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# Kadishman's Tree, Escher's Angels, and the Immunological Homunculus\*

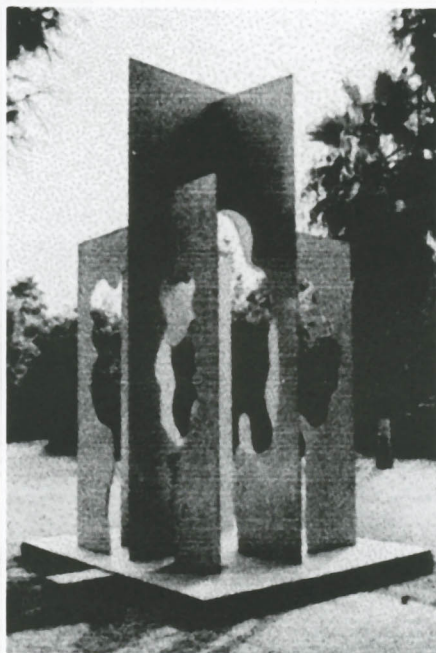
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## **Kadishman's tree**

On the grounds of the Weizmann Institute, near the Graduate School building, stands a statue of a tree done by the Israeli sculptor Menashe Kadishman (Figure 1). It is a statue of a tree despite the fact that there is no material image of a tree. The tree is virtual; it is made of air. The virtual image of the tree was created when Kadishman cut out the silhouette of a tree from five plates of steel. Some of the steel

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*Figure 1.* "Continuum" by Menashe Kadishman. A sculpture of a virtual tree; the background of the tree is made of steel, but the tree itself has no material existence. Real trees can be seen through Kadishman's virtual tree.

plates intersect at right angles, giving the virtual tree a virtual three-dimensional shape. The plates are so artfully joined that the tree silhouette changes as it is viewed from different angles; so a moving observer sees a changing, vegetating image of a tree. In essence Kadishman has presented us with a picture of a tree formed by materializing its background: the plates of steel exist on the grounds of the Institute; the tree exists only in the mind of the beholder. The sculpture is named "Continuum"; but it might be called "Boundary."

### **Escher's angels**

The idea of creating a virtual object by portraying its ground is an old device that did not originate with Kadishman. Escher has put the

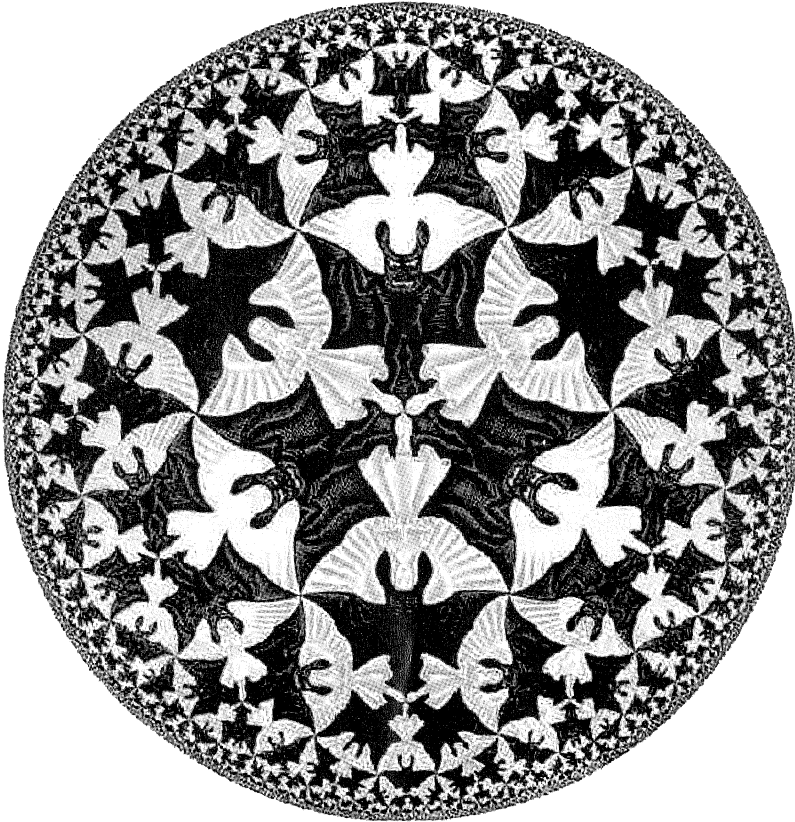


Figure 2. "Circle Limit IV" by M.C. Escher. A print done in 1960 in which angels and devils wage a subject-ground war for our attention. M.C. Escher's "Circle Limit IV" © 2001 Cordon Art B.V. – Baarn – Holland. All rights reserved.

subject-ground distinction to work by making the ground a subject too. A telling example is the print entitled "Circle Limit IV" (Figure 2). In this picture, dark devils alternate with light angels, each serving as a ground for the other subject. Escher's image pulsates as the angels and the devils compete for our attention. We cannot have both angels and devils at the same instant; one form must recede into ground for its opposite to become subject. Kadishman's tree becomes animated by the orbiting movement of its observer; but Escher's

image comes alive through the observer's oscillation of mind between angels and devils.

### **Creation by distinction**

Along with its lessons for the psychophysiology of human perception, Escher's picture of the cosmic conflict between subject and ground calls attention to a principle of existence: the angels emerge from the continuum of the picture and exist only when separated from the devils (and vice versa). To recognize an object in essence is to separate it from its surround, to establish its boundaries and thus define it. In fact, the word *define* derives from the Latin *definire*, to set a boundary.

Definition as establishment of boundaries is even older than is Latin. Religious literature states that the Creator spent the first six days separating one thing from another: earth from heaven, light from darkness, dry land from water, and so forth (Gen. 1:1–19). To crown the act of separation it was only necessary to give names, to conceptualize in mind the distinctions in matter: the darkness was named *night* and the light was named *day*. Since reality is a continuum, an object achieves existence, at least for us, when it can be differentiated from its neighbors to the point of being named. Discrimination is all.

(Parenthetically, note that Adam is charged with the responsibility of giving names to the animals [Gen. 2:19–20]; his first job is to help the Creator with some of the residual details of creation. It would seem that the unfinished, perhaps unfinishable, business of creation is to continue to refine the nameable distinctions among the creatures. Scientists, among others, would so have it.)

### **The immunological distinction**

Now we are taught that immunology is the science of self–nonself discrimination [Klein, 1982]. This implies that the immune system exists to establish the boundary between the self and all the rest; this

distinction defines the self and thus establishes the self. We could equally well put it the other way: the self–nonself distinction defines and creates the foreign. Either way, self-integrity requires discrimination between self and other.

But let us return to Kadishman and Escher. Granted that there exists an immunological boundary between self and nonself, which of them, self or nonself, is the subject and which of them is the ground?

### **The clonal selection paradigm favors Kadishman**

The clonal selection paradigm [Burnet, 1959] is unequivocal in its answer to the question: The foreign is the subject, and the self is the ground. The job of the immune system is to attack; and the subject of attack is the foreign. In other words, if there exists in the mind of the immune system a picture of the self, then that picture, like Kadishman's tree, is virtual and without substance. (My application of the term *mind* to the immune system is obviously a metaphor for the mind of the immunologist; by immune *substance*, I here refer to the functional repertoires of the antigen receptors, T and B, and the antibodies.)

According to the clonal selection paradigm, the immune system is born with a clean slate; the primal immune system consists of an astronomical number of potential receptors and a set of rules that oversees the realization of the receptor potential by the process of antigen selection. The antigens write on the slate and so organize the system: Receptors that see self-antigens are cut out (deleted or anergized), while receptors that see foreign antigens germinate and flourish. Like Kadishman, the immune system erases from the slate of its repertoire the silhouette of the self while realizing that part of the repertoire that constitutes its image of all the rest, the foreign [Burnet, 1969]. According to clonal selection, only the picture of nonself has substance; the picture of the self must be virtual. The immunological self can exist legitimately only as that which bounds the foreign; in health, the self-antigens are an empty class.



Autoimmune disease must result when for any reason or accident there appear elements of the repertoire that can recognize self [Burnet, 1969]. In other words, autoimmune disease must result whenever a virtual self-antigen becomes an actual self-antigen, that is, when a self-antigen becomes an antigen recognized by clones of lymphocytes.

However, in contradiction of the paradigm, healthy immune systems are replete with T and B cells that recognize self-antigens [Avrameas, 1991; Cohen and Young, 1991]. In other words, the immune picture of the healthy self is substantial, not virtual. Finding itself obliged to climb out on a limb of Kadishman's tree, the clonal selection paradigm falls short.

### **The immunological homunculus favors Escher**

Elsewhere I have developed the concept of the immunological homunculus to face up to the truth of natural autoimmunity and to describe how the immune system really views the self [Cohen, 1989, 1991a; Cohen and Young, 1991]. The term *immunological homunculus* was borrowed from the neurological homunculus; both homunculi constitute physiological images of the self encoded by specific networks of cells, neurons if neurological and lymphocytes if immunological. Happily, many of the ideas implicit in the immunological homunculus metaphor can be exposed to view by Escher's "Circle Limit IV" (Figure 2).

Let us suppose for the sake of self-respect that the angels represent the self and that the devils represent the foreign. Which features of Escher's picture express the immune system's view of self and nonself? What is common to both angels and devils, and what is unique to each class? Let us consider four attributes of the Escher forms: substance, essence, origin, and harmony.

## Substance

Escher forms the angels and the devils out of identical substances, which are merely the paper and ink he uses to draw them. Both images, angel and devil, have the same material reality and are equally recognizable. Where they may differ, in fact where ideally they *must* differ, is in the type of response they arouse. We can recognize them both, but for our own good we respond to each differently.

Likewise does the immune system construct the images of the self and the foreign. Both the self and the foreign antigens are recognized by the same classes of elements: antibodies and T- and B-cell receptors. These elements inscribe images of the antigens within the immune system [Jerne, 1974]. The internal images of self-antigens are as substantial as are the internal images of the foreign antigens. Fortunately, however, like Escher's images of angels and devils, we usually respond differently to self and foreign antigens; we cherish and protect the former, and we attack and reject the latter.

Self-antigens and foreign antigens are made of similar chemicals and are apprehended by the same receptor machinery [Cohen, 1988]. The immunological difference between self and foreign antigens, like the psychological difference between angels and devils, is a matter of interpretation. The observer of Escher's picture will appreciate its meaning only if he can recognize and interpret its forms as those of angels and devils before he actually views the picture. In fact, I imagine that an observer from another culture knowing nothing of angels and devils would not even see the oscillation between subject and ground which is the heart and soul of the work; apprehending the print as a single comprehensive subject, he might imagine it to be one of those exercises in tiling devised by topologists. Likewise, the selfness or foreignness of an antigen depends on the interpretation given it by the immune system. Interpretation requires you to know the essence of what you see; otherwise you will not see it at all, or seeing it, you will not know how to respond. Just as Escher's viewer has to know the essence of angel (or of devil), the immune system has to know the essence of self (or of foreign) to interpret what it sees and then respond in an appropriate manner.

## Essence

The quiddity or “whatness” of an entity is its unique attribute or set of attributes that allows us to identify the entity and define it apart from its surroundings. Kadishman’s tree, made of air, can be discriminated physically from its surround, made of steel; but it cannot be identified as a tree unless the observer has had previous experience with trees and knows what the form of a tree is. Escher’s angels and devils are made physically of the same material and so the difference between them is absolutely dependent on the set of preformed ideas of the observer.

The immunological homunculus is the preformed set of autoimmune B and T cells that the immune system has formed about the dominant self-antigens: basic protein (BP), insulin, heat shock proteins, nucleic acids, various critical enzymes, and so forth [Cohen, 1989, 1991a; Cohen and Young, 1991]. These particular self-antigens are immunologically dominant because of the natural autoimmunity that anticipates them. The autoimmunity to these antigens is benign because the system knows that they are self and has prepared regulatory machinery ahead of time to handle them.

Other elements, in addition to the observer’s foreknowledge, are of the essence in both the immunological homunculus and Escher’s picture. The images of angel and devil are minimalistic; only a few features suffice to signify them. The signature of an angel is a winged humanoid with an angelically serene expression. A devil is a horned humanoid expressing devilish malice and the power to harm: teeth, claws, muscles. Wings are optional for devils. Any more detail is superfluous.

The images of angels and devils are universal in our culture: anyone will recognize the forms with fidelity. The images are public conventions that supersede most individual differences between observers.

Similarity, the immunological homunculus is a minimalistic, conventional picture of the self. A relatively few antigens, the same limited set of dominant antigens mentioned above, comprise the system’s image of the self. Moreover, different individuals, even different species, recognize similar sets of self-antigens: Humans and



mice have natural autoimmunity to BP, to the antigens associated with lupus, to thyroglobulin, and so on. The homunculus image is a shared, public convention.

Note that the immune system image of foreign invaders also may be quite minimalistic and stereotypic. A bacterium with  $10^4$  genes and consequently with at least  $10^4$  potential antigens may be recognized and repulsed by antibodies to one or two of them: enteric bacteria by O antigens, group A streptococci by M protein, and so on. Also note that different individuals (and different species too) may focus their responses on the same limited set of foreign antigens. This is despite an astronomical repertoire potentially able to recognize any organic structure. Escher can depict the essence of an angel without drawing in all the feathers, a devil without copying the hooves or scales. The immune system can interpret and dispose of a microbe with no greater detail in memory than a few epitopes.

## Origins

What is the origin of the uniformity of conventions defining trees, angels, devils, and antigens? Why does the immunological homunculus consist of just that particular set of self antigens? How are the standard forms revealed to the systems that have to recognize and interpret them? How does a system know which entities to see as its subjects and which entities are merely background? One thing is sure, experience is critical.

Would Kadishman's tree be recognized by an Eskimo who never saw a tree? Would Escher's angels be recognized by one who never saw an angel? Except for uncommon revelation, few have ever seen real angels. (Devils would seem to be more abundant.) Nevertheless, all have seen representations of angels and devils, and the idea alone is enough for one to experience the subject-ground conflict and to interpret "Circle Limit IV."

What experience endows the immune system with the capacity to interpret whether an antigen is self or foreign? Obviously this question applies to the antigens for which the repertoire has receptors,

antigens to which the system is not blind. Mammalian immune systems are outfitted with T cells that can recognize self-BP [Schluesener and Wekerle, 1985], but each system tends to behave in a benign way to the BP it sees. The immune system does not attack BP unless the BP comes with adjuvants (signals of infection), and even then the autoimmune encephalomyelitis (EAE) attack is usually self-limited and usually cannot be induced a second time, at least in rats in which the experiment can be done [Ben-Nun and Cohen, 1982]. The immune system knows that BP is self; it knows how to behave differently to foreign antigens.

There are two sources of experience that help an individual immune system distinguish between self and foreign antigens: the evolutionary experience encoded in the germline of the species and the somatic experience of the individual.

The germline has been selected to survive infection by parasites of all kinds, and thus it has evolved elaborate sets of cells and molecules that enable it to identify and respond to infection and inflammation without recourse to recognition of specific antigens. Bacterial products (lipopolysaccharide, cell walls, muramyl dipeptide) and viral products (nucleic acids) are recognized by germline-encoded elements expressed in cells (e.g., macrophages, polymorphonuclear leukocytes, natural killer cells) or in molecules (complement components, acute phase proteins). The presence of these signals of infection triggers cell migrations, the expression of adhesion molecules, the secretion of various cytokines, and so forth. Antigens seen in this complicated context are rejected; they are interpreted functionally as foreign. Antigens seen without all of these adjuvant signals are left alone; they are interpreted functionally as self, even if they have a foreign origin. Foreign antigens encoded by the major histocompatibility complex (MHC) elicit powerful immune responses; but it is not clear why allogeneic MHC signals are so compelling.

Note that there are various functional options for carrying out rejection of the foreign; the effector repertoire includes all kinds of T cells (CD8, CD4-TH1, CD4-TH2, double negatives, double positives,  $\alpha\beta$ ,  $\gamma\delta$ , and so forth) and their cytokines and all kinds of B cells and their antibody isotypes. Also note that there are various

options for tolerating self: nonreactivity (anergy) of different types, active suppression (antigen specific, nonspecific, CD8 mediated, CD4 mediated, anti-idiotypic, antiergotypic), blocking antigen, and blocking antibody. Some of these elements overlap and some compete; indeed, some are thought actually not to exist *in vivo*. What matters here is that the particular mix of regulatory elements is surely the product of somatic experience with self-antigens and with foreign antigens. Somatic experience, guided by germline experience, organizes the internal structure of the immune system so that the arrival of a particular antigen can be properly interpreted and an appropriate response can be carried out. Among the outcomes of this internal organization is the formulation of the immunological homunculus; the focus of special networks on a particular set of self-antigens.

Each self-antigen represented in the homunculus must have a good reason for being there; otherwise we (including mice) would not tend to form similar homunculus sets. The reasons are yet unknown, but are probably different for each antigen. Self-heat shock proteins (hsp) are likely to be important for resisting infection [Cohen, 1991b]. But why is BP in the homunculus? I would guess that the germline, physiological functions of antigens are likely to influence the way the immune system organizes the homunculus.

To complete this brief discussion of origins, we must ask whether human evolution has helped the nervous system formulate its somatic images of trees, angels, and devils. At the level of sensory input, evolution certainly has programmed the brain to apprehend boundaries; the retina is hard-wired to see lines [Young, 1988] and the brain will even invent lines to complete pictures [Ramachandran, 1992]. More than that, the brain may be programmed at the cognitive level to recognize certain entities.

Jung and his followers claim that particular primal images are shared by humankind, as a whole and irrespective of a particular culture [Jung, 1968]. I do not know of a definitive cross-cultural study of the images of trees, angels, and devils, but it is clear that humans are very receptive to such images. I doubt if the forms are encoded in human DNA; the receptivity might be. Note that trees are no less mythic symbols than are angels and devils; there are trees

of life, of knowledge, of creation. Even the logo of the Weizmann Institute is a tree. Perhaps the Eskimo we supposed never to have seen a tree would still recognize Kadishman's tree; the human germline, we are told, did originate in Africa [Cavalli-Sforza, 1991]. To use an outmoded term, humans, like other primates, may have an *instinctive* affinity for trees.

In any case, all systems, including those neurological and those immunological, can recognize and interpret actual somatic experience only if they have a built-in image, however primitive, of what they are looking for. The immune system, not only the brain, needs paradigms.

## Harmony

Escher's "Circle Limit IV" comprises an orb (the world) paved in angels (the good) and in devils (the bad). The observer's retina transmits all the forms simultaneously to the brain for processing. The brain interprets the input in the light of its past experience (germline and somatic) and grasps the picture either as light angels on a dark ground or as dark devils on a light ground. Unless experience dictates a pervasive preference, the brain will alternate between the two possible subjects to the delight of the little man (consciousness) who watches the brain processing Escher's picture.

Behind the picture we may infer a lesson in deportment: To experience the orb fully, there is a time to see the angels and a time to see the devils. Total preoccupation with one or the other produces an incomplete, unbalanced picture. The price for such neglect is esthetic in "Circle Limit IV" and may be disastrous beyond. The devils, like the angels, demand due attention. Harmony in and beyond the picture is proper attention to the right subject at the right time, combined with a suitable response.

Harmony is the concern of the immune system: recognition of the right self-antigens and the right foreign antigens, interpretation of the context of recognition and a suitable response. Immunological disease results more often from a defect in interpretation than from a defect in recognition. Everyone has T cells that recognize BP naturally; rats



develop EAE (and people may develop multiple sclerosis) when BP is interpreted as deserving of an aggressive response [Cohen and Young, 1991]. Likewise, lepromatous leprosy develops, not when *Mycobacterium leprae* is ignored, but when it is interpreted to be deserving of a copious antibody response on the interleukin (IL)-4 pathway [Bloom et al., 1992]. The picture loses harmony when an angel is painted darkly (an aggressive response to self) or when a devil is painted lightly (a tolerant response to foreign). If the angels represent the dominant self-antigens encoded in the homunculus, then an inappropriate response (a dark angel) may culminate in an autoimmune disease targeted precisely to the same self-antigen characteristic of benign natural autoimmunity [Cohen and Young, 1991].

Immunologically dominant, but regulated responses to homunculus self-antigens may produce tolerance to the other self-antigens not represented in the homunculus, the nondominant self-antigens. Tissue inflammation caused by infection or infarction can expose self-antigens in a context demanding an immune response; however, the one or two dominant homunculus self-antigens preempt the response to themselves and automatically protect the many nondominant self-antigens [Gammon et al., 1991] from being attacked. We find that strongly activated T cells have the capacity to inhibit the activation of adjacent T cells (Cohen, in preparation). Thus the first clones to be activated can dominate the entire response and determine its specificity. As the first autoimmune clones are likely to be members of the homunculus set, the response is regulated and the autoimmunity remains benign. "Circle Limit IV" illustrates this principle well: A dominant subject makes other potential subjects disappear into the background. In this way, the immunological homunculus can function as a guardian angel against the dangers of random, unregulated autoimmunity.

## Conclusion

Now that immunology has deciphered the molecular biology of how the immune system gathers antigenic data, it can free itself of the

clonal selection paradigm, a fallen angel [Coutinho et al., 1984; Cohen, 1992a–c], and begin the task of learning how the system interprets its data.

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