

At the Edge of Alternative Medicine: the ABO-WCM System

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Abstract:

In the East many traditional complementary and alternative medicines (TCAM) have flourished during the ages: traditional Chinese medicine (TCM), Unani, traditional Japanese medicine (TJM), Ayurveda, etc. Though less known, also in the West, one tradition has asserted itself: Western Constitutional Medicine (WCM). All these ancient medicines have a common denominator: the idea of constitution. Scientific studies have always been concerned with this idea and have tried to identify its features. Several theories have been advanced trying to explain the reality of constitutions, with various successes. Quite recently, a new concept has emerged from biology: the fact that humans are metaorganisms (holobionts). This new way of looking at humans promises to change medicine forever. In this framework, the two forms of classification (WCM and ABO blood grouping) could be seen as not mutually exclusive and can merged into an alternative medical system. On the one hand, the ABO blood type divides humanity into four basic blood groups: A, B, AB and O. This typology is based on glycochemical markers or determinants which have been lately demonstrated to influence health and disease. On the other hand, WCM four biotypes (air, water, earth and fire) have always been in the collective imagination of the West. The proposed new system of medicine defines 16 basic constitutions of individuals based on physical and genetic features. The ABO-WCM system merges ancient medicine of the West with contemporary biological medicine. The resulting new system can aid in identifying the susceptibility to diseases and the necessary dietary advice to exalt the characteristics of each unique human holobiont. In this way, the goal of personalized medicine becomes more easily achievable.

Keywords: TCAM; Biotype; ABO blood group; Constitutions; Holobiont; Glycans.

1. Introduction:

Medicine has evolved over the ages from a supposedly earlier ancient form to what is today known as modern biomedicine, through adaptations and revisions (1). Western Constitutional Medicine (WCM), as it can also be called, is the traditional form of medicine practiced in the west. WCM was also the main system of medicine (SoM) in both Europe (originating from the Mediterranean area) and later transmitted to the Americas for over two millennia until the rise of modern biomedicine (2). The way this form of medicine was practiced until recently was not dissimilar from other systems of traditional medicine taught around the world. Some other famous ancient medicines are: traditional Chinese Medicine (TCM) and or

Traditional Indian Medicine (TIM). Interestingly, these ancient medicines have in common with WCM a solid foundation in constitutional theory (biotypology) that dates back several millennia, if one considers only the Eastern tradition of medicine (TIM, TCM) (3). There are of course differences between these three traditional systems of medicines. One of the major differences is in the number of biotypes that each form of medicine has developed. Notwithstanding this, all three major traditions have a suitably designed framework to take advantage of whatever definitions have been given to the biotype and this has crystallized over the ages.

Yet another interesting fact to notice is the philosophical discourse that has gained momentum over the recent past and that affects

also the present. In most Eastern Countries, an open and constructive dialogue has established itself and been fostered between modern Western biomedicine and all Eastern ancient traditions (4). This productive negotiation, which has allowed the possibility of a choice by the patient of which treatment to initiate, has not occurred in the West with WCM.

The positive dialogue has permitted also the teaching in parallel of traditional SOM with modern Western medical programs of study. This parallel teaching is also granted in major universities and in some countries, traditional medicine is recognized and approved for public use on par with modern biomedicine (5). Although it is recognized that the WCM was the foundation of modern medicine and has influenced profoundly its advancement in recent centuries, still the detachment of biomedicine to its precursor is seen as very harsh and not in alignment with other Countries status. It may be time (and it is possibly well overdue) to change the situation.

WCM has a long history that dates back to Hippocrates in the fifth century BC. WCM based its knowledge of medicine on the Hippocratic traditions which have been reported and expanded by Galen in the second century AD (6). According to this tradition, the main form of cure was dietetics. It has maintained its basic form over the centuries, although several physicians have tried to improve on it. Starting from the Arabs, Avicenna (the medieval greatest authority in Greco-Roman medicine) has copied the works and assimilated the knowledge by developing what is now known as The Canon of Medicine. This text stressed the importance of diet and environment (epigenetics) on health (7). Again, according to this text, as to all past WCM knowledge, each person's susceptibility to disease depends on the diet (2). It is possible, according to these ancient SoM to bring back to equilibrium (health) anybody who is in a state of disequilibrium (illness), through diet.

The notion of humours used in WCM and in Unani Tibb, is also present with different words also in eastern traditions such as TIM and TCM. There is a strong biological basis for the concept of humours as developed by systems theory, due to the fact that these can regulate well integrated physiologic functions (8). All three major traditions (WCM, TIM, and TCM) can thence be called humoral. In this sense, humoral medicines correspond to an equilibrium model, where any

type of imbalance (of humours, dyscrasis, in Greek) results in illness. The final objective and therapeutic goal of these humoral SoMs is the achievement of a balance or equilibrium (eucrasis, again in Greek) [(9), pp. 4-5].

Again, all SoMs agree generally in the workings of the humours, however they are called. The humours, for a lack of a better word, are then the starting point for the various temperaments (krasis, in Greek), which is formed by the different proportions of these in the individuals constitution (diathesis, again in Greek) (10). Another way of understanding the ancient concept of constitution is to view it as the body type of each person. Hence, the constitution of an individual could be defined as the sum-total of all its peculiarities and potentialities, at any single time in the life of a person (11). The constitution of an individual is not just genetically inherited or determined but it is also conditioned by the environment in the early stages of development (epigenetics).

Surprisingly enough, the equilibrium/disequilibrium ratio is the cornerstone of all ancient SoMs and a point that has been confirmed also by recent scientific discoveries. Modern biomedicine should face its precursor (WCM) and come to terms with this SoM, not as something of the past but as equals.

2. Scientific Constitutions:

WCM is a SoM similar to other Eastern traditional alternative medicines (TAM) in the fact that all these TAMs are based on constitutions. Scientific studies and clinical trials have been performed in the field of constitutional medicine and have generated very evidence-based information that confirm the usefulness and correctness of this sort of analysis of the human beings (12). All the results of the scientific data and information concerning the theoretical and practical basis of the concept of constitutions can be used directly to demonstrate the correctness of WCM.

State of the art scientific information in biological science further confirm the correctness of the concept of constitutions.

As a term, biotypology seems to be much more explainable in the light of the current view of biology expressed by the Margulis-Lewontin paradigm. Accordingly, while the human genotype might possess a collection of potential phenotypes, the human phenotype is also governed by environmental agents, among which

there exists the collaborative relationship with diverse microorganisms within us (13). The hologenome, which is the sum of our genetic material and those of our microbial partners, influences the host's phenotype by acting on each component of the holobiont in combination with the host as well as individually (14).

The holobiont therefore becomes the result of this line of reasoning and is viewed as the sum of the host and its microbial residents. An important consequence is that the classic view of medicine is changed forever. The prevention and therapy of diseases now should be based on treatments that focus on restoring the equilibrium of the altered microbiota (15). Essentially, it is being recognized by modern medicine that the microbiota is fundamental in the establishment of health. All microbes wherever they are, whether on our skin or in our guts seem to be vital for our normal mental, physiological, and immune equilibrium (13).

Needless to say that in recent years a growing body of scientific literature show that there are several host-specific microbiomes, located in practically all tissues of the host(16-19). These host-specific microbiomes provide essential functions their hosts (whether animal, plant or fungal) related to the metabolism, immunity, and environmental adaptation. It is impossible to overstate the importance of this relationship between host-specific microbiota and their environment (the host). All multicellular organisms are now shown to contain host-specific microbes (so as to be called metaorganism). These metaorganisms rely on their associated microbes for many aspects of their function, impacting on not just their life history traits such as epigenetic programming, pace and longevity but also their developmental history (20, 21). It is now becoming incredibly easy to show how metaorganisms or holobionts successfully collaborate with microbes in practically every aspect of life. This diverse collection of microorganisms (consisting of bacteria, archaea, protists, viruses and fungi) is harboured in niche spaces in the body of their hosts. They share the resources provided by their animal hosts (food or diet), and as an exchange provide useful metabolic products and genes (in the form of enzymatic capacity) (22).

Given their staggering numbers and ubiquitous presence (23-28), it is not unexpected to learn that these microbial communities influence health and diseases of their the holobiont. There are so many

ways in which the physical body of the holobiont can influence these microbiotas and vice versa that it is currently almost impossible to count (29). Consequently, holobionts should not be deemed as autonomous individuals by any anatomical or physiological criteria. Rather the holobiont should be viewed as highly organized biological units, made up of a diversity of symbionts which are present and functionally completing many fundamental metabolic pathways (30).

As a result, the holobiont concept highlights how the different microbial communities as are reciprocally shaped by our biotypology (defined as peculiar ecological habitats), in the manifestation of various biologic processes. This ultramodern intricate view of the metaorganism requires a holistic framework to comprehend the impact of organismal symbioses in defining ecosystem functioning (31).

If the term dysbiosis is considered as a problem that originates when the microflora is perturbed (32), then this becomes even more crucial for the holobiont. Dysbiosis for the holobiont would mean something similar to a community breakdown, a crisis to be reckoned with urgently. In such cases, disease is manifested and the equilibrium is lost. Only the restoration of the homeostatic equilibrium (in other words, eubiosis) of the microbiota can aid the holobiont and achieve the goal of bringing back the healthy status of the individual (33).

3. Modern Constitutions:

As we have seen, the concept of constitutions is not an old term not useful today to identify anything medically useful, but in actuality it is does point to the way microbes are connected to each individual. Two such examples are reported hereafter: the ABO blood type and the modern version of WCM.

3.1 Modern WCM Constitutions:

WCM biotypologies have always lingered around in our collective conscience. Both WCM and all Eastern SoM have long recognized the existence of individuals with diverse features and have classified them into a finite number biotypes mainly based on physical (or other) characteristics (2, 3). These qualities are distinct from those considered by the ABO constitutions in that they are more tangible, in nature.

Going back through time, according to Galen, one of the founders of WCM, a person's crasis (or, to say, temperament or constitution), can be inferred

from observation of his external features ((34), pg. 69). To clarify, both the physical constitution and psychological characteristics of each person are determined, in Hippocratic terminology, by the balance or blend (from the latin, temperare) of the 4 humours. The four humours (known as yellow and black bile, blood and phlegm) are derived from the ancient concept of the 4 elements of the world (air, water, earth and fire) (35). Although Hippocrates, who was the father of medicine, was considered to be the first to classify people according to their dominant body humors, the origins of the humoral theory could be found in the Old Testament (precisely, in the Book of Ezekiel) (36). Nevertheless, after Hippocrates proposed this theory (and later Galen), the Greeks and Romans believed each individual had its own balanced mix of humours. This combination of the four humours determines the temperament (constitution), not just physically but also psychologically ((37), pg 3-4).

Without considering the development of the 4 WCM constitutions on the psychological field of study, these biotypes did not evolved much (at all) in the course of over two millennia. With the rise of modern science, general medicine became interested only in evaluating the chemical/biophysical side of temperaments. Important figures such as Draper, Pende and Kretschmer, just to name a few studied the various metabolic processes, endocrine activities and other organic reactions of the constitutions (11). From the original four WCM biotypes, several lines of thought emerged all with their own peculiarities. We recall the Italian school, with Di Giovanni (1838-1921), Viola (1870-1943) and Pende (1880-1970) who structured four biotypes (marked by asthenic/stenic and tonic/hypotonic features), the French school with Martiny (1897-1982), who invented the three biotypes (endoblast, mesoblast and ectoblast) and the homeopathic school, with Nebel (1870-1954), Vannier (1880-1963) and Bernard (1912-1994), who maintained the tradition of three biotypes (sulphuric, phosphoric and carbonic) (38). Finally, we come to the American school with Sheldon as its foremost representative. Sheldon in the 1940s introduced the concept of somatotyping as a way to classify the totality of the body on continuous scales which could be expressed in simple values (39). His anthropometric classification of human beings in ectomorphic, mesomorphic and endomorphic was further developed by Heath & Carter who standardized it and made somatotyping the

instrument for defining the physique in sports science (40).

With all the rich history of biotypology, WCM is also in debt to St. Hildegard of Bingen, a twelfth century physician (41). In her books *Physica* and *Causae et Curae*, she expounds the theory of the 4 humors identifying 8 basic constitutions (four per sex). It is this version of the four WCM temperaments that shall be considered henceforth (see next section).

Undoubtedly, the 4 WCM biotypes have fundamentally influenced also psychological thought throughout its entire history (42). From Pavlov to Eysenck, their typologies have always been extrapolated from and compared to the Hippocrates-Galen temperaments (melancholic, choleric, phlegmatic and sanguine) (43). Consequently, the importance and reality of the four humoral temperaments cannot be overstated nor forgotten.

3.2. ABO Constitutions:

Blood typing has been one of the major discoveries in biochemistry in the 20th Century. All humans can be divided into four major ABO biotypes: A, B, AB and O, depending on their blood type (with the exception of the Bombay phenotype due to lack of the H gene, factually creating a separate subgroup) (44). Two enzymes (fucosyltransferases, FUT) are present in human tissues and regulate the expression of ABO antigens in all human tissues (45). FUT1 gene encodes the enzyme for the H (blood type O) antigen, while FUT2 encodes for the secretor enzyme (Se), the presence or absence of which classified people as secretor or nonsecretor phenotype (presence or absence of ABO antigens in secretions) (46). But other two enzymes (glycosyltransferases, GT), encoded by the A and B gene, catalyse the addition of N-acetyl-D-Galactose (NAcGal) and D-galactose (Gal) respectively, on the non-reducing end of H substrates (the terminal disaccharide structure, fucose [Fuc] and Gal) (47). The A, B, and H antigens are complex fucosylated carbohydrates expressed by all individuals of blood group A, B, or O, respectively (48).

Hence, the synthesis blood group ABO/ABH antigens is under genetic control, as primary gene products of specific GTs, which sequentially add precise monosaccharides to the carbohydrate side chains of glycolipids and glycoproteins (49). Similarly, the Lewis gene encodes for enzymes which further act on the same carbohydrate

structures on which ABH genes act, to yield more complete antigens, the Lewis-a (Le^a) and -b (Le^b) antigenic determinants (50). As a consequence of the presence of the Lewis gene, there is a competition for common acceptor and donor substrates between the Lewis and the ABH enzymes (45). All gene loci, ABO, H and Lewis, have been identified and encode for enzymes which are involved only with the final stages of the biosynthesis of the carbohydrate structures (51).

Since the expression of ABO antigens occurs not just on red blood cells but also on all epithelial cells, these macromolecules, which carry serological specificities related to the red cell antigens are called blood group substances (49, 52). The ABO(H) blood group antigens are indeed widely distributed, also in various tissues and body fluids, as glycolipids or glycoproteins (53).

Importantly, it is the FUT2 gene (Se) responsible for the production of ABO histo-blood group substances in the gastrointestinal (GI) tract and secretions (54). To clarify, non-secretors (se or Se^- , or Se^0) have single nucleotide polymorphisms (SNPs), i.e. genetic variations, and do not express ABO antigens in saliva and into body fluids including the GI mucosa (55). Moreover, secretor status, whether functional, weak (Se^w) or non-functional (Se^0) impact on Lewis phenotype so that the presence of certain Lewis antigens is manifested in these individuals (48). Particularly, in Lewis-positive individuals, Se^0 genotype generates the $Le(a+b-)$ phenotype, the secretor genotype causes the $Le(a-b+)$ phenotype, and the Se^w generates the composite $Le(a+b+)$ phenotype (56).

These polymorphisms in the enzyme activities are inheritable traits and influence the phenotype of the individual (52). Nevertheless, human polymorphic genes and diversity have important implications in hereditary diseases (54).

Susceptibility to disease, the hallmark of the concept of biotypology and constitutions are intimately linked to ABO blood groups. It has now extensively been shown that ABO antigens, and relative secretor and Lewis phenotypes, are linked to viral and microbial disease susceptibilities and other diseases (57-67). There is therefore a finite link between the ABO constitutions and the microbial/viral composition of the human body. Viruses and microbes are able to recognize differentially oligosaccharide

structures, especially ABO like structures (glycans) on the human body and preferentially bind to them (68). Given the countless effects that microbes have on all human metabolic and physiologic systems, that we are incessantly continuing to discover, it is no surprise that a genetic disposition like the ABO constitutions can be so fundamental. This fact is ineradicably linked to the human nature, as a holobiont, with all the consequences it has on the delicate equilibrium between the host and its constituent microbial communities (69). The ABO make-up of an individual invariably represents a first and genetically controlled biotypology to be considered for future research.

3.3. The Matrix:

Given the increasing trends towards personalized medicine, which stresses on the genetic background for disease susceptibility exemplified in individual constitutions (70), it is becoming ever more important to be able to characterize different constitutions. With this scope, it is possible to merge together the two typologies previously defined into a coherent model. A typology is a model obtained from the possible combinations between two or more variables, each of which contains a (finite) range of discrete values or conditions (71). The two variables are biochemical constitution (ABO) and physical temperament (WCM).

By leveraging on the physiologic differences in ABO blood grouping, with four distinct types, A, B, AB and O, and merging this with the age-old four elemental constitutions, as synthesized by St. Hildegard, it is possible to divide humankind as in Table 1.

Table 1. ABO Constitutional Biotypology:

HUMANKIND							
AIR (A)		WATER (W)		EARTH (E)		FIRE (F)	
Female	Male	Female	Male	Female	Male	Female	Male
A	A	A	A	A	A	A	A
B	B	B	B	B	B	B	B
AB	AB	AB	AB	AB	AB	AB	AB
O	O	O	O	O	O	O	O

Color-coding is added to represent the typical elemental constitution.

Table 1. Summarizes the division of humankind into four basic constitutive types, which become eight when considering the natural division of sexes and finally, multiplied by four ABO types, for a total of thirty-two ABO constitutive types. Although the number is impressive and may give way to thoughts of impossibility or impracticality in actual clinical settings, this is actually easier than said.

But first, let us define some nomenclature for convenience. In order to more easily classify individuals in this novel biochemical and physical temperament system and in a unique manner, a three letter code will be devised. This code will represent the two main categories of constitution (ABO and physical biotypes) and in the sex of the individual. Thus, the first individual chosen from T, a male of blood group A and air type constitution (Row 4, Column 2), is defined as Air (the basic biotype), Male (the sex) and A, with blood type A (conventionally codenamed as AMA). Conversely, an individual in the same table, a female with blood type O and fire type constitution (Row 7, Column 6), is defined as Fire, Female and O (conventionally FFO). And so on and so forth.

A visually simplified version of Table 1, without the sex categories, is presented in Table 2.

Table 2. Simplified ABO Constitutional Biotypology:

ABO/Elements	AIR (A)	WATER (W)	EARTH (E)	FIRE (F)
A	A	A	A	A
B	B	B	B	B
AB	AB	AB	AB	AB
O	O	O	O	O

Each of the temperaments as outlined in Table 2, have very specific and distinct physiochemical reactivities that make them unique. It would be very interesting in the future to explore the medical features of each individual

One last consideration regarding the constitutions in general. Temperaments that are brought about from any classification are the result of the mixing of the humours, in humoral doctrine and from the presence of the antigens in the ABO classification system. In humoral doctrine, the ratio of the four primary elements that make up an entity will reach a state of equilibrium resulting in an overall quality known as temperament (72). When the

ratio of the humour have reached a single quality it is called singular (classical) temperament, if on the other hand they reveal two qualities simultaneously, it is called combined temperament (73). Each individual has a unique temperament derived from a unique ratio of humors which match the ideal temperament of the individual (74). The temperament is fixed in each individual it has a practically infinite number of variants and variations in the humours are the result of lifestyle (sleep, physical activity, stress) or dietary changes (72). The same occurs with the ABO constitutional biotypology. Alongside a pure biotype there is always one or more combined biotypes, as proposed by Jorjani (75), that take on the qualities of the other adjacent temperament.

3.4. In Practice

This new system is meant to show true complementarity between the two separate and overwhelmingly thought of as irreconcilable approaches. They are not, and this will be demonstrated with two examples.

Let us take two individuals a woman and a man of approximately 30 years of age with no apparent diseases, as those in section 3.3: AMA and FFO. Their relative characteristics according to both types of temperaments (ABO and WCM) are listed in Table 3

Table 3. Some Characteristics of Individuals AMA and FFO:

Characteristics	Source	AMA	FFO
Biological strength	WCM	Weak	Strong
Muscular structure	WCM	Thin (ectomorph)	Well-built (mesomorph)
Metabolism	ABO	Slow	Fast
Predisposition (sports)	ABO	Light training	Hard training
Diet type ¹	WCM	Moist regimen	Dry regimen
Diet type ²	ABO	Mainly vegetarian	Mostly carnivore
Psychological trait	ABO	Tends to be relaxed	Tends to be active
Psychological trait	WCM	Over-thinker (cerebrotonic)	Action driven (somotomic)

This example is not meant to be exhaustive but just typifying.

1 = Following Galen's concept of temperaments, all foodstuff can be reduced to the four basic qualities (76).

2 = Similarly, BTD suggest a particular diet where foodstuff glycans are aligned with each body's own ABO blood typology (77, 78).

As it is obvious from table 3, the first four characteristics relate to the temperamental features of each individual (genetical predisposition, disease susceptibility,). The latter two focus more on possible therapies linked closely and inevitably to each own constitution. Very cursorily, a constitutive diet has been proposed to each biotype depending on the constitutional system (WCM and ABO). Sexual differences should also be taken into account, but have not be included here for the differences are meaningfully seen between individuals with same blood type and constitutions. Sheldon's system of classification has also been utilized, where expressly feasible, for certain WCM characteristics, such as muscular structure (as the system is body shape related) and psychological traits (as it is akin to constitutional psychology) (40).

Any form of somatotyping must account for a continuous classification of physique, which may include many different body types, with every type still reflecting lots of variations (79). By utilizing Sheldon's initial method of somatotyping, built upon the relationship of body type to character, Carter and Heath introduced a newer version which became the standard in sport science worldwide (80). The new somatotyping procedure was scientifically based on anthropometric measurements and equations that relate body physique to a somatotype (81).

It has been shown how the two constitutional theories can in practice be merged into a single new system. This new medical system shows that a fusion of two completely different constitutional medicines is not only possible but advisable, since they are based on diverse founding principles: one is physical (WCM) the other biochemical (ABO blood system).

4. Conclusions:

A new system has been developed to take advantage of the theories and practices of both European traditional constitutional medicine (WCM) and modern biomedicine (ABO blood group system) in the framework of the holobiont. We are coming to realize that humans are much more complex than just mere anatomical,

physiological entities but are true ecosystems of a myriad of diverse species collaborating through unfortold numbers of interactions (22).

This can occur since each system is based on different features (somatic constitution and biochemical markers) that avoid considering the same typology twice.

Recent advancements in scientific understanding continuously confirm the truth of ancient knowledge and traditional medicines (TCAM) in the definitions of biotypes and temperaments, exclusive to each individual. One would only have to look at the incredible variety of temperaments emerged just in psychology in the 19th and 20th Century to understand how deep ingrained in our culture such biotypology really is (82, 83). Nonetheless, the idea of constitutions have at least an importance in that it can help recognizing inherited or typical characteristics of an absolutely unique organism that may determine susceptibility to disease and thus guide use in recognizing the best approach .

Especially, the holobiont concept opens up new prospects of understanding by pointing towards a return to equilibrium (eubiosis) as the ultimate health achievement. The interactions between microbiotas and their hosts characterise the holobiont as a unique and single biological entity (84). These genetic and physical attributes, unique to each individual, allow us to view the human holobiont as a coordinated mixture of many interactions that influence other interactions that make up the whole system (85). Specifically, the ABO glycans (genetic attribute) influence the microbiotas of all human niches to imprint in the physical structure of each holobiont (WCM biotypes) their peculiar characteristics. This novel biotypology system (the fusion of past/physical [WCM] and present/genetic [ABO] constitutions) can be seen as a step forward towards a greater integration of all our knowledge in medicine. The tool should be seen as an aid in understanding our many differences and, as ancient medicines did, utilize them to the benefit of the uniqueness of the person (individualized medicine) (86).

Hence, the need for a more tailored approach of medicine is paramount and is actually materializing as it slowly shifts its focus from a materialistic to a multi-omics viewpoint (personalized medicine) (87). Medicine should embrace the hologenomic perspective that a systems-level framework for host biology is necessary to explain the complex etiologies of

diseases, giving rise finally to precision medicine (88). Or personalized medicine (89), which is what TCAMs have always supported.

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