

# From traditional Mediterranean, Ayurvedic and Chinese medicine to the modern time: integration of pathophysiological, medical and epistemological knowledge

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**Abstract:** This review starts describing traditional Mediterranean, Ayurvedic and Chinese medicine systems. Then, the “psycho-neuro-endocrine-immunology” paradigm is examined and reasons for its increasing popularity in biological and medical scientific sciences. In particular, we focus on how this paradigm helps to understand and integrate in a modern view some seminal observations and symbolic languages from the past. Thanks to current technological possibilities, the future challenge will be to conduct medical and biological forefront research, able to successfully integrate traditional medicine into the newest therapeutic schemes. In conclusion, we propose some epistemological considerations based on different examples of therapeutic integration.

**Keywords:** Integrative medicine; Ayurveda; traditional Chinese medicine; traditional Mediterranean medicine; psycho-neuroendocrine-immunology; cardiovascular research

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## Introduction: aim and methods

In this work we present a narrative overview as an educational article presenting a broad perspective about modern integrative medicine approach, describing its historical premises, and philosophical development. Our aim, discussing integrative medicine theory and context, is to provoke thought and controversy hopefully presenting epistemological perspectives in a balanced manner, stimulating scholarly dialog amongst readers. We do not

present a systematic review of the literature on a specific topic, but we would like to inform the reader about different thought patterns that can guide scientific research and medical treatment.

We referred to our personal experience, electronic databases (PUBMED, Cochrane Database of Systematic Reviews) and authoritative texts (reported in the references section) for the last part of the text dealing with modern biomedical and biochemical studies about integrative medicine. Moreover, in the first historical section, we

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referred to our personal experience and our research conducted so far reading and translating directly from the Sanskrit, Greek and Latin the ancient medical text indicated in the bibliography, along with Authoritative commentaries made on them.

## Traditional medicine

### Greek classic medicine

Greek classic medicine developed from the 5<sup>th</sup> century before current era (BCE) to the 2<sup>nd</sup> century CE in a wide variety of geographic and cultural contexts, ranging from Greek continent and colonies in the islands and coasts of the Mediterranean Sea, to Hellenistic kingdoms and the Roman Empire. This broad range of time, places, and varieties of socio-cultural contexts reflect an extremely rich and complex scientific scenario. Indeed, Greek medicine saw the development of three main medical schools, namely the Hippocratic, the Alexandrian and the Galenic one, and a variety of minor ones. Those schools were represented by physicians, who supported different ideas and approaches, sometimes scarcely reconcilable even within the same school.

The Hippocratic School developed during the 5<sup>th</sup> and 4<sup>th</sup> cent. BC in the Greek island of Cos in the Aegean Sea, close to the coast of current Turkey. According to the tradition, it was founded by Hippocrates (c. 460-377 BCE), a historical figure, who gradually acquired a mythic aura (1-4). To Hippocrates is traditionally attributed a corpus of about 60 texts which, however, are very diverse in style and subject, making the authorship dubious. Indeed, opinions expressed in those texts are so contradictory that it is unlikely for the corpus to represent the work of a single medical writer (3,5). Most texts are exploratory arguments, debating with and criticizing other authors. A sophisticated reasoning is used to understand the mechanisms underlying diseases and to categorize collections of clinical symptoms (2). Merit of the Hippocratic School was to replace the “ontological” concept, where diseases were external “supernatural” entities sent by gods, with a new vision of diseases, as caused by internal factors altering the equilibrium of the body by perturbing its physiology (6). Internal disorders could be caused also by external “natural” factors, such as the atmospheric conditions, the quality of water, food, air or habits of individuals (included their psychic attitudes) and populations. Hippocrates and his followers were inspired by pre-Socratic philosophy, which based its knowledge on

observation and rational thinking for explaining natural phenomena. A cross-fertilization between philosophy and medicine was particularly evident at the beginning of the 5<sup>th</sup> century, represented by paradigmatic figures such as Pythagoras (c. 570-490 BCE) and his disciple Alcmaeon of Croton (5<sup>th</sup> cent. BCE). In the late 5<sup>th</sup> centuries there were other important philosopher-physicians such as Empedocles (c. 490-430 BCE), Diogenes of Apollonia (born c. 460 BCE) and Democritus of Abdera (born c. 460 BCE) (1,2). Empedocles developed the theory of the four elements—air, water, earth and fire—whose different proportional relationship explained the differences between substances. Concurrent with this notion, he also tried to explain human physiology (7). The theory of four elements, combined with the theory of four qualities (hot, cold, dry and wet), became a fundamental theoretical model for the humoral conceptions, which was one of the most important achievements of Hippocratic medicine.

In many important books of the Hippocratic Corpus, such as the *Epidemics*, *Prognostics*, *Regimen in Acute Diseases*, *Affections*, clinical diagnosis and prognosis were two strictly connected moments. The Hippocratic authors tried to find some “regularity” in the great variability of symptoms, course of diseases, patients’ habits, geographic and climatic characteristics of towns and countries, seasons, and so on. They tried to connect all these features using detailed and systematic observations, creating “clinical entities” which, even if often not ascribable to our current nosology, were used as models for many following generations of Western physicians. The principal “physiological” and “patho-physiological” model developed by Hippocratic medicine was that of the humors, which inspired Western medicine for centuries and represents another fundamental achievement of that school. In many books of the Hippocratic Corpus, the body was viewed as a system of conduits (which should not be identified anatomically solely as nerves or blood vessels, not yet clearly identified at that time, but also as “functional metabolic pathways” according to a modern terminology) where factors of diseases could “circulate”. Among them, the “humors” played a leading role. Disorders developed when one or more humors were peccant, morbid, accumulated in some parts or deficient in others. While different kind of “humors” were mentioned in the Hippocratic Corpus, only in the work *On the Nature of Man* a systematic theory was established for the first time. Briefly, health and disease of a man were connected to the reciprocal balance or unbalance, respectively, between four precise humors, namely blood, phlegm, black and yellow bile. Diseases arose

when the mixture of humors became unbalanced, or when one humor became isolated (2). It is important to highlight that in the *Nature of Man* the theory of the four humors is not connected to the four elements of the universe (air, fire, water, earth), and there is no trace of its development into a theory of the four temperaments or of their corresponding character types (1). Only later, and particularly in the work of Galen, the humors were connected with the Empedocles' theory of elements and qualities. Blood corresponded to air, and it was warm and humid; phlegm correlated with water, and was cold and humid; black bile, connected with earth, was cold and dry; and, finally, yellow bile, associated with fire, was hot and dry.

The Hippocratic authors never directly addressed the question whether they could, or should, practice dissection on human beings (1). Of course, a certain anatomical knowledge is evidenced throughout the Hippocratic Corpus, but human anatomy, *per se*, was not practiced. The first medical school in which human anatomy was systematically investigated thought dissection flourished in Alexandria of Egypt under the Ptolemaic dynasty, in particular in the first fifty years of the 3<sup>rd</sup> century BC. The main school representatives were Herophilus of Chalcedon (c. 330-250 BCE) and Erasistratus of Ceos (c. 330-250 BCE) (8-10). The Hippocratic medicine was an "art" almost exclusively centered on clinical problems and the body was viewed as a sort of "black box" in which the humoral patho-physiology was deduced almost exclusively from the observation of input and output materials (11). Herophilus and Erasistratus revolutionized this model by opening the "black box", i.e., dissecting the human body to understand first the normal physiology and afterwards the patho-physiological processes. Thanks to them an unprecedented knowledge of the vascular and nervous systems, as well as of the brain, heart, and liver was achieved. Herophilus distinguished between motor and sensory nerves. The sensory nerves were filled with *pneuma*, which transmitted sensation from the sensitive organs to the brain. The *pneuma* was the result of the inspired air, which was inhaled by the dilatation of lungs and thorax, acting as bellows. The brain was the source of nerves and the unique responsible for all sense and motion. He also distinguished arteries from veins, although he did not fully understand their functions (8,10). He believed that veins derived from the liver and contained the blood which nourished all the parts of the body. Arteries, instead, contained *pneuma* and probably also some blood for nourishing arteries tunicae (10). The presence of two *pneuma*, one inside the nerves and another in the arteries,

anticipated the distinction between *psychic* and *vital pneuma*, which would become canonic in the later tradition (10,11). Erasistratus based his model upon a corpuscular theory. According to this theory, matter consisted of tiny particles interspersed with void. The nutritive particles of the blood were absorbed by the tissues through fine pores in the walls of the capillary veins. This absorption was due to a process of filling the empty spaces formed by the degradation of matter produced in the body by its living activity (12), according to the notion that vacuum tended to fill itself from neighboring matter (13). With regard to the arterial system, Erasistratus believed that it was filled with *pneuma*, which was the product of the process of inhalation of air. The *pneuma* arrived from the lungs to the left ventricle of the heart, which attracted during its diastole. Through the arterial system, the *pneuma* arrived at the muscles, forming the energetic principles of muscular movements: it became, then, the "*vital pneuma*". A part of it arrived at brain ventricles, where it was furtherly transformed into "*psychic pneuma*", responsible of sensations, voluntary actions and intelligence (11). In Erasistratus' physiology, there were three principal systems: the venous, filled with blood, the arterial, filled with *vital pneuma*, and the nervous system, filled with *psychic pneuma*. These systems had no visible communications. So, for explaining how the blood could nourish the arteries and how sensations could arrive where there were no visible nerves, Erasistratus proposed the existence of an invisible system of veins, arteries and nerves, called *triplokia*, supporting the reciprocal and physiological communication between the visible and the invisible structures (14). On the base of this model, Erasistratus derived also a new pathology. Disease were caused by a form of "plethora", that is, an excess of blood which overflowed into either the arterial or the nervous system. If the blood overflowed into the arteries, inflammatory and febrile diseases arose. If it overflowed into the nerves, different kind of "paralysis" developed. Therapy followed this model by reducing the overflowing of blood by means of diets, purges or emetics. Galen of Pergamon (c. 129-216 CE) was a Greek Roman physician who is considered, with Hippocrates, the father of Western medicine (15). Galen was able to reconcile, in an eclectic way, the Hippocratic and the Alexandrian traditions. He integrated the clinical and the anatomo-physiological approaches adding important notions and inspirations from Plato, Aristotle and the Stoics (16). Galen furtherly developed the "Hippocratic" system of humors and incorporated into it the theory of *pneuma* from the Alexandrian school. He

modified the previous concepts by anatomical investigations and vivisections on animals, thus elaborating a new physiological model. In his *On the Complexions*, in particular, he stated that bodies were a mixture of the primary qualities (hot, cold, dry and wet), or better, of their correlated elements, namely air, fire, water and earth (17). In the *On the Natural Faculties*, he further connected to the qualities and to the elements the four humors and establishing four basic “temperaments” (18). In the *On the Usefulness of the Parts* and *On the Affected Parts*, instead, Galen treated the “homogeneous” and “heterogeneous” parts of the “human” body. All these works, described the anatomy, physiology, and a sort of anatomically oriented pathology of men. Galen recovered and developed an “archaic” concept, namely that of “*eucrasia*” (19). The body was in a healthy state if there was a “good mixture” of elements and a good proportion between its anatomical parts, while it became ill if there was a “*dyscrasia*” (literally meaning “unbalance” and indicating, in “modern” terms, a pathologic alteration of the chemical, chemico-physical, immunological characteristics of organic liquids and blood). In his *On the Therapeutic Method* and *On Temperaments*, Galen distinguished eight basic kind of “*dyscrasia*”: in four a single quality was dominant and in the remaining four two qualities prevailed. This model influenced also the therapy, as drugs were created according to the elements and qualities of their compounds and in correlation with the particular patient *dyscrasia* (20). Moreover, Galen further developed the link between humors and age. Galen connected the four humors and the four stages of life in a system including humors, seasons and ages: blood- spring-infancy; yellow bile-summer and youth; black bile-autumn and maturity; phlegm-winter and older age. He used this new correspondence to create an original relationship between the elements, the humors and character.

### Chinese traditional medicine

As in Indian and Greek history, at a certain point, medicine started to be strictly connected with “natural philosophy”, i.e., with the knowledge of the fundamental elements and mechanism of the natural world. In Chinese history this happened, in particular, during the Han Dynasty (206 BC-220 CE). The most classic Chinese medical text, *The Yellow Emperor's Inner Canon of Medicine* stated that: *Although the origins of illnesses are traceable to many causes, all of them result from (something) evil. [...] That is to say, everything that is not part of the normal order in the human organism, (such as) wind,*

*cold, dampness, hunger, fullness, taxation, and idleness, is evil – and not solely the influences of demons and epidemic illnesses (as some authors have claimed)* (21).

With the consolidation of “Imperial Unity”, three concepts were finally codified, becoming the core of Chinese medicine: *Qi*, *Yin-Yang* and *Wu Xing*. The *qi* approximately refers to the energetic feature of the cosmos and the human body, even if, at the same time, indicates a material entity, or, rather, a sort of “psycho-physical matter” ubiquitous in the universe, and characterized according to different degrees of “thickening”. For instance, a stone represents an object with a deeply thickened *qi*, while mind and spirit represent states of *qi* particularly rarefied. “Sky” (or “Heaven”) and “Earth” symbolize the two most extreme opposites, where the first is composed of the maximum rarefaction and dispersion of *qi*, while the second is composed of its maximum condensation and aggregation. Several scholars noted the affinity between the oriental *qi* concept and the Western concept of energy (22,23). *Yin-Yang* represents the bipolar aspect of any phenomenon of the reality, both spatial and temporal, which is characterized by the presence of opposites, but complementary aspects. The concept of *Yin-Yang* derives from the ideas of *yi* (mutation), *pien* (cyclic change) and *t'ong* (mutual permeation) (24). As resumed by Francisco Lozano:

*Yin is associated to qualities such as cold, rest, responsiveness, passivity, darkness, structure, the interior, downward and inward motion, and decrease. By contrast, yang is associated with heat, stimulation, movement, activity, light, the exterior, upward and outward motion, and increase. It is important to observe that these aspects occur only in relation to each other (i.e., cold can be defined only by the knowledge of heat, darkness by the presence or absence of light, and so on). In medicine, yinyang theory would be applied to opposites such as structure (yin) and function (yang), the lower body (yin) in relation to the upper body (yang); however, the concepts of yinyang are never absolute. They are applied to given objects in order to express their relation to other objects, actions, or processes* (25).

Finally, *Wu Xing*, also named “Five Phases” theory, refers to the five “elements”—Fire, Earth, Metal, Water, and Wood—which constituted the essential principles of natural world. The term “element” could be misleading: it should be preferable to translate this concept as “movement” (26,27) or “phase” (28). These components of the reality, in fact, are better understood as five “phases” of cycles of transformation and interrelation. In particular, among them there are connections of “generation” (*sheng* cycle), relationships of “control” or “overact” (*ke* cycle), and



“insult” (*wu* cycle) (29). These cycles, in turn, are ruled by the pivotal dynamic of *Yin-Yang*. These phases, in their immutable cycle of succession, were correlated with cardinal directions, seasons, colors, musical tones, and bodily organs. In connection with the internal tissues, organs and structures associated, they are also fundamental in acupuncture techniques.

An important distinction in Chinese Traditional Medicine is between viscera *zang* (*Yang*) and organs *fu* (*Yin*). Viscera *zang* transform and digest, eliminating impure residuals from solid foods and liquids. The organs *fu* collect pure essences resulted from the transformation processes realized by viscera *zang*. These pure essences, created by *zang* and accumulated by *fu*, are essentially characterized by the *qi*, which represents the vital force needed by all the body's parts for living. The *zangs* store but do not eliminate, while the *fu* eliminate but do not store. What the organs stored was described in the *The Yellow Emperor's Inner Canon of Medicine* as, ‘we read that the liver stores the blood, which contains the soul; that the heart stores the pulse, which contains the spirit; that the spleen stores nutrition, which contains the thoughts; that the lungs store the breath, which contains energy, and finally, that the kidneys store the germinating principle, which contains the will’ (30).

Viscera *zang* are six: stomach, small intestine, large intestine, urinary bladder, gallbladder, and the so called “triple burner”. Organs *fu* are five: kidneys, liver, heart (*xin*), spleen, and lungs.

The five elements, as already stated, are principles of transformation strictly related with seasonal cycles. Health derives from conforming to the activities and characteristics typical of each season, in relationship with the season immediately preceding and the following one, in correlation with all the features analogically connected with each one of the given element, included bodily organs. In the *Canon*, for instance, we find the following statement:

*The three months of springtime are called period of beginning and development (of life). [...] During this period (the body) should be encouraged to living and not to dying; (to it) should be freely given and not deprive it from something; it should be rewarded and not punished. [...] Those who disobey to the springtime laws will be punished with a liver disease. To them, the following summer will brought shivers and changing (in worst); therefore they will have very little to support their development (during the summer)* (31).

Acupuncture is still one of the best known and diffused practices of traditional Chinese medicine, even if it is still debated in culturally Western countries (32-34). The

Chinese name of that practice is *Zhenjiu*, meaning needle and moxa, while “acupuncture” comes from the Latin words *acu* (needle) and *puncture* (34). Probably, the earliest written mention of the practice of acupuncture can be traced in a manuscript found in a tomb of the early Han period: “[...] *When the qi rises at one moment and falls in the next, pierce it with a stone lancet at the back of the knee and the elbow*” (35). Acupuncture emerged in its complete or “orthodox” form during the Han Dynasty, as a product of the *Yin-Yang* and *Five Phases* theories (35). This practice consists in the introduction of hot or cold needles into the body at certain specific points. These points were crucial sites of the “channels” or “meridians” (named *mo*) where the *qi* flowed around the body. They were placed, in particular, where the channels crossed and around the joints (35). The needles could be made of flint, bone, silver, gold, copper, brass or steel, according to different periods, uses, or scopes. For the same reason, they could be of several dimensions (in width and length). Again, in the *Canon*, 365 points are described to correspond with the days in the year, but they could vary with different authors, arriving up to more than 600 points. The theory on which acupuncture was based stated that the body was crossed by a system of *meridians* through which the life-energy known as *qi* flowed. There were 12 principal “meridians”, divided into *Yin* and *Yang* sets and grouped according to their belonging to the arms or legs sections. *Five-Shu points*, next to the nails, form the origin of the 12 *Yin* and *Yang* meridians and are correlated with the five elements. They are particularly important in acupuncture practice (36). These points, in fact, are on the major surface of the body on the fingers and toes, and gradually enter within the body all along the course of the channels. For that reasons, the points on these extremities are particularly susceptible to external pathological factors (i.e., wind, cold and humidity) and consequently are of major importance for therapy (29). They are named according to distance from the fingers or toes and the elbow or knees, respectively. The first, on the surface of fingers and toes, is named *well* (*jīng*), the second *source* (*yīng*), the third *brook* (*shu*), the fourth *river* (*jīng*) and the fifth *sea* (*hǎi*) (29). Their names are based on the analogy between these channels and the nature, where a well could gradually become a river and flows into the sea. Through this circuit, the *qi* moved around the body and health required that the circuit was aligned with cosmic movements. To be “weak”, move in the wrong direction, or be blocked or stagnant inside any part of the body means disease (37).

This extremely complex set of theories, principles, ideas

and practices presents some common basic characteristics which can be summarized as follows. First, the strict relationship and cross-fertilization between philosophy and medicine guided both classic Greek and ancient Chinese physicians in their understanding of the human body as an entity strictly connected with nature and their fundamental elements. The four or five elements were principles regulating both natural phenomena and the physiology of human being. The balance or unbalance of these elements - in their strict relationship with the four humors and *pneuma* of the body, for the Greek Medicine, and the system of *Qi* for the Chinese tradition—determined health and disease. Therefore, the body was seen as an integrated system and its health and disease were correlated to the balance or unbalance of its entire component, both anatomical and psychological. Moreover, the body was an integrated entity with nature. Microcosm and macrocosm were strictly interconnected, so that environmental factors played a major role in determining health and disease. That health and disease were commonly conceived as a state of balance or unbalance between mind and body, namely *pneuma* or *qi* and the elements or humors, means that, in classic Greek and Chinese medicines, the conception that health and disease could be standardized states did not exist. In other words, any individual was a unique product of the interaction between the basic psychic and physical elements that, in turn, was determined by his specific development, habit and interaction with the environment. The bodily and natural principles were categorized not only in a quantitative way, but also according to their qualities and they were viewed always in their interaction with the whole microcosm-macrocosm system.

### Ayurvedic medicine

Āyurveda, the “science” (*veda*) of “(long) life” (*āyus*), is the earliest form of rational medicine of India<sup>1</sup> and one of the few pre-modern medical traditions which continues

to be practiced. Āyurvedic literature, redacted in Sanskrit, consists of compendia (*samhitā*), glosses (variously called *bhāṣya*, *dīpikā*, *prakāśa*, *tippanī*) and digests of *materia medica* (*nighaṇṭu*). The first medical compendia can be dated to the second half of the first millennium BCE, although they have been rewritten and expanded at multiple times across the centuries. By the 19<sup>th</sup> century, Indian scholars arranged the chief *samhitās* in two groups:

- (I) The *brhatrayī*, or “greater triad”, comprising the *Carakasamhitā* (or Agniveśatantra) (1st–2nd century) (38), the *Suśrutasamhitā* (3rd–4th century)<sup>2</sup> (39) and the *Aṣṭāṅgagr̥hasamhitā* of Vāgbhaṭa (6th–7th centuries)<sup>3</sup> (40,41);
- (II) The *laghutrayī*, or “lesser triad”, made of the *Mādhavanidāna* of Mādhavakara (8th century) (42), the *Śārṅgadharasamhitā* (c. 14th century) (43) and the *Bhāvaprakāśa* of Bhāvamīśra (16th century) (44)<sup>4</sup>.

Āyurveda primarily aims at identifying the causes (*hetu*) and the symptoms (*liṅga*) of diseases (*roga*, *vyādhī*) as well as the remedies (*auśadha*, lit. “herbs”) to ensure recovery, adequate quality of life and life expectancy. Although there is general agreement on the scope of medicine, views on pathology, diagnostics and therapeutics may vary to a great deal, thus making it hard to identify a standard. For the purpose of this article, the analysis will be limited to those medical theories, which examine health seekers as integrated within their social and environmental space.

According to a view first attested in the original work of Agniveśa (CaS i.1.54; cf. ii.1.3), the physician (*vaidya*) should try and understand pathological causes by considering the wrong (*mithyāyoga*), absent (*ayoga*) or excessive (*atīyoga*) association of the patient with time (*kāla*), intellect (*buddhī*)<sup>5</sup> and sense organs (*indriya*)<sup>6</sup>.

The conceptualization of the human body and its formation provides the basis for holistic therapeutic approaches. Already in Caraka, we see that the embryo (*garbha*) is made of mother (*mātr* = blood), father (*pitṛ* = semen), the self (*ātman*), wholesomeness (*sātmya*), the juices

<sup>1</sup> Although there is abundant evidence of a healing culture in earlier Vedic civilization, texts like R̥gveda, Atharvaveda and the later Kaus̥ikasutra bear witness to a form of medicine which is primarily ritual.

<sup>2</sup> The core sections of the Carakasamhitā and the Suśrutasamhitā should be dated back respectively to 500 BCE and before 250 BCE.

<sup>3</sup> To Vāgbhaṭa is also attributed the Aṣṭāṅgasamgraha and, among the others, the iatro-chemical treatise known as Rasaratnasamuccaya.

<sup>4</sup> There exist other texts whose original sections might be as early as Carakasamhitā (on internal medicine) and Suśrutasamhitā (on surgery). Amongst these, the Bhelasamhitā (45) and the Kāśyapasamhitā (46) (on obstetrics, gynecology, and pediatrics), both fixated in their actual form between the 4th and the 7th centuries CE. For an exhaustive census and analysis of āyurvedic works, see Meulenbeld's encyclopedic A history of Indian medical literature (47).

(*rasa*) produced by the mother's digestion and mental faculty (*sattva*) (CaS iii.3.3)<sup>7</sup>. Following gastric "cooking" (*pācana*, *dīpana*), food and beverages are transformed into the "three foundations" (*tristhūna*) of the body, namely (I) the seven tissues (*saptadbātu*), (II) the three humors (*tridoṣa*), i.e., wind (*vāta*), bile or choler (*pitta*) and phlegm (*kapha* or *śleṣman*), and (III) excreta (*mala*). (SuS i.14.10-12; cf. ŚāS i.5.11-12).

Since everything derives from food, which in turn results from aggregates (*yukta*) of the modifications (*vikāra*) of the five principal elements<sup>8</sup>, Āyurveda insists on the importance of the way in which a patient and environment relate to each other. Depending on the circumstances of the patient, environmental modifications can be avoided, if dangerous, sought for, if beneficial, or maintained, if appropriate.

Diseases are usually classified as internally caused (*nija*), invasive (*āgantū*) and mental (*mānasa/mānasika*) (CaS i.11, cf. SuS i.1, AHS i.1, BhāPr i.6.2). An alternative frame is provided by Suśruta, who identifies seven kinds of ailments: (I) *ādibalapravṛtta*, resulting from procreation, i.e., hereditary disorders; (II) *janmabalapravṛtta*: congenital diseases; (III) *doṣabalapravṛtta*: conditions resulting by aggravation or imbalance of the humors; (IV) *saṃghātabalapravṛtta*: disease caused by trauma and/or injuries; (V) *kālabalapravṛtta*: diseases resulting from atmospheric conditions; (VI) *daivabalapravṛtta*: diseases caused by the gods; (VII) *svabhāvabalapravṛtta*: conditions depending on natural factors (e.g., old age, hunger, thirst, etc.) (SuS i.24) (48). On each case, etiology is different. For instance, internal (i.e., physical) ailments can be imputed to the blockage of channels, the withholding of basic urges or problems regarding the seven tissues or the three humors. Conversely, invasive diseases may result from factors unrelated to the willing and lifestyle of the patient, e.g., wars, natural disasters, famines, failing policies and bad administration (leading to impoverishment, etc.), and, ultimately, disregarding the appropriate code of conduct (*dharma*). In the case of mental disorders, medical compendia signal as potential causes internal pathologies or external agents (e.g., "demonic" possession, misbehavior, etc.). It so emerges that, unlike what is found in far too

many secondary sources, Āyurveda is not just "humoral" medicine, and certainly the "imbalance" of the *doṣa*s is not the only cause of disease. Also, there is a discrepancy between the earliest tradition and slightly later sources.

Caraka and Buddhist sources call "*dbātu*" not just the seven bodily constituents but also the three humors. Only when the latter are found in the wrong part of the body<sup>9</sup> or are aggravated (*prakupita*), they are called *doṣa*s (lit. "defects", "faults", "vices") and become pathogenic elements (*doṣasaṃgraha*, CaS i.1.57). Conversely, from Suśruta onwards, bile, wind and phlegm are always called *doṣa*. Further to that, it should be noted that whereas Caraka refers to *tridoṣa* ("three faults"), Suśruta says that physical diseases result from the ingestion of foods and beverages which causes the "imbalance" (*vaiśaṃya*) of *vāta*, *pitta*, *kapha* and *śoṇita* (blood) or their "combination" (*saṃnipāta*) (SuS i.1.25b, cf. BheS i.26.34, ŚāS i.5.54) (49-51). This suggests that early Āyurveda was a somehow heterogeneous tradition with medical schools following different philosophical systems and having varied approaches to pathology and therapeutics. Only from around the 7th century, with the *Aṣṭāṅgabṛdayasaṃhitā* and the *Aṣṭāṅgasamgraha* of Vāgbhāta, if we agree on single authorship (52), a clear effort at systematization is discernible.

Since its early stages, Āyurveda indicates three therapeutic courses: the first is about the gods (*daivavyapāśraya*) (e.g., ritual offerings, prayers, austerities, repetition of *mantras*, etc.), the second requires reasoning (*yuktyvyapāśraya*) and the third is about the control of the mind (*sattvāvajaya*), i.e., mental health (CaS i.11.54). More generally, treatment could be ritual (CaS i.30.21) or non-ritual. The latter is further divided into three approaches: without medicines, with medicines and surgical. Treatment without medicine is of great interest in that it demonstrates a profound awareness of the relation between patients, the environment in which they live as well as their own history and personal circumstances. As Caraka points out:

*He [the wise person] should also make every effort to cultivate a knowledge of self, environment, family background, time, strength, and vigor (ātmadeśakulakālabalaśaktijñāna). And he should*

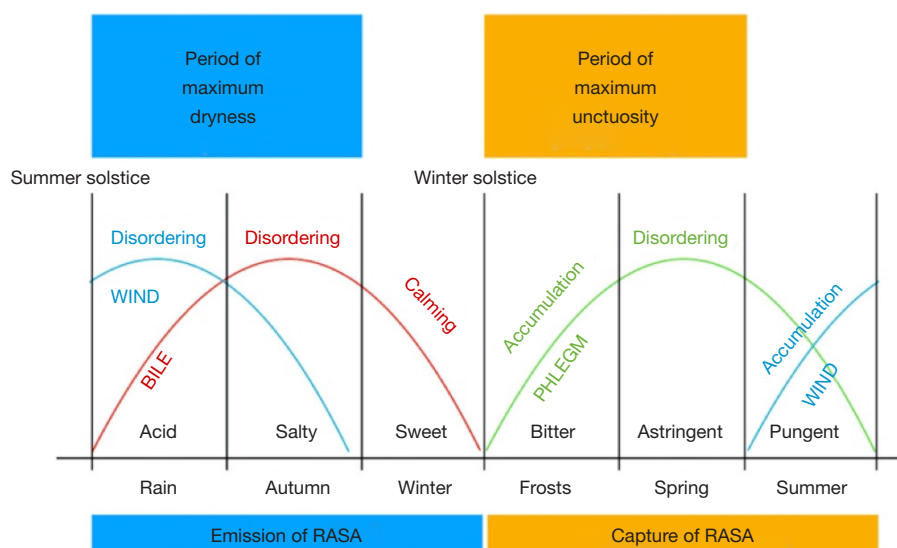
<sup>5</sup> CAS I.8.15-16.

<sup>6</sup> CAS I.11.37, ASAM I.22.7.

<sup>7</sup> In SUS III.5.3, Suśruta considers the formation of the embryo as resulting from semen (*śukra*), blood (*śoṇita*), the self (*ātman*), nature (*prakṛti*) and consciousness (*cetanā*).

<sup>8</sup> The *pañcamahābhūta*, i.e. air (*ākāśa*), wind (*vāyu*), fire (*agni*), water (*āpaḥ*) and earth (*prthivī*),

<sup>9</sup> The wind is primarily located in the intestine, the bile/choler in the navel, and the phlegm in the chest.



**Figure 1** Humors and seasons. Original figure made according (55).

*cultivate people who know about such matters. (CaS i.11.46).*

Therapy without medicines includes, amongst the others, “pointing out dangers to the patient, or in surprising, making forget, agitate, delight, threaten, or strike him or her, or putting them to sleep” (53). Other important approaches concern not suppressing natural urges (*navegāndhāraṇa*) and planning appropriate regimens (*ācāra*). In the former case, which is detailed as early as Caraka, withholding urine, feces, semen, wind but also sneezing, clearing the throat, yawning, hunger, thirst, tears, sleep, or the “panting induced by exertion” (CaS i.7.3-4) are explained as the cause of several diseases. Yet to avoid excessive indulgence in satisfying impulses, the āyurvedic *vaīdya* warns his patient to always keep in mind the importance of decorum and never favor ill will, bad taste and rudeness.

The concept of *ācāra* is equally important. Vāgbhāṭa’s *Aṣṭāṅgahrdayasamhitā*, a text which provides the most effective synthesis of Indian medicine (54), discusses daily and seasonal regimen by examining environment (*cara*) and body (*deha*) in relation to time (*kāla*) and land (*deśa*) (cf. BhāPr i.5). This led Zimmerman to theorize that “Āyurveda represents two sciences in one: a biogeography absorbed into a therapeutics” (55).

Time, which is unambiguously defined by two sets of three seasons (*rtu*)<sup>10</sup> starting respectively with the summer

and the winter solstice, is of the utmost importance in predicting the behavior of the three *doṣas* and therefore developing an efficacious therapeutic plan<sup>11</sup>. This explains the importance of living a balanced life in harmony with nature as well as one’s own social space. The figure below, derived from Vāgbhāṭa’s maxim: “Accumulation, disordering and calming take up three seasons, for wind those which begin with the summer, for bile those which begin with the rains, for phlegm those which begin with the frosts” (AHS i.12.24-25), summarizes at best this relation (55) (Figure 1):

As for land (*deśa*), this is uniquely defined by three kind of soils which in turn permit to classify food, to identify the most suitable physical activity and, more importantly, to prepare drugs. Though Caraka too addressed this issue (CaS i.27.332-333), it is Suśruta who first detailed it with greater articulation:

“The place is *ānūpa*, *jāṅgala*, or *sādhāraṇa*.

*Ānūpa*: the place characterized by an abundance of waters, the uneven terrain, rivers, rains and forests the softness and freshness of the winds, the abundance and height of the mountains and trees; the bodies of its men are soft, delicate and fat, disorders of phlegm and wind predominate.

*Jāṅgala*: the free, flat place characterized by sparsely scattered or rare thorny shrubs, a scarcity of water, rains,

<sup>10</sup> Vasanta (Spring), Grīṣma (hot season), Varṣā (rainy season), Śarad (Autumn), Hemanta (Cool season) and Śiśira (Winter).

<sup>11</sup> See Cakrapāṇidatta’s Āyurvedadīpikā ad CAS I.1.54.



running water and wells, the heat and harshness of the winds, the sparsely scattered or rare rocks; the bodies of its men are tough and dry, disorders of wind and bile predominate.

*Sādhārāṇa*, the place which presents characteristics of both the others at once. Because, in a *sādhārāṇa* place, the cold, the rain, the heat and the wind are equal and the people enjoy an equality of humors, for that reason it is conceived as *sādhārāṇa*. The humors are no longer so strong, originating in the water and transplanted into a dry terrain, or else the converse, for they accumulate in their own place but fail to gain in intensity in another. Whoever behaves in a suitable fashion has nothing to fear from the place, his ways of feeding, sleeping and moving his body, etc., have all the qualities of that place.” (SuS i.35.42-47, translation by F. Zimmerman).

Beside its structural subdivision, place (*deśa*) is more generally considered of two kinds: the land (*bhūmi*) and the body (*deha*) (AHS i.1.23ab). It so appears that the *vaidya* should “create a doubly appropriate relationship: to render the environment appropriate to the needs of the patient and, conversely, to render the regimen of the patient appropriate to the ecological conditions.” (55). In doing so he interprets diseases as a series of factors which may weaken, aggravate or disrupt the balance of humors and tissues and, as a consequence, the relation between self (*ātman*), space (*deśa*) and time (*kāla*).

After advice on daily and seasonal regimen, medical compendia insist on the benefit of adequate physical exercise (*śarīraceṣṭā*), defined as “intentional movement of the body undertaken to gain firmness and an increase in strength” (CaS i.7.30). This is further corroborated by such hygienic norms as bathing, massaging, appropriate choice of clothes (which must be always clean) and diet (*ābhāra*).

Whether we talk of cuisine or pharmacology, two sciences that often overlap (CaS i.26.12), *Āyurvedic* treatises carefully evaluate the proprieties of plants, herbs,

animal products, metals and minerals as well as the way in which they are combined (*samyoga*). To such end, *nighaṇṭus*, glossaries of *materia medica*, were redacted from the 10th century<sup>12</sup>. Since drugs and foodstuff compensate for what the patient lacks (CaS i.1.62), the physician should be familiar with the constitution (*prakṛti* or *svabhāva*) and the requirements of his patient (*upayoktr*, lit. “one who enjoys [food]”) but also with the nature of foodstuff, the ways in which ingredients should be prepared (*karaṇa*), the place (*deśa*) where they are sourced and their seasonality (*kāla*). Next, he should consider the principles of pharmacology, namely the theory of savors (*rasa*). According to such scheme, each and every ingredient has the potential to be beneficial, toxic or capable to maintain the correct equilibrium. This depends on the ways in which substances react based on their qualities (*guṇa*)<sup>13</sup> and savors (*rasa*)<sup>14</sup> (58,59). However, as outlined in an important article by Dominik Wujastyk, the world (*jagat*) can be seen as an ecosystem revolving around basic opposites, namely *agni* and *soma* (60), fire and water, hot and cold, red and white, parched and nourished. *Āyurveda* too, with its strong emphasis on the relations between the environment and the various classes of beings inhabiting it, reflects this view. It is thus not unlikely that Indian medical authorities developed pharmacological principles as well as ideas on body, health and diseases moving from the concept that wellbeing derives from the exchanges between basic watery and fiery categories.

This brief survey, far from being exhaustive, demonstrates how *Āyurveda* has always privileged a holistic approach in which (I) anatomy and physiology, (II) pathology, diagnostics and prognostics and (III) therapeutics require a high degree of flexibility to develop unique strategies to the unique nature and (personal, social and cultural) circumstances of patients vis-à-vis the ever changing features of the environment in which they live. Yet eventually, as Agniveśa first cautioned us, any human

<sup>12</sup> The most important glossaries of materia medica are the *Dhanvantarīyanighaṇṭu*, the *Rājanighaṇṭu*, the *Madanapālānighaṇṭu* and the *Bhāvaprakāśanighaṇṭu* (56,57).

<sup>13</sup> Qualities are listed as ten opposites, namely heavy (*guru*) and light (*laghu*), slow (*manda*) and fast (*tīkṣṇa*), cold (*hima*) and hot (*uṣṇa*), unctuous (*snigdha*) and dry (*rūkṣa*), smooth (*ślakṣṇa*) and rough (*khara*), solid (*sāndra*) and liquid (*drava*), soft (*mṛdu*) and hard (*kaṭhina*), stable (*sthira*) and mobile (*cala*), subtle (*sūkṣma*) and gross (*sthūla*), non-slimy (*viśada*) and slimy (*picchila*) (CAS III.6.10; SUS I.40.10-12; AHS I.9).

<sup>14</sup> *Āyurvedic* pharmacology is built on four concepts: (I) six basic savors: sweet (*madhura*), sour (*amla*), salt (*lavaṇa*), bitter (*tikta*), pungent (*kaṭu*) and astringent (*kaṣāya*); (II) modified post-digestive (*vipāka*) savors; (III) potency (*vīrya*), i.e. the ability to resist to digestive fire; and (IV) special potency (*prabhāva*), which serves to justify exceptions (AHS I.1.14-18).

being is ultimately responsible for their own pleasure (*sukha*) and pain (*duḥkha*) (CaS ii.7.22).

### ***Bichat's and Virchow's models: the dawn of "modern medicine"***

The (Italian) National Bioethics Committee in 2001 defined medicine as "the art and science of diagnosis, treatment of disease, as well as maintenance of health" (61). In this brief definition different conceptual directions are condensed. These conceptual directions have been intertwined in the history of medicine in perennial opposition. We refer to the "rationalist-mechanistic-reductionist-technical-fundamentalist/dogmatic" line of thought, which developed in the West World after Virchow and the "vitalist-empirical-systemic" (62)—typical line of traditional medicines but also the thought of Bichat.

The traditional Morgagni-Bichat-Virchow "genealogy" is presented in all the Manuals of History of Medicine (63) as a key center allowing medical knowledge to acquire "certain"/"scientific" bases about the organization of the human organism and about the passage from a state of health to one of disease (pathophysiology). This interpretation does not express the profound epistemological differences between the three great authors of biomedical thought at the turn of 1600–1800 BC and offers a distorted view of biomedical science as linear knowledge solidly founded on descent into the ever smaller. It means filtering history already starting with a mechanistic/reductionist lens. Presenting the transition from the organ (Morgagni) to the tissue (Bichat) and the cell (Virchow) as fundamental to proceed from a supposed "generic" and "pre-scientific" vision to a "precise" and "scientific" supposed one is anachronistic and misleading. In truth, as Bottaccioli (64) describes, Bichat does not study the tissue as a smaller and therefore "more detailed" and "more precise" level of the organ. The problem between Morgagni and Bichat does not concern the dimensions (macro/micro) nor the location of the pathology (organ/tissue). Bichat wanted to change "the way of considering pathological anatomy" (65), against Morgagni's "topographical logic", proposing to analyze the affections common to each system to then see the specificity of the organ. He proposed to contextualize the disease of an organ focusing on the systematic intertwining of the different tissues composing it.

Bichat did not want to found a "mechanistic" histology but, on the contrary, his scientific program envisaged the construction of a medicine that contemplates the

localization of the disease in a systemic physiological framework. Here the difference towards Morgagni and Virchow is clear. The German pathologist considered the organism as a "federation of cells" where the cell itself, like a monad, determines the whole balance between health and disease (64). From this point of view, there is no linearity between Bichat and Virchow, but a profound diversity of scientific, *systemic*-French- and *reductionist*-German- model. Two models that are still contending the guidance of science and medical practice.

Einstein said: "It is the Theory that allows you to observe Reality." There are no facts without their interpretation. And from a certain way of observing reality derives a certain way of interacting with it.

Thus it has been speculated that doctors/researchers from Virchow onwards, who believe in the "rationalist-mechanistic-reductionist-technical-fundamentalist" model may be seen as focused mostly in mechanistic aspects, may consider science in its exclusive technical sense. According to this rather dogmatic view, human beings can be "technicalized" and calculated and a pathological process represents a deviation from statistical "normality" or a "defect" which, in the history of medicine, was first located in organs, then in cells or in one or more molecules and currently in DNA. The human being is a linear sum of parts. There are single necessary and sufficient causes of disease, which are defined as a "pathological *state*" that must be *quantified*. If a part does not work, it needs to be repaired or replaced. It may not be very useful to invest in prevention, because in any case a machine will sooner or later break because of wear. If men are machines composed of similar parts, then "logical" and "possible" are considered only *standardized* treatments using similar dosages of drugs against *personalized* treatments. Following this thinking, the need for super-specialization of knowledge and for "treatment protocols" derives. Case of non-compliance with protocols may have legal consequences and generate the so called defensive medicine.

The Bichat-type physician/researcher, with an empiricist-systemic orientation, instead, is mostly a reader, an artist (66), considers science as a process of knowledge in progress in its theoretical as well as technical form. He is a prudent scientific being, aware of the problematic nature of the concept of "cause". He is aware of its only *probable* knowledge and therefore constantly tries to "investigate" the single human being in front of him and the processes that involve him before using pre-defined "labels" (67). The interaction between multiple elements reveals properties

that cannot be explained by the individual elements of the system. As Aristotle already said: “the human being is more than the sum of its parts”. The human being is a chaotic and complex network of dynamic processes. Crucial for disease development are alterations of the relationship between the individual with himself and his environment, the lifestyle, the psychological dynamics. Disease development is a progressive process with a network of contributing causes that may be necessary but not sufficient alone to determine the final phenomenon. As in the ancient medicines, space is given to the *quantitative* but also qualitative study of natural phenomena. A sick person needs to be brought back into *balance*. In fact, a “sick car” can have all the parts in order but a bad driver who is responsible for the “dysfunction”. Prevention and rehabilitation is the foundation of this type of vision of man and life (68,69). Individuals are different and specific and the therapy must be individualized (70). The specialization of knowledge and the observations obtained from the study of a population must be relativized in front of the single case that the doctor has in front of him and which may not fall within “rigid statistical parameters” (71,72).

### **Psycho-neuroendocrine-immunology, epigenetics and Biophysics as a possible integration model**

If we consider Hans Selye’s studies on stress (73), the discovery of the multi-organ crosstalk between the nervous, endocrine and immune systems via neurotransmitters, cytokines and hormones (74,75) but also the notion that biological phenotypes are influenced by stable, reversible and heritable epigenetic modulation of DNA (76), then biological reductionism may appear an obsolete epistemological and therapeutic paradigm (77). The “normal” thresholds may be questioned (71,72) as health or illness of a human being actually represent the result of the relationship with himself and with the environment (78,79). Alongside the advent of Psycho-neuroendocrine-immunology and Epigenetics (*Figure 2*), new evidence in the biophysical field is further shifting the scientific center of gravity from the “chemistry point of view” to the “physical point of view” of the human being. Many biological processes are too rapid (90,91) to be explained by chemical diffusion mechanisms based on stochastic variations of solute concentrations or ligand-receptor dynamics. Ondulatory oscillating processes, long-range molecular interactions involving water (92,93), interactions of weak electromagnetic fields (94), cellular behavior regulation

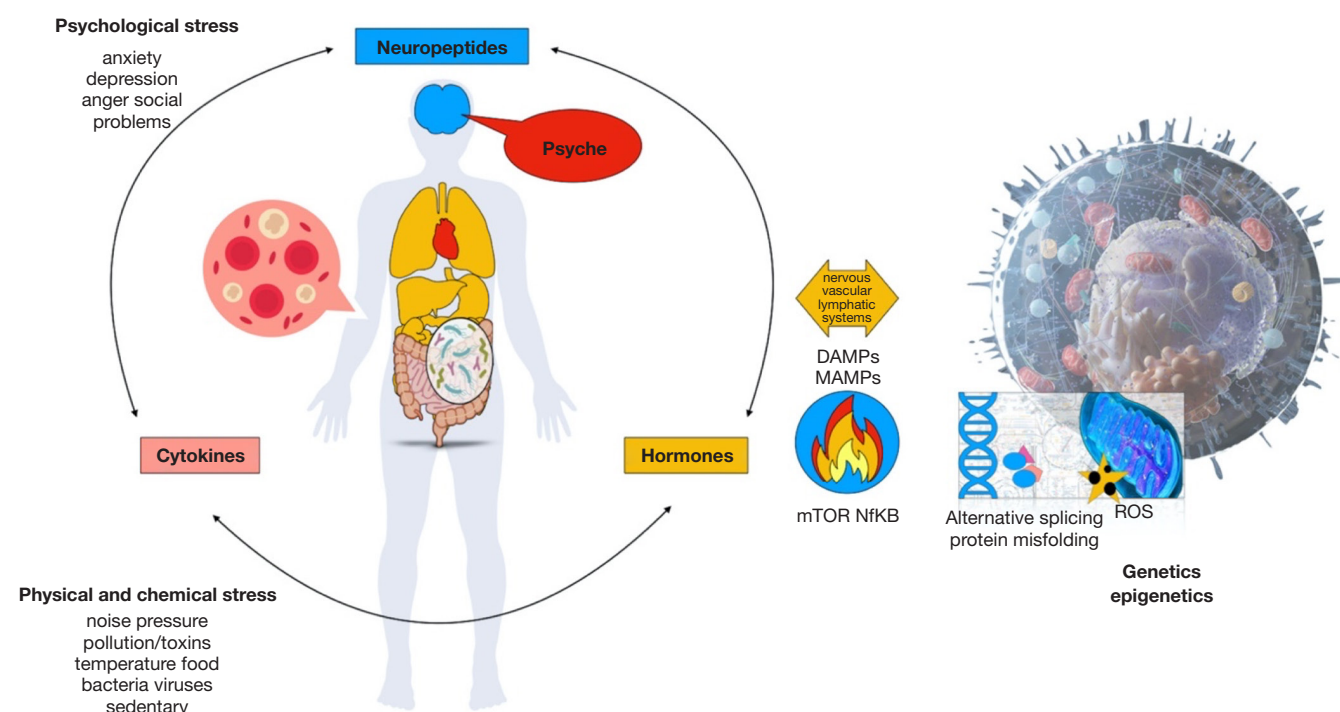
thanks to acoustic waves (95) represent the new frontier of biomedical research. And, probably, they will allow a greater understanding of those ancient knowledge, very refined, but expressed in a language classified as “symbolic” by a “modern man”.

The complexity of nature and of physiological and pathological phenomena is evident, but medicine still needs to draw further adequate methodological consequences from it. In clinical medical practice a reductionist, hyper-specialist and technological, “drug-centric” way is seen. Guidelines and protocols, which are merely focused on (96) statistics erroneously understood as an instrument of “truth” (97,98) can clash with multiform reality (89,96-103). The “etiological therapy” postulates the existence of a single cause deemed necessary and sufficient to explain a pathological process. This is a pre-requisite for “gene therapy” or “antiviral therapy”. This may certainly a useful approach in many cases, however not always. Studies of twins very often show different phenotypic results with the same genome (103) or asymptomatic/not infected subjects are present when exposed to a common infectious agent. There is the symptomatic “suppressive therapy”, typical of pharmacological mechanisms and the “replacement therapy”, “amputative” or “reparative” therapies as in the case of surgery. Some researches described that 30–36% of patients are suffering from iatrogenic diseases (104,105) and from “consolidated therapy” (106-109).

There is one last form of therapy, typical of ancient medicine and modern clinical practice, albeit still a minority: the “regulatory” therapy of the *single* patient. In Integrative Medicine (110,111) the patient is placed at the center of an intervention program. The aims are to re-balance and regulate a series of neuro-endocrine-immune and biophysical networks under tension, proceeding with food changes, physical (physical exercise, massage, acupuncture), climatic-environmental, psychological (mind-body techniques) stimulations along with evidence-based phytotherapy (112-114). It is curious to note that according to the perspective of ancient medicine those symptoms commonly recognized as “mild” or “initial” from “modern doctors” are instead considered by the “preventive view” of ayurvedic physicians the last stages leading to a disease manifestation (114).

### ***A successful combination between traditional and modern medicine: the example of plants use***

The fundamental difference between traditional and



**Figure 2** The big network: a scheme of the Psycho-neuro-endocrine-immune connections and their Epigenetic modulation of DNA expression. Psyche and biological systems are linked. Nowadays, a lot of studies document this bi-directional connection and show how psychological states of mind modify the activity and the balance of biologic systems (such as nervous, endocrine, immune and metabolic systems) and how their functioning could influence the mental attitude (74). Environment, foods, herbs, physical activity and psychologic features influence constantly this network. The heart is in red because of its primary influences on cognitive processes discovered nowadays (80). The old linear correlation between DNA sequences and single proteins (67) has been overwhelmed by the evidence of alternative splicing mechanisms, prions action and epigenetic regulation of DNA expression (81). The term Epigenetics is defined as the causal interaction between genes and their products that allow for variable phenotypic expression. The human organism always tries to maintain its stability by adapting (allostasis) to external (physical and chemical) or internal (psychological) stimuli. In particular, stimuli are divided into physiological or non-physiological. Non-physiological stimuli (physical/chemical and psychological) are able to stress our psycho-neuro-endocrine-immune adaptation system (PNEI) (75) (left panel). The resulting immune activation can potentially affect all tissues and cells (right panel) through the activation of the intracellular transduction pathways linked to mTOR (82) and Nf-KB (83) genes through the mediators of the PNEI system (i.e., hormones, neurotransmitters and cytokines). This will influence the cellular energy metabolism with high oxidative stress and damage from free radicals (84), mis-folding of proteins (85) or their abnormal synthesis (alternative splicing) (86). Thus, cells expose danger signals (87) that are detected by the immune system. The whole process can be resolved with regeneration/repair (depending on the tissue potential) in case of control and resolution of the acute stimulus, or with tissue destruction in case of stress persistence and chronic processes. Of note, the inflammatory activation can be activated by psychological stress alone and the stress activated patterns can be transmitted across generations via epigenetic modulation (83-89).

contemporary medicine lies in the subjective approach to the reality of the former in comparison to the more objective approach of the latter. These two modes are not incompatible as shown for instance in the use of an herb as seen by the modern and traditional medicine/pharmacology.

As described by Schrott and Ammon (115), *Althaea officinalis* Linn—marsh-mallow—it's a common *Malvaceae*

plant in Europe and Asia. Roots and flowers are used for medical applications. It is sweet, oily, slimy, heavy, cold and it is used mostly as a nourishing pulmonary tonic. It is expectorant, diuretic, laxant and an emollient remedy for stomach and intestine (for its mucilagines). It is used in inflammatory diseases of the lungs and intestine and in dyspepsia, vaginal inflammations, dysuria and urinary



infections, mastitis, skin ulcers, rheumatic problems and in states of emaciation (112). Interestingly, in Ayurveda the same use is described (115).

How is that possible? Ancient doctors used to classify the substances based on their qualities: sweet, salty, bitter, astringent, pungent, sour. Modern scientists look rather at the chemical composition of substances by identifying proteins, carbohydrates, etc. in plants. It is interesting to note that mucopolysaccharides, polysaccharides, diterpenes have a sweet taste; iridoides, cucurbitacines, quassinoides, saponines, alkaloids, some flavonoids, chinins or lignanes are bitter; tannins are astringent, piperin, capsaicin or gingerol are pungent and some acids or essential oils are sour (115). Moreover, saponines (mainly bitter taste) have an anti-inflammatory, antiviral, antimicrobial, antipyretic, diuretic and hepatoprotective, hypoglycemic and hypolipidemic, anti-tumoral action (112,115).

For thousands of years ancient doctors used subjective perception about the *qualities* of the constitutive elements to deduce the therapeutic effect of the substances with great precision. Proceeding with perceptions, observations, trials and errors they selected the most effective remedies for their contemporary human beings. Modern technical experimentation has a very young history but may reach [attention to the epistemological limits of technical-scientific research (116)] often similar conclusions as the men who preceded us (115).

### *A dialogue with traditional medicine is possible in different medical fields*

As discussed earlier, the specialization of knowledge is undoubtedly a wealth, but ideally this should be integrated with a systematic overview. In this regard, it may be certainly advantageous to observe “the patient through the heart”, but it would be a conceptual and clinical error to look at the heart, without considering the patient as a whole.

Increasing evidence favor an integrated treatment of various pathological conditions, able to alleviate suffering of people and to reduce healthcare costs (110,117). In addition to the well-known positive effects of healthy eating (118), exercise and smoking cessation (110), the use of herbal medicine (112) and mind-body disciplines seem to be particularly important. For instance, stress as contributor of different pathological states can be ameliorated through different nutritional and phyto-therapeutic, physical or psychological stimulations (119).

Below some interesting examples of cooperation between traditional and modern medicine.

### **Heart diseases**

Often depression and dyslipidemias are present together. From a reductionist's point of view this co-existence may be seen as coincidental and will be treated with a lipid-lowering drug combined with an anti-depressive pill. From a different perspective, depression and dyslipidemias may result from a psychological imbalance with (chronic) inflammation leading to dyslipidemia and depression. In fact, high anxiety and stress levels may lead to higher LDL cholesterol levels. Effort, over-commitment, low reward and effort-reward imbalance are significantly associated with increasing blood lipids and are suggested as a possible link between job stress and coronary heart disease (120).

Furthermore, chronic stress may impair vascular function (121). We have seen that depression (and dyslipidemia) are linked to a pro-inflammatory regulation of the immune system (122,123). Hence, psychosocial factors may act as cardiovascular risk factors along with the well-established ones (i.e., smoke, dyslipidemia, hypertension and obesity) (124). Thus psychosocial factors should be taken into account for the prevention of heart disease (125,126). As confirmed by evidence linking depression in absence of additional risk factors to coronary artery calcification (127).

Starting from these backgrounds, we studied the impact of stress on cardiovascular diseases (76,86,128-135) and we applied some “traditional” knowledge to treat patients after myocardial infarction. Thanks to proper nutrition (Mediterranean diet) and food supplementation (131), to mild-moderate aerobic exercise (131) and stress management (through the use of mind-body disciplines as listening of music or meditation) we observed an initial regression of carotid atherosclerosis and improvement in coronary flow (136), as suggested also by others (137-143). We documented also significant variations of stress hormones, inflammatory (136), and epigenetic markers (144) with simple biophysical and biochemical explanations (95,145).

### **Infective diseases**

Chronic psychosocial stressors are related to alterations in inflammatory activity. Job stress, low socioeconomic status, childhood adversities as well as life events, caregiver stress, and loneliness were shown to augment Th2 response while decreasing Th1 thus influencing the immune response. An interesting study by Rosenkranz *et al.* reports relations among physiological measures of affective

style, psychological well being, and immune function. Negative and positive feelings were elicited by using an autobiographical writing task. Individuals characterized by a more negative affective style mounted a weaker immune response which may relate to higher susceptibility for illness as compared to those with a more positive affective style (146). Furthermore, stress reduction behavioral interventions, such as Tai Chi, enhances vaccine-stimulated levels of cell-mediated immunity to varicella zoster virus (147). Stress increases HIV disease progression (148).

A proper nutrition also supports the immune system (110,117) as well as mild to moderate physical activity (149,150). Several plants exert antiviral, antibacterial and antiparasitic properties (such as *Astragalus Membranaceus*, a plant used in Chinese medicine), *Whitannia Somnifera* (used in ayurvedic medicine), *Liquorice* (used in Mediterranean medicine), *Allium sativum*, *Zingiber officinalis* etc.) (112).

Probably, considering these factors may help to decrease susceptibility to certain infections keeping a healthy immune system. This could be an important consideration in drawing realistic epidemiological mathematical models and for the prevention of infections in the population [a current world-wide issue where the integration of phytotherapy and nutritional supplements seem to be a valid tool to be further investigated (151-157)].

## Cancer

Chronic behavioral stress results in higher levels of tissue catecholamine, greater tumor burden and more invasive growth of carcinoma cells in animal models (158) and in humans (159). Behavioral factors contribute to the crosstalk between tumor and host cells in the tumor microenvironment, and stress effects on host cells such as macrophages seem to be critical for many pathways involved in tumor progression. Some effects are bidirectional in that tumor-derived inflammation seems to effect central nervous system processes, triggering vegetative symptoms and contributing to deregulation of the hypothalamic-pituitary-adrenal axis with downstream effects on inflammatory control (160).

Depression and social isolation seems to play an important role in cancer spreading (161,162). treating depression can prolongs life in cancer patients (160). A randomized clinical trial tested the hypothesis that cancer patients coping with their recent diagnosis and receiving psychological help improved survival time compared with patients, who only received the diagnosis (163).

Additionally, mindfulness based stress reduction for women recently diagnosed with early stage breast cancer showed beneficial effects on immune function with an increase in Th1 INF $\gamma$  levels, enhanced quality of life, and coping with the disease (164). Also in cancer patients the immune system may be strengthened through an adequate nutritional regimen (117), physical activity (117) and the use of natural immuno-stimulants with possible anti-tumor action (i.e., *Artemisia annua*) (112,117).

## Skin diseases

It is well known that skin cells produce stress hormones (165) and a “brain-skin connection” underlying inflammatory skin diseases may be triggered or aggravated by stress (166). Psoriasis lesions disappear when CRH and nervous growth factor (NGF) levels from nervous skin terminals decrease turning off mast-cells activity (167). As recognized by ancient medicine (29,38), many dermatological problems are affected by intestinal problems or food allergies (110,117). A proper nutrition may alleviate skin problems.

## Multiple sclerosis

A relationship in the distribution of multiple sclerosis with latitude and solar radiation was described (168), with higher incidence of the disease in northern countries (169). It is interesting to notice that migrating to areas with higher sun exposition decreases the incidence of the disease (170). Probably these findings are related to the Vitamin D stimulating action on the Th2 immune circuits, decreasing the production of Th1-related cytokines (i.e., TNF $\alpha$  and INF $\gamma$ ) (75). Furthermore Buljevac *et al.* demonstrated that stressful events are associated with increased exacerbations in relapsing-remitting multiple sclerosis and this association was independent of the triggering effect played by of infections (171) but rather be related to the noradrenaline-dependent adrenergic stimulation activation of the pro-inflammatory gene NF-kappa B in monocytes elicited by stress (172). Again the immuno-modulatory action of some foods, phytotherapy, physical activity and mind-body techniques can be exploited this disease (75,173).

## Rheumatic diseases

Psychological stress acting via hormonal and neuronal stimuli may exacerbate rheumatoid arthritis (174). Cognitive behavioural interventions, offered as an adjunct to standard clinical management early in the course of rheumatoid arthritis, is efficacious in improving psychological and

physical disease aspects (175). Association of fasting and vegetarian diet is an effective integrative treatment for rheumatoid arthritis (176). Similar findings are reported for lupus erythematosus too (177,178) and behavioral interventions designed to reduce emotional reactivity may be of therapeutic benefit in chronic inflammatory conditions in general, such as neurogenic inflammation (179).

## Conclusions

Integrative medicine bringing together a healing-oriented and patient-centered sensibility with therapeutic approaches originating from “alternative” and “traditional” medicine may help improving contemporary medicine. Integrative medicine is increasingly recognized as strategic against the epidemic of chronic diseases, which pose a serious concern on health care systems. Further research in this field is needed to further enable contemporary medicine to adopt a systemic perspective based on psycho-neuro-endocrine-immunology connections and epigenetics.

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