SELF AND OTHER

Toward An Expanded View of the Immune System in Health & Disease

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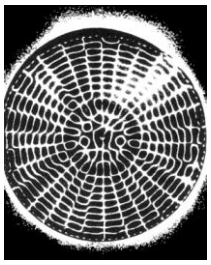
(Acknowledgements to Philip Franses, Daisy Allen, Richard Dryden and our continuing conversation)

'It is to be prayed that the mind be sound in a sound body'
Juvenal



Overview

From the outset of scientific investigation, the application of metaphor has informed and expanded biology . Such metaphors as the Darwinian 'survival of the fittest' (interestingly not Darwin's original metaphor at all) and the selfish gene hypothesis of Richard Dawkins and the neo-Darwinians, have added much value but are exhausted when proceeding beyond the domains of reductionist causality of modern molecular biology. It is becoming increasingly more evident, [1] that mechanisms involving biological co-option and co-operativity are of equal importance in the evolution of higher organisms.

It is crucial here to understand the reciprocity involved in the use and abuse of metaphor in biology. Survival of the fittest and the selfish gene metaphors both come from and reflect back to a capitalist society based on individual greed and marketplace competition. I make no moral judgement here. These are powerful drivers for wealth creation and social progress but this comes at a cost which may be unsustainable. However, it must also be said that given the observation that biological evolution is driven as much by the 'urge to merge' as it is by 'winner takes all' - particularly in the development of multicellular creatures - one would be foolish to assume that a society based solely on individual greed and marketplace competition is the only biologically viable option. To reflect this deeper, more holistic view of evolution it is necessary to develop metaphors based on the simple understanding that in a healthy society self-interest and individual freedom can only be maximised within the context of a shared vision of the common good.

The elucidation of the base pair ATGC coding sequence of the entire human genome is undoubtedly a singular triumph of modern biology, but to more fully understand the functionality of the organism we need to supplement the gene-centred view with a process oriented whole organism approach [2]. The current metaphor, based on the triumph of molecular biology, sees the organism as the hardware executing the master software codes contained within the DNA sequence however Denis Noble [3] and others have pointed out the problems of applying such a relentlessly reductionist approach to the inherently messy world of biology. It is the conversation between the digital (DNA) and analogue coding embedded in constantly iterated feedback loops, responding in a moment by moment dance with the environment which makes organisms so interesting, responsive, resilient and adaptive. Rather than being the master controller of the cell, the DNA sequence may instead be seen as one historical dataset among other more contemporary datasets available to the cell during its particular trajectory within the body. In cellular ontogeny, and by extension whole organism ontogeny, the DNA acts as a sacred text which is brought to life differentially in each generation by a process of cellular hermeneutics [4].

This is why it is necessary to develop new perspectives communicable through new metaphors and viewpoints from which to analyse specific functionalities such as the immune system. In this paper, I will explore emerging views of the expanded function of the immune system in health and disease in both utilitarian and metaphoric mode.

Is the immune system more than a defence system?

The concept of immunity and susceptibility has a long history. Pre-scientific views of disease involved ideas of punishment by supernatural forces, which may or may not be amenable to intervention in the form of sympathetic magic. The modern word immunity is derived from the latin 'immunis', meaning exemption, and it is still used in this context in law as in the phase 'diplomatic immunity'. The gradual development of evidence-based medicine saw the development of agents called vaccines (after the latin 'vacca', cow). Louis Pasteur and Robert Koch, pioneers of the germ theory of disease, together with others, began to explain how bacteria

caused disease and how the body could develop immunity following infection. Thus the science of immunology was born in a very empirical approach to health and disease resulting in the development of vaccines which with increasing safety and efficacy have become cornerstones of modern medicine. It is no wonder then that, with one or two notable exceptions, other non-defensive roles of the immune system have been overlooked. Perhaps it is also noteworthy that our current models and metaphors (military notions of attack and defence) to explain the functioning of the immune system were conceived and nurtured following two catastrophic world wars.

Indeed, it is very difficult to avoid using military metaphors when describing the immune system. Consider the following paragraph which provides a very brief summary of the action of the immune system. For more detailed information refer to 'Roitts Essential Immunology' - a good, comprehensive middle-range text - although there are many other excellent immunology texts across the spectrum some of which are available as free downloads.

Summary of the action of the immune system
Primary defensive barriers include physical and chemical properties of the skin and other epithelial surfaces. Pathogens that breach these barriers meet various types of phagocytic cells drawn in to the fray by chemicals (cytokines) secreted as part of the inflammatory response. At the same time other chemicals help raise the temperature of the body inducing a fever.

This first phase of the immune response is mediated by cells and chemicals which are part of the 'innate immune system', so-called because we are born with it in a preformed and fully active fashion. Innate immunity is sometimes misleadingly called 'non-specific' immunity when it should really be called 'group-specific' since the phagocytes express receptors on their surface which recognise and respond to common molecular patterns expressed on the surface of invasive pathogens. Thus, innate immunity can prevent entry, colonisation and spread of pathogens.

The second phase of the immune response involves adaptive immunity. Phagocytic cells, and indeed most of the cells of the body, can present peptides to T cells of different kinds, whose surface receptors are elaborated by complex genetic processes using DNA code found within a relatively restricted set of genes, to produce a dazzlingly diverse set of T cell receptor proteins. By stochastic means it is possible to produce a virtually unlimited set of T cells with the ability to recognise almost any shape in space. T cells whose receptors have the best fit expand by cloning. T helper cells (Th) can then communicate with naïve B cells which are also primed to the same antigen and which have similar but separately DNA-encoded B cell receptors. If this is an allowed communication, the naïve B cells then clonally expand into billions of antibody producing plasma cells.

These antibodies are secreted into the blood and other parts of the body and become the effector arm of the adaptive humoural immune system. Th cells can also, under the right conditions, stimulate other T cells also binding the same antigen to differentiate and clonally proliferate into killer or cytotoxic T cells which become the main effector arm of the cellular adaptive immune system. (Note here that natural killer (NK) cells have a similar armament to cytotoxic T cells but recognise their targets through relatively non-specific lectin-like binding and are therefore considered part of the innate immune system.) When the threat has been resolved most of these cells undergo apoptosis (or programmed cell death) but a very few specialised T and B cells reactive to the presented antigen may persist as memory B and T cells for up to the lifetime of the whole organism. Should the organism encounter the invading pathogen on second and subsequent occasions, the adaptive immune response is much faster and of much enhanced magnitude. Though not known in the early empirical days of vaccine development, this provides the physiological basis for contemporary vaccination protocols where the body is challenged with killed or attenuated pathogens which stimulate the production of specific memory without causing the disease.

Self and not-self
While writing this brief summary of the immune system, I have tried to use instrumental language only. But, as you see, the military metaphor is already embedded in the way we describe the immune system. Again, I do not wish to make a value judgement. Indeed, as an extended metaphor this helps convey some, but not all, of the flavour of the immune system. When considering how and why such a powerfully armed and potentially lethal defence system does not turn against the body whose integrity it is charged to protect, in what has been

famously termed by Paul Ehrlich as 'horror autotoxicus', McFarlane-Burnett coined a particularly potent metaphor of the 'immune self'. While both innate and acquired systems would identify, vigorously pursue and eliminate anything the body encountered with not-self markers, it would ignore self-markers. However, as we will see, the immunological notion of self and not-self, while useful, is highly contestable.

Firstly, the very notion of a separate and discrete 'immune system' is a useful but abstract construct. In many respects, properties and processes that we refer to as immunity are shared by most of the cells of the body. For instance, nearly all body cells display an individual's MHC class 1 markers loaded with either self or not-self peptides and are capable (like good community watch citizens) of communicating through the two way cytokine discourse with the more professional cells of the immune system, such as dendritic cells.
Secondly, the mucosal immune system normally does not respond to the many and varied not-self peptides produced in the digestion of our food. When this does occur we may develop pathologies ranging from minor food allergies to life threatening anaphylaxis.
Thirdly, the body, as we call it, consists of a superorganism with over ten trillion cells with our peculiar genetic signature - derived from the original fertilised zygote along with its genetically separate, largely maternally-inherited mitochondrial endosymbionts, as well as more than 100 trillion other cells with different genetic signatures. Most of these cells are bacteria. We call these cells commensals. They are usually tolerated by the immune
system and are beneficial in many ways. They help to digest our food and produce vitamins; they encourage the immune system to develop in the right way and prevent colonisation by pathogenic bacteria through a process of niche competition. Interestingly, many of these 'friendly' bacteria can turn into dangerous pathogens when they are moved from one place in the body to another or when the body is immunocompromised. There are over 500 recognised separate species of 'friendly' bacteria in the digestive system alone. The mucosal immune system has to recognise these bacteria and ignore them, while being ever vigilant against very similar pathogens. Clearly this is a hard ask and sometimes the system malfunctions resulting in pathologies such as Crohn's disease.

Autoimmunity
Autoimmune diseases constitute an increasing proportion of the morbidity load in western countries. Typically, autoimmunity is associated with a breakdown of immunological tolerance which allows an immune response to be mounted against the bodies' own cells and tissues. Examples include coeliac disease, diabetes mellitus type 1, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and multiple sclerosis (MS). Many of these diseases are associated with a high level of autoantibodies against a relatively restricted set of auto-antigens. The loss of tolerance seen in spontaneous human autoimmunity is overwhelmingly manifested in B cells. In RA for instance, there are autoantibodies to the constant region of IgG but no corresponding T cell response. In SLE there are autoantibodies to DNA which itself is unable to stimulate a T cell response.

The genesis of tolerance is still not well understood. Indeed, as already noted the very distinction between self and not-self is problematic. Several hypotheses to explain immune tolerance have been proposed including the clonal deletion theory of McFarlane-Burnet, in which self-reactive lymphoid cells are deleted during immune maturation; the clonal anergy theory proposed by Nossal and the idiotype network theory of Jerne, whereby a network of antibodies and mirror-image idiotypes exist in the body capable of neutralising dangerous levels of self-reactive antibodies (see [5]). Though these theories explain much about the discrimination of the immune system, we really are still struggling to understand the genesis of autoimmune disease.
Certainly genetic factors are in play. Genes related to immunoglobulins, to T cell receptors and to the major histocompatibility complexes (MHC) may all play a part in predisposing certain individuals to autoimmunity. Gender too, plays a significant role. Of over 24 million Americans who suffer from autoimmune disease about 75% are female, although for particular diseases such as type 1 diabetes and Crohn's disease men are just as, or even more susceptible.

Environmental factors also have profound significance in the aetiology of autoimmunity. It may be more than a coincidence that the rise in the incidence of autoimmune diseases parallels the ubiquitous use of a variety of chemicals, such as pesticides and plasticisers which are capable of cross-linking both endogenous and exogenous proteins in such a manner as to confuse the process of immunological discrimination. On the other hand, in areas of the developing world where multiple infectious diseases are endemic, autoimmune diseases have a low incidence. Given then, the inexorable rise in the incidence of autoimmune disease in the West,

there are those who advocate the 'hygiene hypothesis'. For several generations, children in the West have had dramatically reduced contact with many common organisms so that their immune systems lack a full immunological education, which may then result in inappropriate self-responses to infections at a later stage. The routine repeated use of antibiotics, especially at an early age, will skew the distribution of intestinal bacteria away from optimal. This may have more profound consequences than previously realised. A recent report [6] has established the critical role of the colonic commensals in peripheral education of the immune system and how this might feed into the action of the thymus in neo-natal and early childhood development. Commenting on possible long-term consequences of antibiotic induced changes in the human intestinal microbiota, Blaser [7] demonstrates a troubling but robust correlation between the risk of developing inflammatory bowel diseases and the number of courses of antibiotics taken during early childhood.

Interestingly, there is some evidence that infection with some species of parasitic worms will alleviate the symptoms of some autoimmune conditions. Again, I do not make any value judgements here. This is not some 'nostalgie de la boue' plea for a return to an imagined golden age of pre-civilisation humanity where average life expectancy was around 25.

During the past century, sanitation and other public health measures, as well as widespread vaccination and antibiotic use have saved countless lives to the extent that average life expectancy in this country has risen from 45 to nearly 80.

The point I do make, however, is the importance of extending our models of the immune system in health and disease. We shall now examine some more holistic perspectives by which we might examine the immune system more from a process-oriented viewpoint.

Information, signatures, discourse and biosemiotics

Information is more than simply a code of instruction, but a route that can be traversed dynamically to give a composite sense of the whole by journeying over the landscape of the particular. This subtle route to the whole is able to bring together different aspects of the self, different particulars of current context, in order to give a whole, moment by moment assessment of the wellbeing of the composite identity (i.e. the organismal self). In particular, the signalling that takes place in the immune system is then the input to this whole distinguishing of informational wellbeing and thus the moment by moment arbiter of self and other.

Equally, questions posed by the whole organism as it moves through the world inform the choices made by the individual processes using signs to distinguish the task of health, a whole bounded integrity, from that of disease, the broaching of this integrity by foreign assailants or indeed by rogue cancer cells.
Information is in the form of dynamic questions put before the whole organism. The choices made by cells to articulate the whole activate signs which distinguish a collective path to health from the threat of fragmentation, introduced by attack from without or within.
At the molecular level these signs include self and not-self antigens and peptides derived there-from; as well as B- and T cell surface receptor proteins which bind these antigen-derived peptides after processing and presentation by cells of the innate immune system (antigen presenting cells, APCs). These presented peptides are bound with exquisite sensitivity and discrimination in the presence of the appropriate highly polymorphic major histocompatibility antigens (MHCs). Given a suitable cytokine cocktail, these initiating events lead through several sequential stages to the elaboration by plasma cells (terminally differentiated B cells) of antigen-specific antibodies and then antibodies to these antibodies, called idiotypes, and so forth leading to a (usually) self-limiting network of sign/object topological reflections as if in a hall of mirrors. Fehr and Caspar have provided a good overview of the implications of idiotype network theory for our understanding of the immune system.[5]
At the cellular level the various players such as the macrophages and dendritic cells, DCs (presenting cells providing a link between the innate and the adaptive immune systems), the T helper cells, Th, (which assist the development and maturation of both cytotoxic T cells, Tc) and antibody producing B cell-derived plasma cells, as well as the long-lived memory cells, constantly communicate in the language of the cytokines. In this continuing conversation it is crucial not only that all voices, including possible danger signals [8] from any body cell, can be heard but that each voice is heard at the right time. The language of the organism then has the role

of distinguishing those actions that promote the assertion of health, carried as an informational imperative, by differentially and decisively responding to those signs indicative of danger - such as pathogen invasion or cancer transformation that threaten the integrity of the whole. Equally, the health of the organism as a whole can be defined as that state which allows the maximum freedom of each individual cell to respond in a moment to moment fashion to these informational imperatives.

Since the immune system is in many respects the example par excellence of biological signalling, further insight into the immune system may be gained by applying a biosemiotic approach in which the various molecular and cellular players (following the principles of Pierce and others) are assigned roles within sequentially embedded and highly iterated triadic relationships involving sign, object and interpretant. This approach has been recently adopted [9]in an extended analysis of signal transduction in B cell activation, but it is yet to yield practical insights.

This biosemiotic paradigm has great potential in uniting top-down and bottom-up approaches to the immune system, and in particular should provide insights into the overall effects of herbs - both in terms of the perceptions of current users and practitioners and possible identification of novel uses, in particular in the treatment of autoimmune conditions. Soukand and Kalle [10] have recently used a biosemiotic approach to examine the role of the plant within a herbal landscape as part of embedded signalling triads, leading to particular therapeutic indications, and in so doing have extended the old herbal concept of the doctrine of signatures. Allen [11] has recently argued that a further analysis of the proportionate relatedness of phyto-, zoo- and anthropo-sign processes in sickness and in health might help address the mind-body distinction. In the next section I will consider the mind-body connection as it may be manifested in the realm of psychoneuroimmunology.

Psychoneuroimmunology

The mechanisms by which social, psychological and physiological stressors impact on the body's immune system have been recently discussed by Lorentz [12]. By adversely affecting the immune system in individuals with poor coping skills, certain constellations of stressors may have a pivotal role in the genesis of some cancers as well as increasing the risk of auto-immune conditions such as psoriasis, rheumatoid arthritis (RA) and multiple sclerosis (MS). Lorentz suggests that clinicians may help patients by employing a suite of practices including (as appropriate for the individual) meditation, relaxation therapy, prayer, therapeutic touch and directed imagery. Though there is conflicting evidence for the efficacy of any of these particular interventions, it is now becoming well accepted that the immune system is regulated in large measure through the inflammatory reflex.

Inflammatory cytokines and endotoxins produced by cells of the immune system act as afferents through the vagus nerve to the brain. Following processing in the brain the motor efferents from the brain inhibit inflammation by suppressing inflammatory cytokine synthesis through the release of acetylcholine in key organs of the reticuloendothelial system. Acetylcholine binds to alpha 7 nicotinic acetylcholine receptors expressed by macrophages and other cytokine elaborating cells, hence suppressing proinflammatory cytokines and limiting tissue damage. Further research into this intimate association between the nervous system and the immune system informed by the pairing and superposition of the neurohomunculus and the immunological homunculus will lead to a profound shift in our view of the immune system. [13]

The immunological homunculus

Unsatisfied with the limitations of the self/not-self divide and the widespread perception that the role of the immune system is restricted to body defence only, Irun Cohen [14][15] began to elaborate his vision of the immunological homunculus. Homunculi (both neuro and immuno) are virtual images of the body, functional maps with ever changing dynamic representations in health and disease. This notion and the view of the immune system as a secondary cognitive system [16] involved in body maintenance was informed by several intriguing immunological phenomena whose significance has only recently emerged from the obfuscating fog of the self/not-self orthodoxy.

The healthy adaptive immune system seems programmed to respond to particular constellations of body molecules. These self-antigens constitute limited overlapping sets of immunodominant epitopes whose expression acts as biomarkers for the health, or otherwise, of particular tissues and organs. Autoimmune

conditions are characterised by aberrant sets of reactivity to the same self-antigens with catastrophic results. Interestingly, this common repertoire of autoantibodies is also subject to aberrant expression in cancer[17]

Cohen referred to the natural autoimmune coherence of the immune system as the immunological homunculus. Using antigen microarray chip technology, Cohen and co-workers identified autoantibodies in the cord blood of immunologically naïve neonates to about 300 self-antigens, including various tissue specific antigens as well as immune modulator molecules such as gelectins and interleukins and the stress proteins hsps 40, 47, 60 and 70 [18]. Referring to this constellation of autoantibodies as the 'congenital immunological homunculus', Cohen suggests that during an individual's life trajectory these self molecules can provide the immune system with the optimal level of biomarker information consistent with the moment by moment management of a healthy inflammatory programme [15].

A suitably optimised diagnostic microarray test employing a panel of these biomarker self-antigens anchored on a microscope slide, has the potential of providing a personalised whole health assessment from a small amount of serum and could monitor subtle effects of therapeutic intervention (in the form of herbal extracts for example) that may not otherwise be detectable. Such a test may be suitable for monitoring the progress of many of the pathological states mentioned in this paper, indicating patterns of appropriate intervention not otherwise obvious.

Extending the idea of the immunological homunculus into the informatics domain, Cohen explored possible mechanisms of immune system cognition and computation [14]. Given the continual feedback and monitoring of the system as a whole by each of its parts, a key aspect of the system is that it is self-referential - it looks at itself looking at the system. This notion of self-reference, also implicit in the previously mentioned idiotypic networks of Jerne (see [5]), points to information in the immune system being distributed in a fractal and holographic manner. Many aspects of the immune system, such as its robustness and adaptability, are consistent with such a view.
This extended view of the immune system has already resulted in proposals to treat autoimmune conditions by vaccinating with appropriate autoantigens.

Mood disorders and the immune system
Aberrant inflammatory responses are pivotal in the pathophysiology of many modern maladies from autoimmune diseases to cancer, and of course the ageing process itself. Given the role of the nervous system in the control of inflammation and the widespread observation that psychological stress (a major factor in the aetiology of depression) can promote inflammation through effects on both sympathetic and parasympathetic pathways, it is not surprising that aberrant inflammatory responses have an important role in the pathogenesis of depression [19]. The association between major depression and immune dysfunction is compelling but until fairly recently has focussed on immune activation and cytokines. Commenting on various clinical and demographic correspondences and the increasingly widespread observation of changes in the autoimmune constellation, Chen et al. [20] have suggested that autoantibodies are primarily responsible for the pathogenesis of depression and, just as in many other autoimmune diseases, the aberrant inflammatory responses are associative rather than causal.

Be this as it may, it is clear that, as already mentioned in the section on psychoneuroimmunology, the immune system and a person's state of mind are closely linked. Owen [21], for example, has recently shown in a cohort of individuals living with AIDS that expressing forgiveness can improve immune function.

Herbs and the immune system
In the recent literature of herbal medicine [22] claims are made for the effects of a variety of herbs on various aspects of the immune system. Allergies, for example, may be treated with variously prepared extracts of chamomile, plantain, nettle, elderflower and milk thistle. Other 'healing herbs' include lime, willow, yarrow, mugwort, dog rose, elderflower, mint and feverfew.

Although of course many of the truly effective contemporary medical treatments and orthodox therapeutics owe their origin to herbal remedies and their descriptions in herbal folklore, there is a relative paucity of mainstream scientific research on the role of herbs in promoting a healthy immune system. In part this can be explained by the difficulty researchers find in funding such research but also it must be said, both conceptually

and operationally, herbalism and orthodox reductionist science occupy different worlds with few bridges to connect them. This situation is however changing.

Many researchers are now investigating the claims of western, oriental and various indigenous herbal traditions and gaining valuable new leads for the development of novel therapeutics. We have recently published work detailing the biomedical activities of some Australian endemic plants that are highly prized in the traditional medicinal practices of indigenous Australians [23][24]
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With respect to effects on the immune system, work in our laboratory at UNE [25] indicates that following ingestion of 'Echinacea Premium' (supplied by Mediherb - each tablet containing ethanolic extracts of 675 mg of E. purpurae and 675 mg E. angustifolia; 2tabs/day for 14 days) a modest, but significantly important, increase in white cell count (WCC) is accompanied by up-regulation of stress protein hsp 70.
A recent review by Gertsch [26] raises the general issue of bridging the gulf between the art and practice of traditional herbalism and the incorporation of the use of herbal extracts into the 'target network' of cause and effect in evidence-based medicine. Gertsch makes some interesting suggestions very pertinent to problems inherent in addressing the scientific study of the influence of herbs on the immune system.

Therapeutic herbal mixtures are almost always taken by mouth and clearly any effects of specifics contained within are modified by intestinal processes of digestion and assimilation. Equally, however, the reciprocating effects of such extracts on the intestinal commensals and subsequent immunomodulation and peripheral re-education of the immune system with subtle but possibly profound influence on the immunohomunculus must be taken into account, as well as the summative effect of individual metabolites on specific targets. It is at this level that the complex molecular mixtures constituting herbal extracts may exert their most beneficial effect on the immune system and health in general.

An important technical tool to study the effects of herbs on the immune system at this level involves an investigation of the effects on the expression of the autoantibody biomarkers of the immune homunculus using antigen microarray chip technology as previously mentioned.
Such an approach would also be of value in attempts to gain a useful overview of the immune system in any or all of the pathophysiologies previously mentioned in this article, and may well lead to gentler and more effective treatments for a range of maladies affecting an ageing population.

Mens sana in corpore sano
Given the thrust of the preceding sections the often quoted latin phrase from the poet Juvenal might serve as a convenient talisman for a healthy immune system.
We have seen a move away from the notion of the healthy immune system as a tightly regimented and rigorously disciplined body defence force capable of absolute discrimination between an objective immune self and not-self and thereby dealing with any threat to the self in a timely, efficient and essentially pre-programmed manner. We have seen a move toward the notion of the immune system performing its crucial defensive role as part of its wider role as a self-referential organ of cognition; a fully integrated embodied mind, a part of the whole but containing a map of the whole in all of its parts.

Self and not-self should no longer be seen as discrete objective categories but as fluid and negotiable processes; a dance through space and time, an endlessly fascinating conversation where bodily health is expressed most fully at the fractal interpenetrating boundary between self and other.

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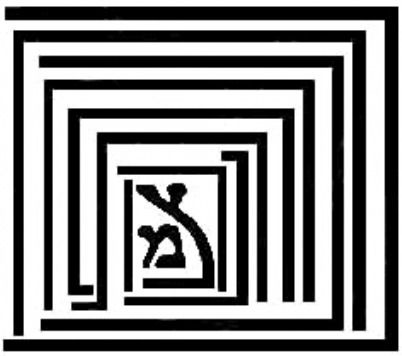

The path into the center winds in a clockwise pattern, and the path back unwinds counterclockwise. The spiral is a basic form of nature, although the labyrinth spiral is more complex. The path inward cleanses and quiets the mind. The unwinding path integrates and empowers on the walk back out.

(A labyrinth composed of the first letters of each of the ten sefirot. Based on a published edition of Pardes Rimmonim by Moses Cordovero)

The starting point of the ancient geometric thought is not a network of intellectual definitions or abstractions but instead a meditation upon a metaphysical unity followed by an attempt to symbolize it visually.