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THE IRRESISTIBLE FASCINATION
OF MEDICAL THEORIES ABOUT OPPOSITES

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SUMMARY

THE IRRESISTIBLE FASCINATION
OF MEDICAL THEORIES ABOUT OPPOSITES

Theurgical medicine was a part of the eternal fight between good and evil and health was reconciliation with the gods.

This duality characterized ancient medicine, i.e. greek medicine after the homeric age or chinese traditional medicine. In the passage to medicine of observation due to the School of Cos duel between good and evil becomes the substrate of new medicine and the balances between opposites represented by elements and qualities were the fundamentals of the humoralism.

Fascination of opposites continues for centuries up to now, both in western and far eastern medicine: yin/yang, antibody/antigen, cAMP/cGMP, oncogene/antioncogene are examples of this attractive theory.

Although fundamentals of biological and medical observations are the basis of theories of opposites, the trend is to overcome reality and today represents, following idealism in the 19th century, an unconscious ancestral reminiscence of theurgical philosophy and medicine.

In writings of classical ancient time, such as in homeric poems, a duality between god and devil (θεός and δαίμων) is not present, because the only duality is between gods, who stated

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the fate and humans, who suffered the fate, with heroes as attempt of bridge to invain force the fate. Originally, the term δαίμων, which in following centuries represented opposition to god, is from δαίωμα, that is to decide fate (good fate or unfavourable one). In ancient mythology the fate was guideline for humans and heroes were great performers, with any personal possibility of different interpretations. The first change was the appearance of heroes winner by using mind, such as Oedipus and Cadmus, in place of heroes killer of monsters with the sword, i.e. Theseus and Jason⁽¹⁾.

The war of Troy represents the final conclusion of this age, with not yet necessary heroes killing needless heroes and the emerging of the myth of the man who search knowledge more than killing of enemies: modern man is born with Odysseus, who refuses in the island of Calypso immortality and choses to be only a man, single-handed sailor in the sea of the unknown, sometimes discoverer and sometimes ship-wrecker. And with the advent of the predominance of logos, dialectics is emerging⁽²⁾.

Dialectics as philosophical method is clearly formulated first by Heraclitus, who stated, as reported by Aristotle, that conflicts between opposites produce all things of the world. Aristotle discussed the importance of opposites and affinities in the Treatise 'Ἐθικόν Νίκομάχειον and in the Μεταφυσική⁽³⁾: opinion of Heraclitus is evidenced and compared with the ideas of Alcmaeon of Crotona and of the Pythagorean School. Alcmaeon — Aristotle says — maintains that duality is an intrinsic characteristic of the human kind (white and black, good and bad, big and little, etc.), while in the Pythagorean School the dichotomy of reality had a mathematical origin: in fact in pythagorean mathematics the even number may be divided in two parts and reaggregated.

These philosophical theories were well known in the 5th century B.C. (when the new medicine was developed by Hippocrates and his School), surviving for centuries from Aristotle up

to the scholastic medicine and philosophy. And Hegel reported in his *Logic* the thinking of Heraclitus: after the homeric age opposites are present in the philosophical thinking up to now.

Is this true for natural sciences and for medicine too?

As ancient and medioeval medicine were largely dependent on naturalistic views of ancient Greece, may be interesting to note the analysis of the thought of Aristotle, who was living just after Hippocrates: for him differentiation occurs following a natural teleology and the principle of opposites is one of rules:

Further, one should divide by opposites. Opposites are differentiated one from each other, for example whitness and blackness, straightness and curvedness. Therefore if one of two is differentiated, the division must be made by its opposite, not one by swimming and the other by colour⁽⁴⁾.

In the works of Aristotle opposites may be found as rule of continuity of species and sex is the governing principle (αρχή) of generation, together with the soul (nutritive soul for incoming life). Thus, an interaction of opposites (so called: DGA 716 b 1) in copulation is the basic principle of reproduction. Castration demonstrates the loss of the opposite's quality (DGA 716 b 5). The same asexual reproduction requires a meeting of two components, like in sexual reproduction: warm mud and active form of soul (DGA 716 b 14: also spontaneous generation requires the two components). In fact, for Aristotle meeting sex-opposites is the general principle for generation of higher living and only primitive life, as represented by vegetative livings, is excluded:

For perhaps at same time it will also be clear in what way formation from contraries has its place in all things that arise from semen (DGA 724 b 7-9).

And again:

We must now resume and state what is the primary nature of semen, as it is called.

Now every substance, whatever it may be, that we find in the body, must of necessity be one of the following: (1) one of the parts which are there in accordance with nature, in which case it will be one of the uniform or non-uniform parts (literally: non-homoeomerous or homoeomerous - *ἀνομοιομερόν / ὁμοιομερόν*); (2) one which is there contrary to nature, e.g., a tumour; (3) residue; (4) colliquescence; (5) nourishment (DGR 724 b23-26).

Biological principles of ancient medicine derived from both four humors theory of Hippocratic School and naturalistic view of Aristotle: health/illness balance depends from the individual constitution (*κράσις* in greek, *complexio* in latin): the body is a mixture of different primary qualities (hot and cold, dry and humid, etc.).

Thus, elements as constituents of the nature as well as of the human body are present in the presocratic philosophy and later on in the medicine. The classical western medicine is a continuous sequence of theories founded on a balance of elements, mainly presented as opposites: is it a biomedical reality or is it a paleosemantic residue of theurgical medicine, in which the balance/unbalance between good-health and evil-sickness is the double reality of the same general thought?

Opposites in ancient western medicine: contraria contrariis

Few centuries later, Galen represents the encyclopedic witness of ancient medicine and *Ars medicinalis* or *Ars medica* is the summa of his thought: in the chapter XXVIII theory of opposites is clearly explained. When sickness is beginning, the therapy is the administration of the opposite of the "evil", which is the unbalanced element.

At the beginning of a medioeval manuscript of *Ars Medicinalis* we may read:

Medicina est scientia salubrium et insalubrium et neutrorum; which is

Medicine is science of health, illness and neutral,

that means "of healthy situations and not healthy situations and balanced"⁽⁵⁾.

The concept of Galen was expressed by his therapeutical principle *contraria contrariis*, by which cure is conceived as administration of the opposite quality of that shown in the disease.

Galen regarding therapy says that *nesesse est per contraria fiat corum alterius in alterum translatio* with the aim (*maxime generalis scopus*, he says) of *contrarietas*. And concludes:

Quoniam quod aegrotat bene valenti est contrarium, per contraria est ab illo in hoc via⁽⁶⁾.

And in the *Methodi Medendi*, liber XI, says that:

unum esse omnium morborum communem curationis scopum contrarietatem ipsam⁽⁷⁾.

Almost in the same period, Celsus (1st century A.C.) had clearly explained this principle in an ethiological view:

Evidentes vero eas appellant, in quibus quaerunt, initium morbi calor attulerit an frigus, fames an satietas, et quae similia sunt: occurrurum enim vitio dicunt eum, qui originem non ignorarit⁽⁸⁾.

Celsus, regarding therapy, observed that prescriptions should be found on the opposite (i.e. in digestive diseases):

Cognito igitur eo quod ex his est, si corpus adscriptum est, digerendum esse; si profluvio laborat, continendum... (DM, p. 18),

that is:

When we know the cause of the disease, if there is a costipation, a purge should be taken, if there is diarrhoea we need astringe.

And when burning fever flares:

in ipsis accessionibus oleo et aqua refrigerandus est (DM, p. 142),

that is

in the same attack cooling oil and water should be used.

In the medicine of imperial Rome the general principle of opposites is applied to therapy by imposing the opposite quality or element of that for which the patient is suffering⁽⁹⁾.

It may be observed that at the dawn of medicine of observation, from Hippocrates to Galen, the very simple principle of opposites was the guideline for the developing profession.

Opposites in traditional medicine of China

The medical thought where theories of opposites are clearly present since more ancient time is the Chinese, as indicated by the most authoritative medical compendium of ancient China, which is the *Canon of Medicine* attributed to the so called Yellow Emperor Huang Ti (about 2,600 B.C.). This book explains that medicine is based on five elements (fire, air, water, earth, wood) and on their balance⁽¹⁰⁾.

Later on, philosophy and culture have been developed and revised by K'ung Fu-tzu (Confucius, 5th century B.C.) and precepts transmitted for generations: ancient China was very conservative and the first not sporadic contact with European culture

has been only a millenian later, through the heretical Nestorian Christians, dispersed from Constantinople in the 5th century A.C.

Thus, independently from European influence, religion in China was defined better than in classical mythology: a paradise was conceived to exist, where after death the souls lived in immortality. Both human and natural world were categorized under the complementary, yet opposing, principles of *Yin* and *Yang*⁽¹¹⁾ and Chinese medicine too has used the qualitative principles of *Yin/Yang* and the five elements (*wuxing*). Their finely graded derivations were used to qualify all phenomena of nature and human life: *Yang* is a positive force and *Yin* is the negative one. The absolute principle of the universe is the *tao* (Taoism is a behaviour rule, more than a philosophy or a religion): *tao* is well-being, due to a right mixture of *Yin* and *Yang*, and the imbalance may produce sickness.

The life as balance of elements induced a humoral medicine like in ancient Greece. This principle was applied to all livings, as can be found in a book of Zootaxonomy of a period ranging from the Zhou Dynasty to the Western Han Dynasty (before 3rd century B.C.: may be of 1st century) entitled *Cirri of history: confirmation or opposition to the five elements*.

In the 2nd century A.C. a *Treatise on Febrile Diseases caused by cold (Shanghan Lun)* has been compiled by Zhang Zhongjing⁽¹²⁾: because health is indicated as balance between cold and warm, the treatise is useful for the analysis of true and wrong about these theories.

An absolute prevalence of *Yin* and dispersion of *Yang* occurs in febrile disease by cold (clause 346) or in case of diarrhea (clause 348). Clauses with fever due to the evanescence of *Yin* (and prevalence of *Yang*) are also described (i.e. clause 347): health is the consequence of the appropriate balance.

In 1973 Goldberg and coworkers explained relationship and mechanism of action of cyclic AMP and cyclic GMP as balance

between opposites, like living opposites elements of the *Yin-Yang* confucianism⁽¹²⁾.

The observation that in certain conditions levels of the two nucleotides "act in opposition to one another" was assumed as general metabolic law of regulating cellular functions: "...biologic regulation in simple terms remains a process imposing positive and negative controls on cellular events".

But is it true?

Today, we know cellular metabolic events in which only one of the two nucleotides is affected (i.e. modulation of G-proteins activity) and we think that they act more in a network of secondary mediators than in a duality system. This is an example of hasty fall into the trap of opposites, which are acceptable as generic philosophical theory or as a first temporary scientific explanation, but not as medical permanent thought, because not supported by univocal experimental data.

The modern medicine: immunology

The most representative examples of biomedical terms opposing one to another and introduced in contemporary biomedicine concerne immunology and molecular oncology.

Immunological concepts as today are conceivable had their first ancestor in the ancient medicine of far East (India and China) with variolization (inoculation of material taken from pocks of patients). Again, the head of mummified pharaoh Ramses V (12th century B.C.) displayed smallpox scars in the skin and Emperor Marcus Aurelius died of it (180 A.C.). Only at the end of 18th century Edward Jenner introduced vaccination against smallpox taken from cow (1798). Later on applications of bacteriology give rise of inoculations of attenuated cultured microorganism to produce specific protection against infections⁽¹³⁾.

At the end of 19th century the term immunity appears in scientific literature and it means forces antagonistic to infec-

tious diseases and more particularly antagonistic to microorganism and toxins; for Behring activity is due to the presence of specific antitoxins⁽¹⁴⁾. Originally, immunity derives from the latin word *immunitas*, which is to be free of any charge (i.e. taxes and military service) and translated to medicine "free or resistant to infectious diseases"⁽¹⁵⁾.

Later on, biological activities against microorganisms were found in the "immune" serum. The relative reactants were called according to the type of visible reaction: bacteriolysins, agglutinins and precipitins were the inducers, whereas bacteria, agglutinogens and precipitinogen respectively were the reacting substances.

Antibody today is described as a molecule able to recognize and to react with a specific complementary structure: the terms which today we use for the reacting molecules (*epitope* and *paratope*, as suggested by Jerne) mean that the reactants produce not more than an interaction between two molecules, like an enzyme and the specific substrate.

If this is true, which were the phases for developing this terminology at the end of the last century and in the first half of this century?⁽¹⁶⁾

May be interesting the analysis of medical books of german general pathologists in the last decade of 19th century, which is the period of incoming immunity in medical doctrine:

If a man is very resistant to a pathological agent, we call this state immunity and depending from the grade we distinguish a relative immunity from an absolute immunity. ...Against malaria, thyphus, diphtheria, scarlet fever and even against measles and smallpox many persons are immunized for the life... In some infectious diseases ...a new infection is mitigated by a previous infection of the same sickness or of a similar (vaccine) and a variable immunological protection takes over....

But no explanations were offered:

We don't know from which derives the immunity which is acquired after overcoming an infectious disease¹⁷.

Few years later we can find questions about the nature of immunological reactions:

The discussion about the nature of reacting properties of the body against infectious diseases essentially is the question if reaction... depends by the higher or lower potency of the cells or by the composition of humors...⁽¹⁸⁾.

Thus, according to Birch-Hirschfeld, cellular and humoral immunology were identified, the first as "war of cells against pathogenetical microorganisms", the second due to "blood serum... without cells" and other characteristics of the immunity are described:

a) vaccinations as attenuated or modified infections; they lessen more heavy diseases;

b) vaccinations may be induced by using not only microorganisms but also "products of metabolism of bacteria, without living germs";

c) passive immunity is detected: the immune serum from an animal is active also in other animal (if injected in the same and other species) in both preventing and attenuating the same disease.

At that time terminology was very clear and if toxins were the toxic principles of bacteria, antitoxins were the active substances present in the serum of immune animals: substances were named as opposite on the basis of biological action.

In the following years knowledges rose and terminology slowly changed.

Metchnikoff replies against "objections contre la théorie phagocitaire de l'Immunité, (qui) proviennent uniquement de la connaissance insuffisante de celle-ci"⁽¹⁹⁾. Landsteiner, working

on blood cells, identified antigenic groups, that he called agglutinogens (1900).

In an other field (immunological local reactions) Arthus affirms that "le deux états d'anaphilaxie et d'immunité son donc distincts" (ref. 19, p. 35) but he doesn't speak of antigens, term which is generalized few years later in a chapter "Antigènes et Anticorps" of a small wide spread treatise of Nicolle and Boquet (1926). They say that cells contain proteins of colloidal nature, which induce (provoquent), when injected in animals,

la formation de substances antagonistes ou anticorps spécifiques. D'où le nom d'antigènes qui leur a été donné par Detre Deutsch⁽¹⁹⁾.

The explanation for the term is not clear, because proteins have the property to *induce* the formation of an antagonistic molecule (antibody); but an inducer of substances cannot be "anti" but "pro".

Unfortunately, research on the two fields (toxins and immune reactants) was following two different ways, one improved by progress of chemistry of proteins, the other studied under biological and cellular points of view.

And terminology has changed and each field had its "anti", antibody for immunologists and antigen for immunochemists.

Why antibody? Body is the antigen? And antigen is anti what? Priority in the use the opposite term was for the humoral factor (antitoxin) and the more appropriate term (immunoglobulin) was introduced by Arne Tiselius only in 1937⁽²⁰⁾.

The availability of synthetic antigens and analysis of genes codifying for immunoglobulins have clarified the nature of immunological phenomena, such as the molecular basis of antigenicity and immunogenicity and the genetic bases of structure and function of immunoglobulins and of regulation of production of molecules of immunity.

Because the priority of introduction of opposite term is for

antibody, may be interesting a research about the rise of the term antigen.

Antigen derived from the greek (ἀντί = against and γένος = product) and may have two meanings, the first one for a substance which may trigger an immune response (immunogen), the second for a substance which specifically reacts with the immunoglobulin.

Deutsch introduced the term antigen to indicate a substance antagonistic to serum reactant, that is... antibody. For Deutsch also immunity and virulence are antagonistic: when there is an antagonism of an animal for a microorganism antibodies are produced; antagonism of microorganisms for animals is due to "antigens", which are defined by Deutsch as "generator of antagonistic substances". Wrong is that "immunizing substances + antigens induce a new compound with indistinguishable properties of the two substances" (see p. 72 of ref. 19, Deutsch): today we may think that such properties are of haptens, but they are not joined to other part of antibody, because they are part of the antigenic molecules!).

We can explain the mistake, analyzing works of Deutsch, just after Ehrlich formulated theories about immunity and cellular immunology (fig. 1, quoted by Deutsch, ref. 19, p. 87). According to Ehrlich's theories, Deutsch (writer more than scientist, active in the first quarter of this century) says that immunological reactants are conjugates of 3-5 single reactants, i.e. cells, reactant body of serum, complement of reaction, body interactive with complement, toxins. Ehrlich does not use the term antigen, which is wrong in this context, because it is not against something, but is part of inducing molecule (hapten, we say today). The hurried Deutsch introduces the word, as follow (Deutsch, ref. 19, p. 72):

Only after the works of Ehrlich and of the school of Metschnikoff-Bordet, who elucidated intimal mechanism of immunization and of

formation of substances able to induce immunization, a speech about certain bodies and not only of effects may be performed.

About the mechanism of action of immunizing substances we can state the following general rules:

I. the action of each immunizing substance is specific: specificity is referred to that substance which introduced in the animal body during immunization stimulates the production of corresponding immunizing substance.

We name this substance, according to Deutsch (Ann. Inst. Pasteur 1899, p. 710) with generic term of antigen (acronymus of generator of antagonistic substance) to indicate relationship with immunizing substances. Antigens of antitoxins are toxins, antigens of precipitins are the corresponding albuminoids.

II. Action of immunizing substances derives from the affinity between the substance and the corresponding antigen, in a combination=immunizing substance+antigen, in which properties of the two substances are undistinguishable.

Thus, the erroneous terminology was formulated by Deutsch misinterpreting the model of Ehrlich, in which molecules such as complement are indicated with an aptophoric group (bound to intermedial body, now antibody) and with a toxic (lytic) group. Deutsch believed that molecule that we call antigen is a double molecule compound, showing two functions (hapten and immunizing property) for two molecules. And he celebrates the mistake conferring to the reacting molecule the opposite name antigen!

The new and more appropriate terminology of the two reactants are *epitope* (which is the antigenic determinant) and *paratope* (which is the reacting immune molecule or antibody). These terms, introduced by Jerne, liberate immunology from the ambiguity of double negative "anti" and from the links to opposites.

Oncogenes and antioncogenes

Molecular biology has introduced opposite terms, like codon-anticodon for molecular recognition of genetic code.

More recently a family of genes has been discovered in tumor cell; they are present in retroviruses (RNA viruses encode into DNA by the enzyme reverse-transcriptase) and in human cells and called oncogenes (abbreviated: *v-onc* for viral oncogenes and *c-onc* for cellular oncogenes). Cellular oncogenes have been highly conserved throughout evolution leading important functions in growth, differentiation and development of both normal and tumor cells: their alterations (mutation, amplification, translocation) are related to cancerogenesis, because they interact with cellular proteins (growth factors receptors, protein kinases, etc.) or modulate nuclear activity with regulatory effects on cell growth. If oncogenes promote cancer growth, other genes, called anti-oncogenes, suppress oncogenesis. The retinoblastoma anti-oncogene (Rb) has been isolated in 1986 by molecular genetic methods: the neoplastic phenotype of retinoblastoma and sarcoma cells is suppressed by the transfection of cloned Rb gene.

Anti-oncogenes don't antagonize any known single oncogene: thus, they appear to operate through oncogene un-related mechanisms (Rb anti-oncogene encodes a nuclear phosphoprotein that forms protein complexes with adenovirus oncoproteins) and up to day the term anti-oncogene is wrong if referred to oncogene, because cell proliferation is regulated by a network of mediators (phosphorylating enzymes, cyclic nucleotides, phosphoinositol, calcium, etc.). Rb anti-oncogene is "anti" only regarding its own effect and not for an antagonistic action against a specific oncogene.

Conclusions

Dualities are present in the history of thought as derivation of ancestral balance between god/good and devil/evil.

We have observed that in ancient greek philosophy and

medicine, opposites may be found only after the heroic age (before neither the duality gods/devils is present and the only opposition is between gods, who determined the fate, and humans): when Odysseus took place of Achilles and naturalistic philosophy had introduced the method of observation, dualities become stable part of human thinking in ancient Greece and later on of the western philosophy and naturalistic sciences.

Opposites theories are present in greek philosophy (Heraclitus, Pythagora, Plato, Aristotle) and medicine (Hippocratic School, Galen), as well and in the same period in ancient China, where principles of opposites (*Yin / Yang*) became crucial components of the chinese religious and medical thinking.

Because new discoveries produce classifications, a tendency to use a terminology of dualities was coming from religion (Confucius, Christianity) and metaphysics and reached scientific speculation as more simple classification: in fact, in a first phase every new discovery is presented as opposition to something or as balance between opposites (i.e. qualities in ancient greek medicine).

The antinomies of modern medicine that we have reported (antigen/antibody, cyclic nucleotides, oncogenes/antioncogenes) are rapidly demonstrated uncomplete and more complex systems take place of the dualities first described; in fact, in many cases in ancient as well in contemporary medicine, such a classification is proved to be wrong or at least uncomplete when new knowledges are added: there is an unconscious tendency of "immortalization" of new theories or findings, to make the discoverer like a god, we say with Hippocrates (ἵητρος φιλόσοφος ἰσόθεος, that is "like a god is the physician-philosopher").

This is not true glory, as demonstrated by the term antigen introduced by an obscure scientific writer as second opposite to the previous called term antibody. Deutsch searched the fame and found a mistake, corrected by the Nobel laureate Jerne, who received notoriety by experimental results!

The erroneous tendency to classify as opposites is not exclusi-

ve of medical thought: may be remembered the case of dualistic theories in chemistry. O. Tachenius (17th century) affirmed that neutral salts are the combination of acids and alkali; later on Lavoisier and Berzelius made analyses to determine combining proportions of chemical elements and developed a dualistic electrochemical theory, widely accepted for many years. This theory (every compound is a combination of two opposites, one acid, the other alkaline) was unable to explicate combinations of organic compounds and in the same inorganic chemistry such theory cannot explain substitution of an electropositive ion (i.e. hydrogen) with a strong negative one (i.e. chlorine).

The hurry for ordering certainly has a practical aim, but is also hiding a tendency to fix ideas for ever, which cannot be true in scientific observations. We note with von Helmholtz:

Reality is much more rich than more imaginary speculations and elements of modern chemistry take the place of the four old metaphysical elements, fire, water, air and earth, becoming 65.⁽²²⁾

Thus, for Helmholtz tendency of ruling in medicine is expression of the immaturity of a new phase. It may be observed that the more simple ruling, i.e. through opposites, is fascinating because it brings near the duality of religion.

In ancient medicine this fact may be understood: in a period in which empirical medicine was just newborn, the hippocratic "physician philosopher is like a god" is related to the essential role of reasoning in such a medicine, but shows also — as Helmholtz says — that

...those sons of medical science (the hippocratic physicians) did not have tendency for a long time term planning and would like to be like god during their life ...therefore lower was the criticism against philosophers. Everyone speaking about a cosmological system, in which well or unwell reality should be enclosed, felt philosopher... and the importance of the work was on thought, logic and completeness of the system. May be understood as in a juvenile phase a so high valuation occurred...⁽²³⁾.

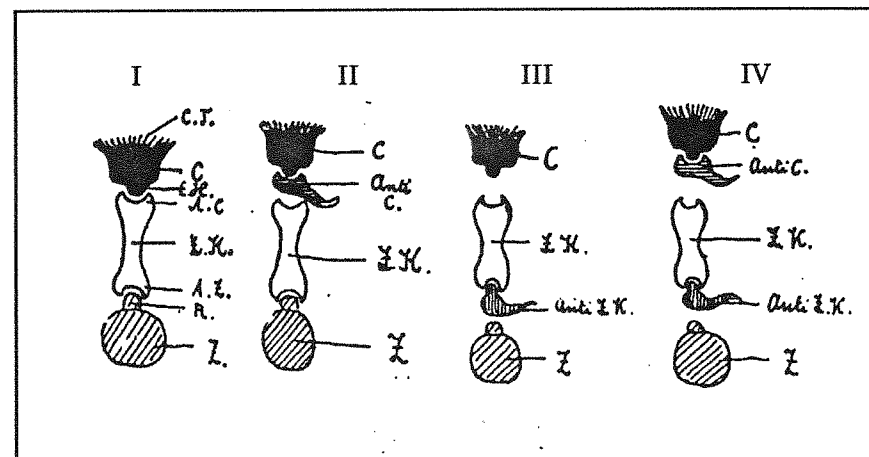


Fig. 1 - The original picture by Ehrlich about toxin-antitoxins reactions as reported by Deutsch and Feistmantel, ref. 19, p. 87

Legend to figure:

- C = Complement (alexin of Bordet and Buchner)
- CT = toxic group (lytic) of complement
- CH = aptophoric group, which has affinity property of complement
- ZH = intermediate body, with AC=body with affinity for complement and AZ=body with affinity for cells
- Z = sensitive cell (zell)
- R = side chain of cellular receptor, responsible for the affinity of the chain with the immunizing body

Different types of reactions have been shown. From the left:

- I = action of hemolysin
- II = action of anti-complement (anti-c.)
- III = action of anti-amboceptor (anti-intermediate body = anti ZH)
- IV = double action

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DPA: ARISTOTLE, *De Partibus Animalium* (Parts of Animals) transl. by A.L. Peck, Loeb Classical Library, Harvard Univ. Press, Cambridge, Mass., 1937

DM: CELSUS (Aulus Cornelius), *De Medicina*, transl. by A. De Lungo, Sansoni, Florence, 1985

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HOMER, *The Iliad*, trans. by R. Fitzgerald, Doubleday, N.Y., 1974

HOMER, *The Odissey*, transl. by R. Fitzgerald, Doubleday, N.Y., 1961

- 1) Homer does not distinguish between gods (θεοί) and evils (δαίμονες) (PLUTARCH, *The setting of oracles*, 415 a-b, 416 f); after the homeric age heroes from killer of monsters (Theseus against Minotaurus, Jason against the dragon that guarded the Golden Fleece) became winners by using logics (Oedipus with Sphynx; Cadmus with Thyphus); Cadmus saves Zeus and Zeus cannot admit the savage by a heroic man: heroes must be killed and they are killed in the wear of Troy. On this argument see: GRANT M., *Myths of the Greeks and Romans*, New American Library, N.Y., 1986.

In ancient Greece divine is what avoids any mediation: with the divinity we cry or laugh, says Sophocles (Ajax, 383). And the homeric hereafter is indifference: for all the humans death is going down (σκότος αιώης) into Hades (Iliad 17, 365; 18, 129). The fate and "I must do it" as design of gods are the rule for humans: "Gods and not you are the origin of the wear", says Pryamon to Helen (Iliad 3, 164) and the wear is will of the gods: "τί δέϊ πολεμίζεμεναι Τρώεσσιν Ἀργείους" (Iliad 9, 337), that is "why must Argives fight against Trojans?" (on this argument see: RUSSELL B.J., *The Devil in the Ancient World*, Cornell Univ. Press, N.Y., 1984);

Orphics first introduced a philosophical and religious difference between human good and human evil, without influence of fate; they destroyed olympic theology by abolishing sacrifices to gods (see: GRAVES R., *The Greek Myths*, Hazell Watson & Viney Ltd., London 1960, p. 30 ff.); such distinction through Plato (Plato, Republic 364e, 531a) was consolidated by Christianity: before Plato there was in the greek philosophy a dichotomy between what it must do (determined by the fate) and the good (PLATO, *The Laws* 937a); thus, philosophy of Plato dissolved the image of gods.

- 2) Oedipus is the first hero winning not with the strenght but with logos (answer to the enigmatic question on the man by the Sphynx), like Cadmus won Thyphus from hundred heads by using deception and music (NONNUS, *Dionysia* I, 385).
With Odysseus supremacy of mind occurs: not a hero but the mind is the winner of Troy and Odysseus represents the end of myth of heroes and the beginning of the

supremacy of human intelligence (see Odysseus in the island of Calypso — Odyssey 5, 160-233 —

"If... you would stay here... and be immortal..." says Calypso, but the answer of Odysseus, after remembering Penelope who "...must die", was: "Let the trial come... (and) pulled his tunic... and then took thought for the... voyage". The choice of Odysseus was to be a man.

- 3) ARISTOTLE, *Etica Nicomachea* (Ἠθικόν Νικόμαχείον), transl. by M. Zanatta, Rizzoli, Milan, 1986. For Aristotle conflicts derive by natural forces:

Καὶ περὶ αὐτῶν τούτων ἀνώτερον ἐπιζητοῦσι καὶ Φυσικώτερον, Εὐριπίδης μὲν φάσκων ἔρᾶν μὲν ὄμβρου γαίαν ξηρανθεῖσαν... καὶ Ἡράκλειτος τὸ ἀντίξουν συμφέρον καὶ ἐκ τῶν διαφερόντων καλλίστην ἄρμονίαν καὶ πάντα κατ' ἔριν γίνεσθαι.

that is:

"About these problems few persons search a more appropriate and naturalistic explanation: they are Euripides, who affirms that the dry ground loves rain... and Heraclitus; according to him opposite is useful and from opposites come wonderful harmony and everything come by conflict" (1155b).

See: Fragments of Heraclitus, which may be found in D.K. 22 b 8. The first fragment was directed for medicine.

See also Alcmaeon, Fr. 4 (Diels-Kranz B4) for health as equilibrium between qualities (ισονομία) and disease as domination of one quality over its opposite (μοναρχία).

- 4) ARISTOTLE, DPA 643a31; on the same argument see also DGA 716a 4-9.

- 5) GALEN, *Ars Medicinalis* (Τέχνη Ἰατρική), Iuntae ed., Venice 1541. ch. "Quid sit medicina"

Τέχνη Ἰατρική (Kühn's I, 305-412) was a compendium of general principles of medicine, containing conception of healthy, morbid, not healthy or neutral conditions, doctrine of signs of diseases (semeiology) and ethiopatogenesis.

The canon of the text was stated in Alexandria in the 6th-7th centuries A.C. (TEMKIN O., *Studies on Late Alexandrian Medicine*, Bull. Inst. Hist. Medicine 3 (1935), 405-430) and translated in syriac by Hunayn ibn Ishaq (9th century) and in Latin by monks (CASSIODORUS, *De Institutione divinarum litterarum* 1, 21, 2). It is contained in the manuscript *Ambrosianus G* 108 inferior (9th century), together with hippocratic *Prognostica* and *De Aeribus, aquis et locis* and other works of Galen.

Ars Medicinalis had an essential place in the curriculum of medical schools, for many centuries, from Alexandria to Italian medieval Universities. Commentaries on the *Ars medicalis* were a classical obligation of teachers, as demonstrated by works of Taddeo Alderotti, Bartolomeo da Varignana, Mondino de' Liuzzi, Dino del Garbo, Pietro d'Abano, Gentile da Foligno and Pietro da Forlì (active between 13th and 14th century in the Universities of Bologna, Padua, Florence, Siena and Perugia).

The College of Medicine and Arts of the University of Bologna stated in 1378 that the final examination for the degree in Medicine should be regarding *Ars Medicinalis* and *Aphorismi* (BERNABEO R.A. and D'ANTUONO G., *The Medical School of Bologna*, Firma Libri, Bologna, 1988).

- 6) GALEN, KÜHN, vol. X, p. 650.

- 7) GALEN, KÜHN, vol. X, p. 735.
- 8) CELSUS, *OM*, p. 8.
- 9) In the chapter XXVIII of the *Ars Medicinalis* Galen explains that the opposite of hot illness is the cold and of cold illness (cold, chill) is the hot. These principles may be applied to incoming diseases: otherwise when a disease is in advanced phase the patient should be cured by evacuation of humors, such as by bleeding, vomiting, skin traspiration or evacuation of urines.
See: NIEBYL P.H., *The non-naturals*, Bull. Hist. Medicine 45 (1971) 486-492 and OTTOSON P.G., *Scholastic Medicine and Philosophy*, Bibliopolis, Naples, 1984.
- 10) The Treatise *Nei Ching* (Canon of Medicine) was orally transmitted until the 3rd century B.C. and revised many times: the more ancient manuscript is of the 8th century A.C.
For a comment see: GUOHAO LI, MENGWEN ZHANG and TIANGIN CAO, *Exploration in the History of Science and Technology in China*, Shangai Chinese Classics Pub. House, Shangai 1982; see pp. 213, 410 and 563.
Five instead four of ancient Greece are the elements, because five was the sacred number of philosophy for China, from late antiquity to Confucius.
- 11) Early medical writings are attributed to the Emperor Fu Hsi, author of the first *Yin-Yang* composition (as figures of lines producing eight trigrams, which represent different conditions).
- 12) ZHONGHONG ZHANG, *Treatise on Febrile Diseases caused by cold (Shanghan Lun)*, New World Press, Beijing, 1986: the treatise was written the 2nd century A.C. and contains 398 clauses of diseases mainly related with cold and therapies by using herbs and drugs.
Yin and *Yang* duality is extended to many aspects as below exemplified:
Yin: positive - active - male - light - dry - warm
Yang: negative - passive - female - dark - humid - cold
Reinterpretation of *Yin/Yang* has been recently proposed by a comparison of the two principles with cyclic nucleotides: GOLDBERG N.D., HADDOX M.K., NICOL S.E., GLASS D.B., SANFORD C.H., KUHEL F.A. JR., ESTENSEN R., Biological regulation through opposing influences of cyclic GMP and cyclic AMP: the *Yin Yang* hypothesis, *Adv. Cyclic Nucleotide Res.* 5 (1975) 307-330. These Authors adfirmed:
...we concluded that there are a numer of biologic systems in which cyclic GMP and cyclic AMP seem to impose strikingly contrasting, often antagonistic, regulatory influences. We believe that this concept of biologic regulation through opposing actions of two cyclic nucleotides is well described by the ancient oriental concept embodied in the term *yin yang*. *Yin Yang* symbolizes a dualism between opposing natural forces... (which) may enter into a mutual interaction that results in a synthesis... (p. 309).

- 13) In the Middle Ages epidemics of smallpox were considered a frightening event. The practice of inoculation of scabs from pocks (known in India and China in the prechristian age and later on in caucasian regions and Turkey) was unknown in Europe until Lady Montague wife of the British Ambassador in Constantinople (who inoculated her children in 1717) was coming back in England. Jenner inoculated himself with the turkisk method using cowpox. The new method had been called vaccination from the latin "vacca", wich means cow (JENNER E., *Inquiry into the Causes and Effects of the Variolae Vaccinae*, London, 1798). Smallpox vaccination was prescribed by law in England (1835), Germany (1874), Italy (1888), France (1902).
Practice of vaccination was extensively introduced at the end of 19th century. Under the incentive of the studies on bacteriology of Louis Pasteur many vaccines were prepared by using cultures of bacteria. The vaccine against carbuncle was introduced in 1881 and Robert Koch, the german bacteriologist who found the bacillus of tuberculosis in the sputum of open consumptives (1882), was sent to Egypt in the summer of 1883 to study the agent causing cholera; thus, comma bacillus was identified and later on cultured in 1892 by Pettenkofer during epidemics in Hamburg.
- 14) Specific immunity was described first by Behring and Kitasato, who obtained the bacillus of tetanus in pure culture and prepared the specific toxin from tetanus. They used the word "immune" as response to a toxin (VON BEHRING E. und KITASATO S., *Ueber das Zustandekommen der Diphtherie-Immunitat und der Tetanus-Immunitat bei Thieren*, Deutsche Medizinische Wochenschrift 49, 4 Dec. 1890). They speak about "tetanus immunsirt... die toxisschen substanzen, welche die tetanusbacillen produciren..." and quote communications presented at the X International Congress of Medicine (1890) in the session about "the problem of immunity": "C'est en effet cet état bactéricide qui constitue la vaccination ou l'immunité acquise" (Folgendes) and more "la vaccination détermine dans l'organisme des modifications chimiques qui rendent les humeurs et le tissu peu favorables à la végétation du microbe, contre lequel on a prémuni l'animal" (Roger, Contribution à l'étude de l'immunité acquise).
- 15) The latin word *Immunitas* (from *munus*, wich is gift, service, job) originally is a political and civil term for exemption and translated "free or without any charge" of taxes or military services, corresponding to the greek word ἀτέλεια (see Vocabolario della Lingua Italiana già compilato dagli Accademici della Crusca, Firenze, 1859); Herodotus says ἀτέλεια στρατηγῆς καὶ φόρου, that is "without military service and taxes" (3, 67). Other words that have been derived from the latin *munus* in european languages are munificent and remunerate.
- 16) For story of serological reactions and of elucidation of antibodies: CHASE M.W. and KUHNS W.J., *Specificity of serological reactions*. Landsteiner centennial, Ann. N.Y. Acad. Sci. vol. 169, 1970; see also EDELMAN G.M., *Antibody structure and molecular immunology*, Science 180 (1973) 830-8.
- 17) ZIEGLER E., *Treatise of General Pathological Anatomy and Pathogenesis*, Tubingen, 1882 (italian transl. by L. Armanni, Naples, 1887), pp. 42-44.

- 18) BIRCH-HIRSCHFELD F.V., *Handbook of General Pathology*, Italian transl. by B. Morpurgo, Vallardi, Milan, 1892, pp. 248-240: both humoral (in the serum) and cellular (phagocytes according to Metschnikoff) immunity are supposed and regarding humoral immunity it is well explained that it is present in the blood and active in other animals when they are injected with immune blood serum (without cells, according to the experiments of Buchner on the typhus, it is underlined).
- 19) About immunology, in the first decades of 20th century:
METSCHNIKOFF É., *L'Immunité dans les maladies infectieuses*, Masson, Paris, 1901.
DEUTSCH D. and FEISTMANTEL K., *Vaccini e Sieri* (Italian translation by Belfanti S. and Ascoli M.), Rosenberg & Sellier, Turin, 1905.
NICOLLE M., *Les Antigènes et les Anticorps*, Doin, Paris, 1920.
ARTHUS M., *De l'Anaphylaxie à l'Immunité*, Masson, Paris, 1920.
NICOLLE P., BOQUET A., *Eléments de Microbiologie générale et d'Immunologie*, Doin, Paris, 1926 (see p. 269).
It is worth noting that about in the same period a famous scientist (Arthus) don't treat of antigens, whereas a modest one (Nicolle) is dedicating to this argument a book.
- 20) TISELIUS A., *Electrophoresis of serum globulins*. II. Electrophoretic analysis of normal and immune serum, *Biochem. J.* 31 (1937) 1464-1470.
- 21) For oncogenes and antioncogenes see: SEEMAYER T.A. and CAVANESE W.K., *Molecular Mechanisms of oncogenesis*, *Lab. Invest.* 60 (1989) 585-599; GOUDIE R.B., *What are antioncogenes?*, *J. Pathol.* 154 (1988) 297-298; HOROWITZ J.M., YANDELL D.W., PARK S.H., CANNING S., WHYTE P., BUCHKOVICH K., HARLOW E., WEINBERG R.A. and DRYIA T.P., *Point mutational inactivation of the retinoblastoma antioncogene*, *Science* 243 (1989) 937-940; SPANDIDOS D.A., ANDERSON M.L.M., *Oncogenes and onco-suppressor genes: their involvement in cancer*, *J. Pathology* 157 (1989) 1-10; Spandidos says that approximately 40 oncogenes have been described mainly through studies on retroviruses and by *in vitro* functional analyses such as transfection of transforming genes into 'normal' cells. Because they are more difficult to be identified, only a handful of onco-suppressor genes have been described so far, but potentially they could number as many as oncogenes. Although some properties of oncogenes have been identified, we do not know in detail the role that these genes play in normal cells or how genetic damage contributes to malignancy. The effect of oncogene expression on a cell depends both on the cell type and on the oncogene, and in some circumstances oncogenes act as onco-suppressor genes and vice versa. Thus, up to now the term anti-oncogene is generic and not referred to a mechanism of action.
- 22) Hermann von Helmholtz studied medicine in the Berlin University (1838-1842) sustained by a residency at the Military Institut Friedrich-Wilhelms (together with Virchow). He was professor of physiology in the University of Königsberg (1849), of Berlin (1855) and of Heidelberg (1858). Later on, in the University of Berlin he had

appointments as Professor of Physics (1871) and as Rector (1876), the latter before Virchow (nominated in 1893). Helmholtz applied mathematics and physics to medicine: he studied optical physiology, acoustics and elaborated theories about conservation of energy.

For biography and works see: *Opere di Hermann von Helmholtz* (Works of H.v.H.), edited by V. Cappelletti, UTET, Turin, 1967.

Works quoted in this article: VON HELMHOLTZ H., *Über das Ziel und die Fortschritte der Naturwissenschaft*, Innsbruck, German Congress of Natural Sciences, 1869; VON HELMHOLTZ H., *Zeit des Ueberganges* (Science of the Nature), 1859, Conference at the University of Heidelberg.

Regarding considerations about elements of ancient naturalistic sciences, it may be observed that in the same period Mendeleev described the periodical system of elements (1859).

- 23) The development of naturalistic and medical thought in ancient time was treated by Helmholtz in Berlin in a speech to the students of the Medical military Academy (*Das Denken in der Medizin*, Berlin, 1877, reported in VORTRÄGE und REDEN, Braunschweig, vol. 2, 1896, pp. 165-190). In *Das Denken in der Medizin* (Thought in Medicine) Helmholtz analyzed the relationship between philosophy and medicine in ancient medicine (see also the comment by V. Cappelletti, cit., pp. 535-578).
- 24) To L.R.A. are due parts concerning history of medicine, to L.F. parts concerning medical knowledges. Correspondence should be addressed to L.R.A., Via A. Fusco 107, 00136 Rome, Italy.