

The past, present and future of meridian system research

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Acupuncture points and meridians have been discovered to have high electric conductance which is related to high density of gap junctions. Neurohumoral approach in acupuncture research was instrumental in establishing the scientific validity of acupuncture. Recent advances in the morphogenetic singularity theory suggest that acupuncture points originate from the organizing centers in morphogenesis. This theory explains many puzzles in both developmental biology and acupuncture research, including the distribution and non-specific activation of organizing centers and acupuncture points, the high electric conductance of acupuncture points, the polarity effect of electroacupuncture and side-effect profile of acupuncture, as well as the ontogeny, phylogeny and physiological function of the meridian system and chakra system. Most of these have not been explained by any neurohumoral theory. In several 'prospective blind trials', research results have supported its corollary on the role of singularity and separatrix in morphogenesis, the predictions on the high electric conductance and the high density of gap junction at the organizing centers. These advances have implications in multiple disciplines of biomedicine beyond acupuncture.
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ACUPUNCTURE AND THE MERIDIAN SYSTEM

In 1996, the US Food and Drug Administration reclassified acupuncture needles and substantially equivalent devices from class III (premarket approval, investigational use) into class II (special controls) which includes medical devices for general use such as scalpels and syringes (Food and Drug Administration 1996). Hundreds of randomized controlled trials on acupuncture have been published (Koptchuk et al. 1996). Positive results of acupuncture were demonstrated in a variety of conditions such as renal colic (Lee et al. 1992), migraine (Hesse et al. 1994), osteoarthritis (Christensen et al. 1992), Raynaud's syndrome (Appiah et al. 1997), stroke (Naeser et al. 1992, Hu et al. 1993) and low sperm quality (Siterman et al. 1997). A systematic review of the high quality acupuncture antiemesis randomized controlled trials showed consistent positive results across

different investigators, different groups of patients, and different forms of acupuncture point stimulation such as electroacupuncture, laser, acupressure and manual acupuncture (Vickers 1996). The success of acupuncture has sparked many studies on the nature of the meridian system which is the foundation of traditional acupuncture theory. According to the Standard Acupuncture Nomenclature proposed by the World Health Organization (WHO 1991), there are about 400 acupuncture points and 20 meridians/vessels connecting most of the points. Since the 1950s, it has been discovered and confirmed by researchers in several countries with refined techniques (Pomeranz 1997) that most acupuncture points correspond to the high electrical conductance points on the body surface (Comunetti et al. 1995, Bergsman & Wooley-Hart 1973, Wensel 1980, Nakatami & Yamashita 1977, Reichmanis 1988) and vice versa (Eory 1984). The high skin conductance of the meridian system is further supported by finding a

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high density of gap junctions at the sites of acupuncture points (Mashansky et al. 1983, Cui 1988, Fan 1990, Zheng et al. 1996). Gap junctions are hexagonal protein complexes that form channels between adjacent cells. It is well established in cell biology that gap junctions facilitate intercellular communication and increase electric conductivity. Acupuncture and meridian points have also been found to have higher temperature (Zhang et al. 1996), higher metabolic rates and carbon dioxide release (Eory 1984).

NEUROBIOLOGY AND ACUPUNCTURE

In acupuncture analgesia, the peripheral nervous system has been shown to be crucial in mediating the effect. The analgesia can be abolished if the acupuncture site is affected by postherpetic neuralgia (Bowshe 1998) or injection of local anesthetics (Chiang & Chang 1973). In other effects of acupuncture such as anti-hyperglycemic effects, studies have shown that local blockade of peripheral nerves or denervation did not interfere with the acupuncture effect (Liu 1998). In the 1970s, the relation between nervous system and acupuncture analgesia was explored by examining the cortical evoked potentials, single unit discharges and neurochemistry associated with acupuncture. For example, the projecting area of PC6 was mapped at the cortex and was found to overlap with the cortical splanchnic projection area. It was proposed that the cerebral cortex plays an important role in the mechanism of acupuncture inhibition of visceral pain (Chen et al. 1986). This type of study brought forth the Meridian-Cortex-Viscera correlation hypothesis (Anon. 1976) which states that: 1. The meridian system is an independent system connected via the nervous system to the cerebral cortex; 2. It acts through neurohumoral mechanisms (Chang et al. 1983). Recently, the activation of visual cortex by stimulation of BL67 was mapped by functional MRL (Cho et al. 1998). The result showed that the activation of visual cortex by stimulation of BL67 – a point at the little toe which is used to treat eye-related disorders, is similar to that of visual light stimulation. A generalized acupoint-brain-organ model was proposed that acupuncture first stimulates the corresponding brain cortex via the nervous system, thereby controlling the chemical or hormone release to the disordered organs for treatment.

In the mid-70s, the discovery of endorphin induction in acupuncture analgesia and its blockade by naloxone marked a milestone in establishing the validity of acupuncture in mainstream science

(Pomeranz & Chiu 1976, Mayer et al. 1977). Animals which respond poorly to acupuncture analgesia can be rendered good responders by treatment with D-phenylalanine which inhibits the degradation of met-enkephalin (Takeshige et al. 1990). A close relation between acupuncture and the nervous system is also indicated by the large overlap between acupuncture points and trigger points – points of maximum tenderness in myofascial pain syndrome (Melzack et al. 1977). These results have led some practitioners to believe that the meridian system as described in the classic acupuncture literature does not exist and that all the effects of acupuncture are mediated through the nervous system (Ulett 1992, Mann 1998). Other scholars regard the neurally mediated acupuncture phenomena as possibly ‘minor or secondary effects’ and ‘not the central core of the mechanism of acupuncture’ (Pearson 1987). The neurohumoral theory of acupuncture has been mostly descriptive with little predictive power.

DEVELOPMENTAL BIOLOGY AND THE MERIDIAN SYSTEM

The traditional concepts of the meridian system have been studied from the perspective of morphogenesis. The relation between the meridian system and embryogenesis has been noted for decades (Mann 1971). The ‘gap junction – embryonic epithelial signal transduction model’ (Mashansky et al. 1983) in the mid-80s proposed that the meridian system contains relatively under-differentiated epithelial cells connected by gap junctions which transduce signals and play a central role in mediating acupuncture effects. The morphogenetic singularity theory (Shang 1989) published in late 80s applied the singularity theory of mathematics to explain the origin, the distribution and non-specific activation phenomena of the meridian system.

Acupuncture points are singular points in surface bioelectric field

Epithelia usually maintain a 30–100 mV voltage difference across themselves (Jaffe 1977). This voltage is the potential difference across cell layers, not membrane potential. An acupuncture point which has high density of gap junctions and high electric conductance will also have local maximum electric current density – a converging point of surface current. This is a singular point of abrupt change in electric current flow. A singular point is a point of discontinuity as defined in mathematics. It indicates a point of abrupt transition from one state to another.

Small perturbations around singular points can have decisive effects on a system. As James Maxwell observed: 'Every existence above certain rank has its singular points ... At these points, influence whose physical magnitude is too small to be taken account of by a finite being, may produce results of the greatest importance' (Winfree 1980.) The pattern of electromagnetic field on the human scalp mapped by SQUID (Superconducting QUantum Interference Device) (Cohen et al. 1980) shows a singular point at the surface electromagnetic field where the surface magnetic flux trajectories converge and enter the inside of the body. This point coincides with the acupuncture point GV20 Baihui (Dr Magnus Lou, personal communication). The converging pathway of magnetic flux on the scalp coincides with the Governor Vessel in the meridian system. It is a separatrix which divides the surface magnetic field into two symmetrical domains of different flow directions. A separatrix is a trajectory or boundary between different spatial domains (Vinogradev 1992) and often connects singular points. Morphologically, the Governor Vessel is also the axis of symmetry on the scalp. This pattern is consistent with the pattern of the meridian system, but different from the distribution of any major nerve, lymphatic or blood vessel on the scalp (Fig. 1).

The role of electric field in growth control and morphogenesis

A variety of cells are sensitive to electric fields of

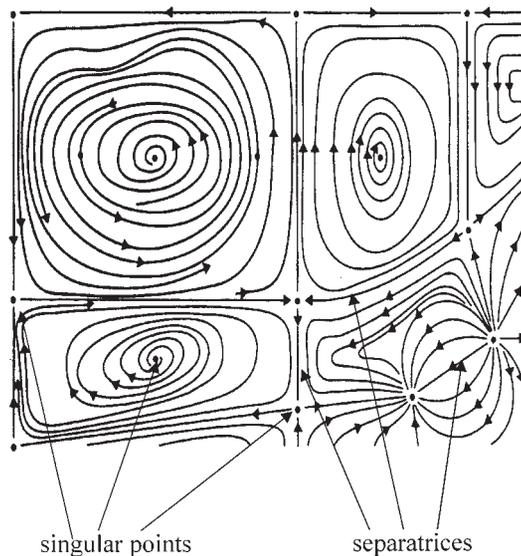


Fig. 1 Illustration of singular points and separatrices (modified after Figure 2.1 in: Mesterton-Gibbons. *A Concrete Approach to Mathematical Modeling*. Wiley; 1995: 47. Courtesy of John Wiley & Sons). This also approximates the pattern of acupuncture points and meridians – the singular points and separatrices of electromagnetic field on body surface.

physiological strength (Erickson 1985). Somite fibroblasts migrate to the negative pole in a voltage gradient as small as 7 mV/mm (McGinnis & Venable 1986). Asymmetric calcium influx is crucial in the migration which can be blocked or even reversed by certain calcium channel blockers and ionophores (Cooper & Schliwa 1986). In most cases, there is enhanced cell growth toward cathode and reduced cell growth toward anode in electric fields of physiological strength (Nuccitelli 1984, McCaog 1987). Fast growing cells tend to have relatively negative polarity. This polarity is due to the increased negative membrane potential generated by the mitochondria at high level of energy metabolism (Chen 1989). Imposed electric fields can cause polarization of mouse blastomeres (Wiley & Nuccitelli 1986). The anterior-posterior polarity (Marsh & Beams 1952) and dorsal-ventral polarity (Kalega 1985) in lower animal morphogenesis can be reversed when the polarity of the imposed external electric field is opposite to that of the intrinsic bioelectric field.

Organizing centers have high electric conductance

In development, the fate of a larger region is frequently controlled by a small group of cells, which is termed an organizing center (Meinhardt 1982). Organizing centers are the high electric conductance points on the body surface (Shang 1989). The amphibian blastopore, a classic organizing center,

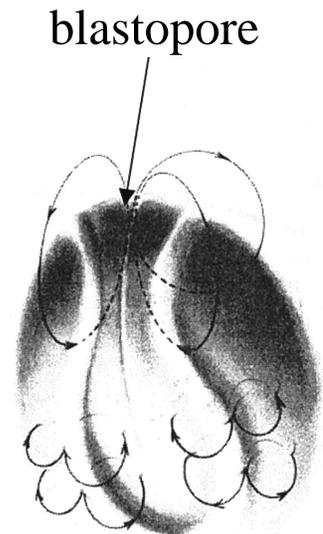


Fig. 2 Ionic currents traversing an embryo (Shi & Borgens. *Dev Dynamics* 1996; 202: 102. Courtesy of John Wiley & Sons). The blastopore, a classic organizing center, has high electric conductance and current density. A steady blastopore current persists after early embryogenesis. The electric fields polarize the embryo and serve as cues for morphogenesis. These results confirmed earlier predictions. (Shang. *Am J Clin Med* 1989; 17: 119–127.)

has high electric conductance and current density (Hotary & Robinson 1994). Similar phenomena have also been observed in higher vertebrates (Jaffe & Stern 1979). The high conductance phenomenon is further supported by the finding of high density of gap junctions at the sites of organizing centers (Laird et al. 1992, Yancey et al. 1992, Coelho & Kosher 1991, Meyer et al. 1997). At the macroscopic level, organizing centers are singular points in the morphogen gradient and electromagnetic field (Shang 1989). Disruption of the intrinsic electric field at the organizing center can cause malformation (Hotary & Robinson 1994). Change of electric activity at the organizing centers correlates with signal transduction and can precede morphologic change (Nelson et al. 1989, Shang 1993). For example, an outward current can be detected at the site of a future limb bud (an organizing center) in amphibians several days before the first cell growth (Nuccitelli 1988).

Acupuncture points – organizing centers

Both acupuncture points and organizing centers have high electric conductance, current density, high density of gap junctions and can be activated by nonspecific stimuli. Therapeutic effect of acupuncture can be achieved by a variety of stimuli (Vickers 1996, Altman 1992) including electricity, needling, temperature variation, laser (Hornstein 1997), and pressure. Similarly, morphogenesis of organizing centers can be induced by various stimuli such as mechanical injury and injection of nonspecific chemicals (Meinhardt 1982, Toivonen 1978).

Based on the phase gradient model in development biology (Shang 1989, Winfree 1984), many organizing centers are at the extreme points of curvature on the body surface such as the locally most convex points (e.g., the apical ectodermal ridge and other growth tips) or concave points (e.g., the zone of polarizing activity). Similarly, almost all the extreme points of the body surface curvature are acupuncture points. For example, the convex points include EX-UE11 Shixuan, EX-LE12 Qiduan, ST17 Ruzhong, ST42 Chongyang, ST45 Lidui, SP1 Yinbai, SP10 Xuehai and GV25 Suliao. The concave points include CV17 Danzhong, KI1 Yongquan, SI19 Tinggong, GB20 Fengchi, BL40 Weizhong, HT1 Jiquan, BL1 Jingming and CV8 Shenque.

Based on these similarities between acupuncture points and organizing centers, it was proposed that acupuncture points originate from organizing centers.

Why do auricles have the highest density of acupuncture points?

The distribution of acupuncture points and organizing centers is closely related to the morphology of the organism. For example, the auricle, which has the most complex surface morphology, also has the highest density of acupuncture points. According to the WHO, 43 auricular points have proven therapeutic value (WHO 1991), which consist of 10% of the acupuncture points of the whole body. Although an auricle has no important nerves or blood vessels and no significant physiological function other than sound collection, auricular morphology is one of the most sensitive signs of malformations in other organs. Auricular malformation has been observed in Turner syndrome, Potter syndrome, Treacher-Collins syndrome, Patau syndrome, Edwards syndrome, Noonan syndrome, maternal diabetes, atherosclerosis (Petrakis 1995), Goldenharr syndrome, Beckwith syndrome, DiGeorge syndrome, Cri-du-chat syndrome and fragile X syndrome. It is recommended in a standard textbook of pediatrics that any auricular anomaly should initiate a search for malformations in other parts of the body (Cotton 1996).

Meridian – Separatrix – Boundary

At early stages of embryogenesis, gap junction mediated cell-cell communication is usually diffusely distributed which results in the entire embryo becoming linked as a syncytium. As development progresses, gap junctions become restricted at discrete boundaries, leading to the subdivision of the embryo into communication compartment domains (Lo 1996). These high conductance boundaries or separatrices are also major pathways of bioelectric currents and are likely to be the precursors of meridians. Separatrices can be folds on the surface or boundaries between different structures (Shang 1989, Lee & Malpeli 1994). It was proposed that interconnected cells in the meridian system remain under-differentiated and maintain their regulatory function in a partial embryonic state (Cui 1988, Shang 1989). In consistence with this theory, it has been observed that the most apical part of folds remain undifferentiated in morphogenesis (Toivonen 1978), as well as organizing centers such as zone of polarizing activity (Ros et al. 1997) and apical ectodermal ridge (Carlson et al. 1998). The attributes of separatrix are consistent with the observation in the *Inner Classic* (Nei Jing) that meridians distribute along the boundaries between different muscles. For example, part of the lung meridian runs along the borders of biceps and brachioradialis.

Part of pericardium meridian runs between palmaris longus and flexor carpi radialis. Part of gall bladder meridian runs between sternocleidomastoid and trapezius. Trigger points also tend to locate at the free borders of muscles (Baldry 1998). The Governor Vessel and the Conception Vessel are part of the axis of symmetry on body surface that divides between many different structures. They are also regarded as the convergence of all meridians in traditional acupuncture.

The role of the meridian system in evolution and physiology

In ontogeny, the development of organizing centers in the growth control system precedes the development of the nervous system and other physiological systems. The formation and maintenance of all the physiological systems are directly dependent on the activity of the growth control system. Based on the morphogenetic singularity theory, the meridian system originate from a network of organizing centers. As the individual embryonic development recapitulates the evolution of the species, (ontogeny recapitulates phylogeny) the evolutionary origin of the meridian system is likely to have preceded all the other physiological systems, including the nervous system, circulatory system and immune system. Its genetic blueprint might have served as a template from which the newer systems evolved. Consequently, it overlaps and interacts with other systems but is not simply part of the nervous system,

immune system or circulatory system. The growth control signal transduction is embedded in the activity of the function-based physiological systems. The regulation of many neural, circulatory or immune processes is through growth control mechanisms such as hypertrophy, hyperplasia, atrophy, apoptosis with shared messenger molecules and common signal transduction pathways involving growth control genes such as proto-oncogenes (Baldwin 1996, Berczi 1994, Bailey et al. 1996, Miano et al. 1996, Tanaka & Samuel 1994). Acupuncture also induces the expression of proto-oncogene c-fos (Pan et al. 1996, Lee & Beitz 1993). Many 'non-excitabile' cells have shown electrochemical oscillation, coupling, long range intercellular communication (Shang 1993, Rink & Jacob 1989, Nedergaard 1994) and can participate in the meridian signal transduction.

A unified basis of the meridian system and chakra system

Based on the morphogenetic singularity theory, the distribution of the meridian system is related to both internal and external structures, and not solely determined by nerves, muscles or blood vessels. The distribution is a result of morphogenesis. Therefore, acupuncture points which are not at obvious extreme points of surface curvature or meridians which are not at obvious boundaries can be vestigial or more related to internal structures. The under-differentiated, inter-connected cellular network is

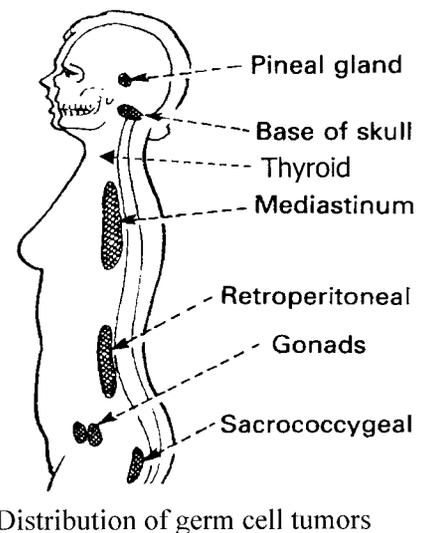
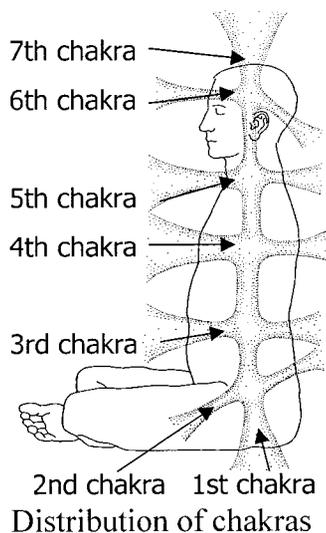


Fig. 3 Just as the distribution of pheochromocytoma correlates with the distribution of sympathetic ganglions, the distribution of germ cell tumors (figure modified after Govan et al. Pathology Illustrated 4th ed. London: Churchill Livingstone, 1995: 150) correlates with undifferentiated cells in human body which are likely to be involved in the regulation of growth control and physiology as part of the 'inner meridian system'. This distribution also correlates well with the chakra system used in yoga and acupuncture, suggesting a unified structural basis for chakra system and meridian system (figure modified after Fig. 1 by Stux In: Basics of Acupuncture. 3rd ed. Berlin: Springer-Verlag, 1995;287). Courtesy of Springer-Verlag & Dr. Gabriel Stux.

not limited to the body surface. One type of the least differentiated cells is the germ cell. The primary tumor distribution pattern of a certain cell type reflects the distribution of its normal counterpart. For example, the distribution of primary pheochromocytoma reflects the distribution of normal sympathetic ganglion cells. The germ cell tumors (Azizkhan & Caty 1996, Kountakis et al. 1994) have a midline and para-axial distribution pattern which spans from the sacrococcygeal region, through anterior mediastinum, tongue, nasopharynx, to pineal gland. It appears to concentrate at seven locations: sacrococcygeal region, gonads, retroperitoneum, thymus (Dehner 1990), thyroid (Gonzalez-Crussi 1982), suprasellar region, and pineal gland (Kretschmar 1997). The pattern resembles the chakra system used in yoga and acupuncture (Stux 1997), suggesting the existence of under-differentiated cells which may be highly interconnected in a normal state as part of the 'inner meridian system' and provide important regulatory functions (Nichols et al. 1997). It is likely that there is a hierarchy in the degree of cell differentiation and function in the meridian system with the germ cell system (major chakra system) as the least differentiated and constitutes the central core of the regulatory system. The more superficial meridians and acupuncture points are more differentiated and further down in the hierarchy.

Mechanism of meridian system based diagnosis and therapy

As the electrical conductance of organizing centers varies with morphogenesis, the conductance of acupuncture points also varies and correlates with physiological change (Cumunetti et al. 1995) and pathogenesis (Saku et al. 1993, Oleson et al. 1980). The fact that the change in electric field precedes morphologic change (Nuccitelli 1988) and manipulation of the electric field can affect the change (Smith 1988) may shed light on the diagnosis (Oleson et al. 1980, Ischenko et al. 1991) and treatment of many diseases. According to the morphogenetic singularity theory (Shang 1989), the network of organizing centers retains its regulatory function through high levels of intercellular communication correlated with relatively low levels of cell differentiation during and after embryonic development. This prediction is consistent with the finding that the under-differentiation and high electric conductance persist at the organizing centers after early embryogenesis (Shi & Borgens 1996). The organizing centers communicate with other parts of the body to maintain proper forms and functions. Gap junctional communication has been shown to play a

crucial role in morphogenesis (Ewart et al. 1997). The gap junction genes can also behave as classical tumor suppressor genes both in culture and in animal tests in restoring growth regulatory properties to metastatic cancer cells (Hirschi et al. 1996). An anomaly inside the organizing center network may be detected by measuring the electrical parameters of some points on its surface at the early signal transduction stage and treated by manipulation of the interconnected organizing centers.

The activation of organizing centers is likely to be involved in the restoration of proper form and function in wound healing and stress response. Acupuncture can speed up the wound healing process (King et al. 1989) and cause an exaggerated systemic wound healing and stress response (Wong & Bryton 1982, Lin et al. 1980). The response can include excessive release of endorphin which stimulates epithelial cell growth (Kishi et al. 1996) as well as analgesia. Other neuro-humoral factors induced by acupuncture such as serotonin (Cheng & Pomeranz 1979) and ACTH (Malizia et al. 1979) also have growth-control effects (Pakala & Benedict 1998).

In acupuncture, the often nonspecific perturbation at singular points (acupuncture points) may not directly antagonize a pathological process but may indirectly adjust the process and restore normal function by activating the network of organizing centers in the organism. For example, acupuncture at ST36 suppresses hyperfunction and stimulates hypofunction of the gut motility (Li et al. 1992). The normalizing effect of acupuncture as explained above is less likely to cause the side-effects resulting from directly antagonizing a pathological process which often overlap with other normal and beneficial physiological processes. Therefore, proper use of these meridian system based techniques causes few side-effects (Holden 1994, Carneiro & Li 1995, Shiraiishi et al. 1995, Marwick 1997) as demonstrated in randomized controlled trials (Lee et al. 1992, Hesse et al. 1994).

A principle in electroacupuncture is that positive (anode) pulse stimulation of a point inhibits its corresponding function while negative (cathode) pulse stimulation enhances the function (Kenyon 1983). This polarity effect is similar to the finding that cell growth is enhanced toward cathode and reduced toward anode (Naccutelli 1984, McCaig 1987), consistent with the theory that the mechanism underlying acupuncture overlaps with that of growth control.

Summary

The morphogenetic singularity theory outlines the common ground shared among the meridian system,

chakra system and modern sciences. It is compatible with the findings from neurohumoral studies. It explains several phenomena and puzzles in both developmental biology and acupuncture research. These include the distribution of the meridian system, chakra system and germ cell tumors, the non-specific activation of acupuncture points and organizing centers, the high electric conductance of acupuncture points, the polarity effect of electroacupuncture and side effect profile of acupuncture, as well as the ontogeny, phylogeny and physiological function of the meridian system. Most of these have not been explained by any neuro-humoral theory. In several 'prospective blind trials' (Hotary & Robinson 1994, Laird et al. 1992, Yancey et al. 1992, Coelho & Kosher 1991, Lee & Malpeli 1994), researchers who were unaware of the theory, confirmed its corollary on the role of singularity and separatrix in morphogenesis, and its predictions of the high electrical conductance and high density of gap junctions at the organizing centers such as blastopore and zone of polarizing activity.

Techniques involving the stimulation of the meridian system such as acupuncture and qigong (McGee et al. 1996, Lu 1997) may activate the self-organizing system of an organism and improve its structure and function at a more fundamental level than symptomatic relief. Development of these techniques may enable the diagnosis and treatment of a pathologic process at the early signal transduction stage prior to the anatomical or morphological change.

PROSPECTS

The advances reviewed above have broad implications in biomedicine beyond acupuncture. The current stage of meridian system research is analogous to that of physics in early 19th century – at the transition from Newtonian mechanics to electromagnetics. Many details of the current theories remain to be clarified and tested.

Besides the neurohumoral studies, the following directions of research are likely to be important in further understanding acupuncture and the meridian system:

- Mapping of the meridian system and the dynamics of its electromagnetic field with high resolution techniques such as SQUID
- The relation between the physical parameters of the meridian system and various pathological or physiological changes, including changes during acupuncture and qigong practice
- Develop acupuncture related techniques of early diagnosis and treatment, and established their cost-effectiveness

- Clarify the role of the meridian system in morphogenesis and growth control
- Cell differentiation and signal transduction in the meridian system
- Mapping the body surface curvature through embryonic development and study its relation with the meridian system
- Chronobiology of acupuncture (Li et al. 1994) and meridian system
- Pulse analysis, the interaction between circulation and meridian system (Wang et al. 1998).

ACKNOWLEDGEMENTS

I thank Drs David Diehl, James Gordon, Richard Hammerschlag, Magnus Lou, San Wan for their help and Drs Mesterton-Gibbons and Gabriel Stux for permission to use figures in their books.

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