under Taoist and Buddhist influence, the ability to preserve the ‘three treasures’—the Shen, the qi, and the Jing, which are ultimately three forms of qi—is discussed. The first is the mental–spiritual aspect; the second is the qi that we produce with our lifestyle and habits (including good nutrition); and the third is the qi that we have inherited from our parents, which can be dispersed or preserved and, to a certain extent, nourished by behaviour.

Qi is the fundamental principle of a human being; the human body is made up of qi, and at the same time, it unifies the body. Therefore, it must be safeguarded and nourished in accordance with the qi of the sky, represented by the seasons. Otherwise, qi and its movement can become pathological owing to accumulation, deficit, stasis, or wrong circulation. Acupuncture is an efficient tool for correcting qi that circulates in the

meridians. The meridians, vessels, or channels (in Chinese, *jing*) constitute a network that involves the entire human body, in which blood (*xue*) circulates, as well as qi.

The meridians were compared with rivers, tributaries, channels, and reservoirs in the.

*Huangdi Neijing Ling Shu* (spiritual pivot) text.

There is a system of 12 main channels connected by tributaries and channels.

Over the centuries, Chinese doctors have structured into a large network consisting of 12 main channels, (*jing mai*), eight extraordinary channels (*qi jing ba mai*), and several dozen secondary channels encompassing the human body. The 12 main channels were structured into six pairs, each connecting two organs. Therefore, six pairs were formed according to the logic of yin and yang: liver–gallbladder, heart–small intestine, spleen–stomach, lung–large intestine, kidney–bladder, and pericardium–triple burners. Of the eight extraordinary channels, the two fundamental channels travel along the median line, starting from the perineal area and arriving at the face, one dorsally and the other ventrally. The channel that travels along the ventral line is called *ren mai* (conception vessel) and represents the yin, whereas the channel that travels along the back is called *du mai* (governing vessel)

and represents the yang. Now, although some pairs are plausible even to the Western mind (e.g., liver–gallbladder and kidney– bladder), others are rather bizarre, for example, the lung–large intestine pair. Recent studies have confirmed this connection physiologically and pathologically.

Physiologically, research in recent decades has consolidated the knowledge of the mucosa-associated lymphoid tissue, which connects the respiratory portion (nasopharyngeal-associated lymphoid tissue and bronchus-associated lymphoid tissue) of the immune system to the digestive portion (gut-associated lymphoid tissue; [Dang and Marsland, 2019](#)).

Pathologically, the most recent example of a connection between the respiratory and intestinal systems (gut–lung axis) is the course of SARS-CoV-2 infection. The virus enters the respiratory mucosa and selectively spreads to the intestines, causing both respiratory and intestinal symptoms. Dysbiosis, along with barrier damage and the resultant inflammation, may facilitate disease development. Translocated bacteria, immune cells, and inflammatory mediator release in the gut–lung axis may contribute to COVID-19-associated organ deterioration ([de Oliveira et al., 2021](#)).

Furthermore, ancient Chinese medicine has identified relevant connections between the liver, heart, and brain (liver–heart–brain). To understand these connections, another pillar of ancient Chinese physiology: *wu xing*, the Law of Five Agents or Five Phases, should be recalled. According to [Graham \(1986\)](#), one of the foremost scholars of ancient Chinese civilisation, the ‘five phases’ was first theorised in a chapter of the *Shujing* (The Book of History, compiled in the 5th century BC) titled *Hongfan* (The Great Plan). The five phases have a relationship with each other, which is called ‘generation’: each movement is produced by the one that precedes it and produces the one that follows it.

This relationship is also known as mother–child law. Wood is the mother of fire, the mother of Earth is the mother of metal, and the mother of water is the mother of wood. Each agent corresponded to an organ: wood to the liver, fire to the heart, earth to the spleen, metal to the lungs, and water to the kidneys. Each organ must have a yin–yang balance. For example, if there is an excess of yang in the liver, the heat released will be transferred to the heart, which may be damaged, and the brain because the heat moves to the top. The symptoms that identify this liver-originating imbalance include chest tightness, a lump in the throat, and headache at the top of the head. Chronic imbalances can include basis of cardiovascular, neurological, and psychiatric diseases.

Scientific physiology has long described the central role of the liver in inflammatory processes with the production of ‘acute phase proteins’ (CRP, C-reactive protein), cytokines, and chemokines. Recent studies have revealed that proinflammatory molecules released by the liver can activate the heart- and brain-intrinsic immune system to the by stimulating inflammatory processes underlying cardio- and cerebrovascular events ([Fioranelli et al., 2018](#)). The liver simultaneously releases anti-inflammatory substances under certain conditions. For example, in animals that butyrate, one of the ketone bodies released by the liver of animals after a fasting period, reaches the brain and binds to numerous gene sites with anti-inflammatory effects ([Cornuti et al., 2023](#)).

This knowledge of the interconnections between organs and systems, which ancient Chinese medicine places at the centre of medical theory and practice and is increasingly being developed through modern scientific research, opens new possibilities for treatments, pushing therapists to go beyond the limits of their own specialisation and embrace integration with other disciplines and professionals in the field of care.

### Integrated care and the patient’s rule: Yang sheng, Nurturing life

During the 4th century BCE, a specific reflection on the nature of human life and how it could be prolonged began to develop ([Unshuld, 1985](#)). The third chapter of the classic Daoist [Zhuangzi \(2020\)](#) is titled ‘The Lord of Nurturing Life’. The sapient Pao Ding instructs Duke Hui of Liang on how to nurture life (yang sheng).

The ‘nourishment of life’ constitutes a practical application of the worldview of a sage, who is distinguished from the common man precisely by his self-awareness and thus the technical ability he possesses to maintain health by following the path. The pillars of the ‘nutrition of life’ are highlighted below:

- Respect for natural rhythms by tuning breaths to those of the seasons and those of day and night. In one of the Mawangdui scrolls, the physician Wen Zhi claims to have three thousand files on his ‘Practice of the Way’; of all the indications in this vast body of doctrine, the main one is sleep.
- Capture and proper internal circulation of qi using breathing, meditation, and inner visualisation techniques.
- Physical exercise in the form of movements that facilitate qi circulation by unblocking its stagnation and accumulation, such as Daoyin in ancient times, recently developing famous practices, such as Tai ji quan and Qi gong.
- Nutrition: According to the classic Han syncretic [Huainanzi \(2010\)](#), we are what we eat (anticipating in this Ludwig Feuerbach); this is why one of the chapters of this text launched the watchword ‘abstain from grains’, which were judged to be earthly, heavy, dense in nature and therefore, bad food for those who aspire to reside in the heaven. This abstinence constituted a form of fasting that, according to [Huainanzi](#), improves health and makes one insensitive to heat, cold and poisons, which makes it possible to drink large quantities of wine without getting drunk, a habit peculiar to great men, as indeed the Symposium recalls with regard to Socrates.
- Control of sexuality by males, of course, given the time. However, this goal was not ascetic. Although a man falling prey to the passion of sex is criticised, abstinence is not proposed because it ‘causes anxiety and damage to the heart’. Similarly, the techniques used during coitus must allow the wise man to spare his semen, which is a concentrate of the fundamental essence of the *Jing*, and preserve it in the right kidney. He must practice coitus without ejaculating each time, instead rationalising seed dispersion.

In recent decades, nutrition in modern life has attracted increasing interest from researchers and healthcare professionals. It is increasingly evident from major epidemiological and targeted experimental studies that most diseases afflicting humanity are rooted in the bad relationships that human beings establish between themselves and the environment. Pollution, global warming, and the structure of nutrition and contemporary work and social life shape the urban environments, lifestyles, and behaviours that are the roots of modern pathologies. This knowledge has important implications for human health.

This research has extensively documented the effectiveness of lifestyles not only in prevention, but also as an integral part of the treatment of all chronic diseases (psychiatric, neurologic, and internist) dominant in affluent countries. ‘There is growing scientific evidence that shows that dietary modifications have strong positive and negative effects on health over the course of one’s life’ wrote the [WHO, FAO Expert Consultation \(2003\)](#) in a seminal document, indicating the return of the centrality of nutrition for human health after its blackout in the second half of the 20th century. In the recent decades, diet has become a topic of great interest in psychiatry, because people with severe psychiatric disorders have poor-quality diets and diet positively influences people’s states of mind and psychiatric symptoms ([Firth et al., 2018](#)).

A seminal study by [Zhang et al. \(2009\)](#) showed that excessive caloric intake causes inflammation of the hypothalamus, a crucial cerebral area for both energy balance and neuroendocrine system, including the stress-control system. In addition, other biological pathways could plausibly link diet with mental health, including inflammation, oxidative stress, mitochondrial signalling, tryptophan–kynurenine metabolism, and gut microbiota composition ([Marx et al., 2020](#)).

The gut–brain axis, although poorly considered in medical education ([Damasio, 2018](#)), has won a prominent place in neuroscientific research,

highlighting the bidirectional gut–brain relationship (Rao and Gershon, 2016) that controls hunger and satiety. The gut influences social behaviour, emotion, and stress response modulation. The picture has become complete with the study of the gut microbiota, which includes vast ecosystems comprising an exorbitant number of microbes, including viruses, fungi, and bacteria. They play several important roles in digestion, metabolism, vitamin, and short-chain fatty acid synthesis, and immune regulation. Numerous neuroactive substances are released from the microbiota, reach the brain through blood. Numerous neuroactive ed from the microbiota, reach the brain through blood circulation, and ascend through the autonomic nervous fibres (particularly the vagus nerve).

Health professionals are urged to adopt an integrated approach to care that enhances the role of the patient based on a competent and empathic relationship fostering the implementation of knowledge and health practices in the patient's life, as well as establishes care based on the recognition of the mutual communication between psyche and biological systems.

Psychological and mind–body interventions not only improve the mental state and well-being of a person, but also change their epigenetic signatures. A systematic review (Lopresti, 2017) investigated the role of psychotherapy, particularly cognitive behavioural therapy, in reducing chronic inflammation in patients with depression.

Although the studies were somewhat heterogeneous, most research have shown a clinically significant decrease in at least one inflammatory biomarker within a wide range of markers examined, such as the serum cytokine (TNF- $\alpha$  and IL-6) concentrations, nuclear transcription factor (NF- $\kappa$ B) expression, immune cell count, and innate and acquired immunity (natural killer cells and T lymphocytes) activity.

A recently published systematic review and meta-analysis of 56 randomised controlled trials (RCTs) with 4060 participants has shown that psychosocial interventions, including cognitive behavioural therapy and other forms of psychotherapy, are associated with reduced inflammatory marker levels and increased antiviral immunity (Shields et al., 2020).

Several studies have investigated the effects of mind–body therapies (MBTs), such as meditation, tai chi, qi gong, and yoga, on the biological markers of brain inflammation. Furthermore, a seminal review by Bower and Irwin (2016) that included 26 trials confirmed the anti-inflammatory effects of MBTs on circulating inflammatory markers such as CRP. Two psychoneuroendocrinology-based meditation (PNEIMED) controlled studies in healthy middle-aged and young volunteers showed that salivary cortisol levels reduced under basal and stressful conditions (Bottaccioli et al., 2014, 2020). Notably, a combination of meditation and psychological interventions (COBMINDEX) was effective in patients with Crohn's, increasing well-being and decreasing inflammatory markers associated with the disease (Nemirovsky et al., 2021).

Moreover, a meta-analysis (Buric et al., 2017) highlighted that the practice of meditation was associated with a general profile of gene expression characterised by a significant underregulation of genes and proinflammatory signalling pathways, with NF- $\kappa$ B as the key factor. Additionally, the findings of a study on the immunoregulatory effects of qi gong are of interest; it not only lowers the inflammatory component of innate immunity, but also enhances B- and T-cell activity (Feng et al., 2020).

Clinically, high-quality studies are increasing, documenting high and moderate efficacy for some mind–body integrative interventions, such as mindfulness for schizophrenia, attention deficit hyperactivity disorder (ADHD) and post-traumatic stress disorder (Vancampfort et al., 2020) and biofeedback and neurofeedback for depression (Fernández-Alvarez et al., 2021) and ADHD (Lambe et al., 2019). However, more RCTs are needed (Rahmani et al., 2022).

Collectively, the results of such research show the potential mechanistic mediating the transduction of nutritional and psychological interventions (psychotherapy, meditation, and mind–body techniques)

into gene expression patterns and inflammatory process regulation (Bottaccioli et al., 2022).

## Medicine and philosophy

Medicine, as theoretical knowledge and practical coded texts taught after the exceptional Egyptian debut in the second millennium BCE, spread to Greece, India, and China from the sixth to the fourth century BCE. The systematisation of medical and philosophical knowledge is a closely intertwined process. The first significant Greek and Chinese medical works were strongly influenced by nascent philosophical reflection and, in some cases, were contemporary to the teaching and works of philosophers in the fifth and sixth centuries BCE.

In Greece, Pythagoras inspired Alcmaeon who shaped Italian medical schools. Ionian naturalism and, subsequently, Anaxagoras, Democritus, and Protagoras provided categories, concepts, and scientific discoveries on humans that inspired the great medical and cultural movement initiated by Hippocrates. This, in turn, provided important elements for the platonic reflection in constant dialogue with medical theory and practice.

In Greece and China, it is common to find doctors who are also philosophers, such as Alcmaeon, Galen, and Sun Simiao, or philosophers and scholars with strong medical and scientific cultures, such as Aristotle and Zhang Zhong, who have made significant contributions to the advancement of medicine from a practical point of view.

In China, Confucian and Taoist philosophy (with comments on the ancient oracular and sapiential text *Yi Jing*, which was reported as an oral text in the ninth century BCE and as a written text in the fourth century BCE) provided the fundamental concepts (the *yin/yang* and the five agents or phase theories) that were put in place in the first great ancient medical treatise, *Huangdi Neijing* (The Inner Canon of the Yellow Emperor), whose basic materials were contemporary to Hippocratic texts, although it was written in the first century BCE (Harper, 1998).

Until a few years ago, even among scholars of ancient medicine and Greek philosophy, the Hegelian idea of the doctor as a technician in diagnosis and therapy and the philosopher as an encyclopedic scholar who illuminated the various fields of physics, logic, ethics, and metaphysics was dominant. The search for wisdom, which is inherent in the word 'philosophy', was not a characteristic of the philosopher, but, following Hegel, of the Eastern sages (which to him, philosophers were not) or, at most, extravagant philosophers of low stature, such as the cynics, who were begging on the streets of Athens and whose symbol was Diogenes, who lived in a barrel.

The unorthodox research of an outsider such as the French Michel Foucault (2022), in the seventies of the last century, did not pique the interest of the Academy much.

Thereafter, slowly, even the Academy noticed the more classic but no less revolutionary work of Pierre Hadot, who was also a colleague of Foucault at College de France. In a series of fundamental works, Hadot showed that ancient philosophy was a philosophy of life and a way of life, and that teaching philosophy implied answering the fundamental question of how to live.

Hadot documented that with the end of antiquity, philosophy passed from 'philosophy of life to discourse on discourse', transforming the philosopher 'From a wise man to the artist of reason'. In this research, the French philosopher also shows the indisputable analogies between Chinese and Greek philosophy' (Hadot, 1985; Bottaccioli, 2020).

Recently, the crisis of the reductionist model in medicine and psychiatry and, at the same time, the crisis of analytic and postmodern philosophy (Esposito, 2010, 2021) has prompted a revival of interest and dialogue between scientists and philosophers. Advances in research and the proposal of new interpretative models, particularly in immunology (Tauber, 2018; Pradeu, 2019; Esposito, 2023), have prompted a dense exchange between the two fields of knowledge.

Traditionally, philosophers have largely ignored immunology, seen as a specialised biological science dedicated to the study of the

molecular dimensions of vital phenomena.

However, recently, the situation has been changing as concepts and suggestions emerge from the study of the immune system concerning central philosophical problems such as the definition of individual, the relationship between individual and physical and social environment, holism and reductionism, and the vision of human evolution. Recently, an interdisciplinary group including philosophers, science historians, immunologists, and theoretical physicists published an opinion in the Proceedings of the National Academy of Sciences explaining why science requires philosophy (Laplante et al., 2019).

According to the authors, 'philosophy and science are situated on a continuum. [They] share the tools of logic, conceptual analysis, and the rigour of argumentation. Philosophers who possess significant scientific knowledge can contribute to the advancement of science at all levels, from theoretical to experimental elaboration'. In our opinion, the opposite is also true: philosophy, not only in the specialist department of the Philosophy of Biology, can find important stimuli and new data on which to work regarding traditional, albeit crucial, philosophical problems.

We need a philosophy to support and stimulate the process of the unity of knowledge that can be discerned even in molecular science, such as immunology. We need a philosophy that relates to science in its making and unmaking without feelings of inferiority and extraneousness, at a time when the social horizon has collapsed into a confused present that is poor in human meaning. The crisis of the great nineteenth- and twentieth-century narratives, which would have freed philosophy from the ballast of ideological systems, has not produced a renewed connection with life—the only possibility, in our opinion, for regaining a crucial position in the intellectual and cultural universe of the twenty-first century. On the contrary, in the new millennium, philosophical reflection appears to be carving out a 'modest' space for itself that does not provide for the contrast to the 'desertification of the future' after the collapse of the great narratives (Bauman, 2020; Bodei, 2006).

The relationship with science appears crucial for escaping this condition for both philosophy and science. For philosophy, that should break the ghetto as knowledge to initiate and construct itself as an ideal place for public discussion. For science, whose fundamental advances, coinciding with paradigmatic crises, occur when 'more and more scientists turn to philosophical analysis' (Khun, 1996).

## Conclusions

In this crucial phase of serious dangers and development opportunities for humankind, a new science for man and a new care model are urgently needed that use all instruments to help human health, from ultra-modern pharmacological and surgical ones to ancient and clinically valid unconventional ones, but within a framework that puts human beings, their skills, and capacity for self-regulation at the centre. They are the main actors, and it is on them that cultural and economic investments should be made.

After more than 2000 years, how to nourish life should be relearned according to modern science and technology, but with the same inspiration as both Eastern and Western ancients. For these reasons, we wish that *Brain Behavior and Immunity Integrative* succeeds in its mission of integrating scientific, cultural, and clinical information.

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## Credit authorship contribution statement

The authors contributed equally to the conception, writing and revision of the article.

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