Running Title: Digestive Enzyme Secretion and Intuition: Part II

Digestive Enzyme Secretion, Intuition, and the History of Science: Part II

Foundations of Science 14 (2009): 331-349
DOI 10.1007/s10699-009-9163-1

Lois Isenman, Ph.D.
Resident Scholar
Women's Studies Research Center
Brandeis University

Mailstop 079
515 South St
Waltham, Massachusetts 02454

e-mail: lisenman@brandeis.edu
tel: 617-332-2580

ABSTRACT: A companion paper explored the role of intuition in the genesis of an alternative theory for the secretion of pancreatic digestive enzymes, looking through the lens of three philosophers/historians of science. Gerald Holton, the last scholar, proposed that scientific imagination is shaped by a number of thematic presuppositions, which function largely below awareness. They come in pairs of opposites that alternately gain cultural preeminence. The current paper examines three thematic presuppositions inherent to both the generally accepted model for digestive enzyme secretion and most consciousness-centered views of higher-level cognition---discreteness, reduction, and simplicity. Since they often build on each other, together they are referred to as the *simplicity worldview*. Also considered are the three opposite thematic assumptions inherent to both the alternative model for digestive enzyme secretion and intuition-friendly views of higher-level cognition---the continuum, holism, and complexity---together referred to as the *complexity worldview*. The article highlights the potential importance to scientific knowledge of this currently less favored worldview.

Keywords:

Digestive enzyme secretion
History of science
Intuition
Unconscious cognition
Subliminal perception

The companion paper explored the role of intuition in science as viewed through the lens of three eminent historians/philosophers of science, Karl Popper, Thomas Kuhn, and Gerald Holton. The work of the third scholar, (Holton, 1973, 1988) illustrates the importance of largely unconscious thematic presuppositions in tuning scientific imagination and thought. They come in pairs of opposites that tend to fuel scientific controversy and alternately gain preeminence.

As a case study the paper examined the controversy about the nature of digestive enzyme secretion in the pancreas. It focused on the possible influence of intuition in the development of a radically different alternative called the Equilibrium Model, put forth by Stephen Rothman (1976, 2002). This dispute, which may in time prove less settled than is generally assumed, pits at least three of Holton's presuppositional pairs against each other.

These same opposing thematic pairs help illuminate the contemporary debate about the role of high-level intuition---or sophisticated and novel unconscious knowledge---in intellectual activity. One of these antithetical pairs shared by both controversies is discreteness vs. the continuum. The second is reduction vs. holism and the third simplicity vs. complexity. The three are not completely independent of each other. Certain choices tend to go together and by building on each other can come to characterize a worldview.

I will discuss two of these partially overlapping thematic pairs as they relate first to digestive enzyme secretion and then to novel unconscious cognition, pointing out some parallels between them. I will then consider the third pair more generally as opposing worldviews. One of my goals is to highlight the potential importance of the less favored worldview shared by intuition-friendly perspectives on cognition and the Equilibrium Model for digestive enzyme secretion. Another is to deepen understanding of the complex and elusive mental capacity we call intuition, and a third is to take a new look at the Equilibrium Model.

1. DISCRETENESS VS. THE CONTINUUM

1.1 Digestive Enzyme Secretion---Discreteness: The established model for digestive enzyme secretion (Palade et al., 1962, Palade, 1975) emphasizes discreteness, or separateness, at a number of levels. Newly synthesized protein is always isolated from the cytosol, or watery interior of the cell, in membrane-enclosed vesicles. It moves through a set of vesicular compartments that extend from where it is made near the blood-facing side of the cell to where it is secreted at the opposite, duct-facing side of the cell (see companion paper Figure 2, Isenman, 2009). When signaled by nervous and hormone messages that food is on its way, the storage or zymogen granules, the final vesicles, greatly increase their rate of fusion with the duct-facing membrane, enhancing secretion into the duct.

The model grounds digestive enzyme secretion in what is sequential and fits the clear logic of purpose. The exocrine pancreas functions as an isolated module whose protein output is integrated with the rest of the organism by only this one event, the fusion of the zymogen granule with the duct membrane. Formed and accepted to a considerable extent around visual evidence, it envisions digestive enzyme secretion as a fixed set of discrete steps dedicated to delivering protein to the gut.

More recently (stimulated in part by observations of Rothman and Isenman, 1974) the traditional model appended a rapid secretion pathway in which newly secreted enzyme is carried directly to the duct by small vesicles. It is seen as a discrete, or non-interactive, parallel pathway responsible only for constitutive or basal secretion---secretion in the absence of stimulation (Kelly, 1985). Enzymes from the two pools mix only after they have been secreted from the cell.

1.2 Digestive Enzyme Secretion---The Continuum: The Equilibrium Model for digestive enzyme secretion offers a continuous rather than discrete perspective at a number of different levels (Rothman, 1967, 1975, 1980, 2002). Digestive enzymes can be free in the intracellular medium and move individually molecule by molecule across membranes---in contrast to the discrete, or 'quantal', and unidirectional vesicle transport and secretion indicated by the generally accepted model. After entering the intracellular medium, newly synthesized enzyme may cross any of a number of membranes that are bidirectionally permeable to them (Figure 3, Isenman, 2009). These include the storage granule membrane (Liebow and Rothman 1976**;** Gonz and Rothman, 1995), the usual

secretory membrane into the duct (Liebow and Rothman, 1975; Isenman and Rothman, 1979a) and the blood- or extracellular fluid-facing surface, the 'wrong' side of the cell (Liebow and Rothman, 1975; Isenman and Rothman, 1977, 1979b). Bidirectional, concentration-dependent fluxes of each enzyme species across these membranes make the compartments defined by them to a greater or lesser extent continuous with each other.

The rate of movement of each digestive enzyme is governed by its relative concentration in the various compartments and by its permeability in each direction across the different membranes. Some of the newly synthesized enzyme enters the slowly turning-over storage pool, while some remains in the cytosol and is rapidly secreted. The two pools are interactive and both contribute to basal secretion (Rothman and Isenman, 1974).

The permeability of the membranes depends on a variety of hormonal as well as nervous factors. Certain ones appear to increase permeability only to specific digestive enzymes (Rothman, 1967) and/or only across certain membranes (Rothman and Isenman, 1974), and perhaps sometimes only in one direction (Rothman and Isenman, 1974), which can account for some of the anomalous findings from the Rothman laboratory. Upon stimulation, enzyme release from the storage granule occurs first into the soluble pool of enzyme in the cytosol, or intercellular medium, which functions as a final common pathway for secretion.

Reversible concentration-dependent fluxes equilibrate enzymes across the blood-facing as well as the duct-facing limiting membrane of the cell. Instead of an isolated module with a single one-way pathway delivering digestive enzyme into the gut as envisioned by the generally accepted model, the exocrine pancreas is integrated with the rest of the organism by two different bidirectional pathways. In addition to digesting food in the gut, its products may participate in a variety of other physiological processes within the organism.

1.3 Cognition---Discreteness: Models of higher-level cognition focused heavily on consciousness tend to emphasize discreteness rather than the continuum. They understand the hidden machinery of mind to be made of many discrete parallel modules whose purpose is primarily to serve consciousness (Baars, 1988; Edelman and Tononi, 2000; Dehaene et al., 2003). The modules interact minimally and report independently to the conscious mind. Consciousness-focused theories view the unconscious aspects of mind as having only a circumscribed role in the kind of novel and sophisticated intellectual activity that characterizes many intuitions. Like the traditional model for digestive enzyme secretion, they tend to stress structural and/or functional architecture, top-down control, and limiting assumptions about purpose.

The influential and generative Global Workspace Model proposed by Baars (1988, 1997, 1999, 2002), which I will use as an example, provides a sophisticated version of a consciousness-focused model. Consciousness, along with working memory (a very small and very short-term memory buffer), coordinates the activity of the various independent

modules of the cognitive system. This, *the workspace,* provides centralized distribution of information to the different modules. A limited capacity distributor, it broadcasts only a single discrete and consistent message at a time, which is chosen by competition between potential sensory inputs, internal images, and ideas. Its serial frames are governed by goals that are conscious, or previously so but now represented in awareness by images of intended states. They are also governed by certain previously conscious contents that currently function as unconscious context elements.

The workspace also receives relevant messages back from various unconscious modules, which can gain entrance. It functions like a community blackboard that allows the independent modules or processors to interact once they successfully compete for access. (Each word, for example, represents a separate processor.)

Access to the workspace confers the subjective experience of consciousness---its phenomenology. At the same time it also makes information global accessibility---availability to all processors---which in turn allows it to be used for judgment, control, planning, and report (Block, 1990). Recently the global workspace has been equated with reverberating activity in a parietal-frontal network linked by long-distance loops to sensory areas in the back of the brain (Dehaene et al., 2003).

Information from different modules can combine only after it has become conscious by being globally broadcast---e.g. entering the workspace. Novel binding between different

sensory aspects of perception occurs in the workspace. Likewise novel mental connections are made in consciousness, although once made they can become automatic.

Workspace Theory, just like the traditional model for digestive enzyme secretion, proposes two *discrete* cognitive pools that combine only in awareness. One is conscious and the source of novel connections. The other is unconscious and consists of automatic, habitual information, and also other information stored in memory.

The activation of appropriate information from memory and transfer to the conscious mind occurs when cued by material in the workspace. Memory transfer is a discrete process, since the workspace is limited by working memory with its restricted processing capacity (Miller, 1956). However the memory module (like zymogen granules) can bundle or chunk numerous items previously connected at a conscious level.

1.3.1 Using intuition as a probe---experimental evidence: An important limitation of Workspace Theory is that it gives short shrift to the extended intermediate region between the conscious and unconscious mind, where so much of intuition occurs. A large number of observations now suggest that information that is not available for conscious report can nonetheless undergo substantial cognitive processing and significantly influence subsequent cognition. For example, early work on intuition using remote associations demonstrated that subjects can recognize that three words---such as, playing, credit, report---have a common associate at better than chance level even when they can not determine what it is (Bowers et al., 1990; Bolte and Goschke, 2005).

Moreover unreportable common associates can prime, influence the timing or content of, subsequent cognitive activity (Jung-Beeman and Bowden, 2000). Studies also demonstrate that subjects can determine if fragmented, unrecognizable pictures---indistinct gestalts---nonetheless represent coherent objects as opposed to scrambled objects or meaningless designs (Bowers et al., 1990; Volz and von Cramon, 2006).

Neuroimaging studies with invisible stimuli also suggest a blurring of the boundary between conscious and unconscious mind. Experiments in which stimuli are prevented from coming to awareness, using a variety of different techniques, suggest considerable depth of processing nonetheless occurs. Masked stimuli have been shown to undergo semantic activation, or meaning extraction, which can influence subsequent cognition (Dehaene et al., 1998; Naccache and Dehaene, 2001; Nakamura et al., 2005; Gaillard et al., 2006). Cross-sensory modal semantic activation (auditory/visual) of subliminally presented numbers has also been shown (Nakamura et al., 2006).

A recent report indicates that subliminal stimuli can generate widespread stimulation of frontal, or executive, regions of the brain (Lau and Passingham, 2006). Moreover at least some subliminal stimuli are able to exert negative control over conscious function (van Gaal, et al., 2008; Schleghecken et al., 2009) or initiate one of two alternate previously set tasks that evoke activity in different regions of the brain---i.e. determine if a word refers to a concrete object, or if it is bi-syllabic (Lau and Passingham, 2007). Executive control functions such as these are considered the exclusive property of consciousness in Workspace Theory, and indeed in most theories of mind function.

Such reports resonate with implicit learning studies in which subjects abstract from conscious stimuli without awareness of doing so complex unreportable relationships that influence subsequent behavior. These studies suggest there is often a large intermediate region between material being conscious and unconscious (Cleeremans and Jiménez, 2002; Destrebecqz & Cleeremans, 2003; Dienes and Scott, 2005; Norman et al., 2006; Norman et al., 2007; Fu et al., 2008.) This appears true for both the content itself and for evaluative, or metacognitive, knowledge about this content. Several implicit learning experiments also suggest that the executive function might be able to act flexibly on information that cannot be reported (Norman et al., 2006, 2007; Fu, et al., 2008).

Sometimes some of the information from the intermediate range is available in the fringe of consciousness.[1] The fringe region is more readily experienced by some than others (Crawley et al., 2002; Norman et al., 2006; Fleck et al., 2008). It can also greatly expand (Isenman, 1997).

Taken together, the evidence suggests that neither the widespread availability of information in the brain nor the experience of consciousness is necessarily the discrete event proposed by Workspace Theory. Instead the two appear to be continuous, or at least graded, as well as separable functions. This is consistent with the premise inherent

[1] Global Workspace Theory acknowledges that both *fringe feelings*---evaluative feelings such as feelings of rightness---and *fringe intuitions* have a role in cognition. *Fringe feelings,* according to the model, are found largely in working memory and summarize previously *conscious* contents. In contrast *fringe intuitions*, including fringe images, represent coalitions of processes only weakly gaining access to the workspace. This seems to conflict with the notion that access to the workspace is an all or none phenomena (Dehaene et al., 2003). Also see other potential problems mentioned in section 1.3.2.

to sophisticated intuition that the availability and complex novel processing of information can precede its conscious awareness.

1.3.2. *Using intuition as a probe---experiential evidence:* Workspace Theory does not exclude the existence of sophisticated intuition, but can only account for it by trying to explain it away. According to Baars, creative unconscious problem-solving can be called into action by conscious broadcasting of a problem leading the solution to just pop into mind (Baars, 1988 pp. 236-237).[2] He sees this as an example of what he calls the conscious-unconscious-conscious triad. But unlike problem-solving initiated by conscious concerns, intuitions need not be initiated by previously conscious content. Even when they are, they may take us far beyond any question the conscious mind might ask. In either case, they would seem to reflect a deeper intentionality than consciously instigated problem-solving.

Another problem with the Workspace treatment of intuition is that sometimes the complex novel strands of information that go into an intuition are not available to consciousness until after the final insight comes to awareness and often not even then. We sometimes find ourselves wondering, "How in the world do I know that?" The workspace model does allow that new connections may occur very quickly. Baars offers the ad hoc suggestion that complex intuitions depend on fleeting instants of

[2] Baars approaches sophisticated intuition in part by trying to reduce it to insight, which he claims Workspace Theory can explain. Broadcasting the problem recruits the relevant processors to the workspace. The conscious insight then represents the forging of the coalition. However this would be a violation of the constraints of the theory if the coalition includes novel information not previously available to awareness, since this requires the making of novel connections below awareness. (He proposes instead that such novel connections are initially made consciously and then forgotten.)

consciousness that are not remembered and build on each other (1988, pp. 68-70, 236-238).

Another closely related issue is that the multiple individual strands of information that often go into an intuition may only have value in novel and complexly intertwined relationship to each other. How the strands that must combine could do so---especially if they are not already givens in the situation---is unclear. The various processors that go into the solution would have to compete independently for access to the workspace---but on what basis? Intuition would have to depend on potential candidate processors gaining access individually in a 'trial and error' fashion and then forming the complex collaborations required to address the problem or need.

A final problem I will mention in this regard is the occasional proclivity of sophisticated intuition to encode itself in fanciful images, such as Einstein's adolescent image of riding on a light beam. Einstein himself credits the image with containing the germ of the Special Theory of Relativity, which took him the next 10 years to develop. Sometimes these imaginative images make little or no sense in the moment and only reveal their meaning over time. I will provide a personal example of this in a subsequent section. Slow-release images that encode complex intuitions suggest that the cognitive accessibility of unconscious information required for sophisticated knowledge can considerably precede its appearance in awareness as insight. Like some of the experimental work mentioned earlier, they provide a substantial challenge to Workspace Theory.

1.4 Cognition---The Continuum: Intuition-friendly views of cognition, rather than postulating a series of discrete unconscious modules or processors that report independently to the conscious mind, stress the continuity between various facets of the unconscious mind.[3] This allows sensory binding as well as novel connection-making to occur below awareness. More and more evidence suggests the possibility of links between sensory modules---direct and indirect, innate and acquired---made outside of consciousness**.** (For a review, see Driver and Noesselt, 2008; see Budinger and Heil, 2006 for a neuroanatomical study.)[4]

In a similar vein, intuition-friendly models of cognition view the unconscious mind as continuous with the conscious mind. They emphasize the parallel interconnected, or associative, nature of much of cognitive processing in which multiple simultaneous strands of information interact (for example, see McClelland et al., 1986; Elman et al., 1996; Cleeremans and Jiménez, 2002). Bidirectional connections (or *reentrant connections* as they are often called in the brain) interconnecting every level allows all information in the system---i.e. new information, both conscious and unconscious, and all information encoded in memory---to mix in an associative or parallel interactive way prior to awareness.[5] Thus novel connections are made below awareness instead of, or in

[3] Some of the material about intuition-friendly models of cognition is an abbreviated form of material that appears in Isenman (forthcoming).
[4] For potentially related work on *synesthesia*, or mixing of the senses, see Mulvenna and Walsh (2006); Sagiv et al. (2006)
[5] In the Connectionist Model described in Cleeremans and Jiménez (2002) and Cleeremans (2008), all experience results in learning---or changes in the strength of connections between neurons in networks (see note 6). Representations, in contrast, are patterns of activations across networks and are "constantly causally efficacious." Stimulus intensity is an important determinant of whether or not these patterns of

addition to, in consciousness. Just as digestive enzyme secretion in the Equilibrium Model draws from the cytosolic pool that interconnects all digestive enzyme and serves as a final common secretory pathway, consciousness may draw from an unconscious pool that interconnects all information in the system and serves as a final common cognitive pathway.

Information that is weakly encoded can influence information that makes it to awareness---nudging it in one direction or another (Cleeremans and Jiménez, 2002). Even a very small change may sometimes provide the crucial ingredient required to crystallize an intuition.[6] This depends heavily on the emotional/motivational system, which functions to a large extent below awareness.

Moreover individual pieces of knowledge too weakly encoded to come to consciousness on their own, may join forces and appear on the fringe of awareness as a vague intuition---motivated by purposes that are not necessarily available to consciousness. Weakly encoded information can also join forces with other strongly encoded information that is nonetheless implicit in the sense of unattended. This might occur because top-down conscious attention is otherwise occupied (Dehaene et al., 2006), a representation cannot integrate with other conscious content because of inconsistency (Dienes and Perner, 2003; Edelman and Tononi, 2000), or because it is an unattended higher-level meaning of contents available to awareness (Jackendoff, 1987).

---

activation become conscious, although it is one of a number of interactive parameters. For simplicity I am combining most of these parameters together under the notion of strength of encoding.

[6] Gaillard et al. (2007) have confirmed that even a single presentation of a subliminal stimulus can lead to durable changes in neural activity.

Using one or a combination of potential mechanisms, sophisticated concepts can develop under the radar of consciousness---sometimes in an instant and sometimes over a period of time. The process is guided by evaluative, or metacognitive, signals that may appear in consciousness or its fringe, but also seem to function below awareness (Bowers, 1990; Mangan, 1993, 2001; Isenman, 1997; Metcalfe, 2000; Dienes and Scott, 2005; Norman et al., 2006). It is responsive to emotional and motivational influences that are not necessarily conscious and may never have been. This continuous perspective emphasizing the potential governing role of novel, high-level unconscious connections in breakthrough thought contrasts with perspectives that view entrance to consciousness necessary for widely distributing as well as organizing unconscious resources in order to generate sophisticated and novel intellectual activity.

2. REDUCTIONISM VS. HOLISM

Reductionism vs. holism is another pair of contrasting preconceptions echoed both by the digestive enzyme secretion controversy and the controversy over the potential sophistication of unconscious cognition. Reductionism as I am using it here implies that a system can be understood by examining its principal part or parts. Holism, in contrast, implies that mutually interconnected parts can have novel and unpredictable properties.

2.1 Digestive Enzyme Secretion---Reductionism: The traditional model for protein secretion originated in studies that broke pancreatic cells into discrete structural

components at various times after adding radiolabel and examined each component individually under the electron microscope. The researchers then constructed a narrative sequence from the visual evidence and the goal of digestive enzyme secretion---getting the enzyme to the gut. This strongly reductive enterprise was guided by paradigmatic assumptions that determined the conditions used and played a significant role in interpreting the data (see Rothman, 2002 for a detailed discussion).

Other possible interpretations of the data were dismissed as inconsistent with the assumption of a single unitary pathway for pancreatic digestive enzyme secretion (for example, see Caro and Palade, 1964; Isenman, 1980, pp. 11-20), an assumption now known to be wrong. When a new pool was added, again it was characterized in a reductive rather than dynamic way; it provides only basal secretion. Supporting and reinforcing all this was a historical notion we now also known to be mistaken---that basic chemistry and physics do not allow proteins to cross membranes. A large number of different mechanisms have now been described that allow proteins to cross membranes (for example, see Gumbart and Schulten, 2006; Lee at. al., 2006; Wu et.al., 2006; Joliet and Prochianz, 2005; see Wickner and Schekman 2005 for a review and Isenman et al. 1995 for a more general review of mechanisms).

2.2 Digestive Enzyme Secretion---Holism: The equilibrium model came into being to explain the variable response patterns---the real-world messiness---the standard model could not easily account for. Under different conditions, digestive enzyme secreting cells respond differently. This messiness remains hidden from those focused exclusively on

understanding the principal parts with respect to the system's most apparent purpose and their reductive tools.

Instead of the structural evidence that largely underlies the traditional model, the equilibrium model is based on kinetic evidence and highlights dynamic processes below the level of resolution of the electron microscope and other imaging tools. The intersecting fluxes it reveals across the various pancreatic membranes automatically integrate the movement of digestive enzyme throughout the cell. They assure that the transport system can respond nimbly to hormonal and perhaps nervous messages signaling different needs in the gut. The flexibility inherent in the model also allows it to account for contingencies not yet studied and perhaps not yet observed.

My dissertation work, for example, in part showed an equilibrating flux of digestive enzyme out of *the wrong side of the cell*—--the extracellular or blood-facing side---where zymogen granules are not found (Isenman and Rothman, 1977; Isenman et al., 1999). The steady-state concentration of the enzyme I followed is low in the extracellular medium compared to the duct, but since the volume of the blood and the extracellular fluid is relatively large, the amount of secretion out of the 'wrong side' of the cell is significant. The function this enzyme might serve is unknown. Yet low concentrations of pancreatic digestive enzyme are a normal constituent of blood, and increased levels are often diagnostic of disease.

In contrast to the traditional view that envisions digestive enzyme secretion as a closed system with a set purpose, the Equilibrium Model views it as an open system, readily amenable to short- as well as long-term adaptation. Holistic in conception, it stresses the underlying processes that *mutually* interconnect different elements. Digestive enzyme movement is integrated within the cell by the complex interrelationship of the different fluxes across its various permeable membranes, which allows it to function as a whole. It is also well integrated into a larger interconnected whole---the rest of the human organism. Depending on internal state and external conditions, the system can take many different configurations. Thus it can form many different potential wholes and have many different potential functions.

2.3 Cognition---Reductionism: Like reductionism, conscious cognition excels at breaking things down into their component parts, isolating the apparently important ones, and comprehending each in as much detail as possible. The reductive program attempts to abstract or separate the 'players' as much as possible from their context. This allows it to understand the functioning of the principal components or structures apart from their real world messiness. Mathematics, perhaps the most sophisticated cognitive activity, completely abstracts symbols and thought from real world contexts. It de-contextualizes thought.

The Global Workspace Model embodies the reductive approach. It affirms consciousness as the synthesizing agent of the mind as well as the goal of all attentional resources---as the principal player in higher-level cognition. What is called the *contrastive approach* is

then used to characterize the difference between the neural states associated with a certain object when it is conscious and when the same object is in some way prevented from becoming conscious. This approach may prove less straightforward than it initially seemed.

Most reportable stimuli do seem to correlate with widespread activity reverberating in the frontal-parietal/sensory circuits Workspace Theory now associates with global broadcasting. Yet even if this activity is necessary for consciousness, it may not be sufficient. Observations by Lau and Passingham (2006, 2007) suggest it instead represents the increased performance/information processing load that generally accompanies but is separable from consciousness (also see Freeman, 1998). A large number of studies mentioned before show that unreportable stimuli can undergo significant higher-level processing and sometimes flexible top-down control---once the gold standard for consciousness (also see below).

2.3.1 Attention: Workspace Theory further enshrines the reductive urge by limiting consciousness to what is center stage under the spotlight of attention.[7] Attention is not seen as identical to consciousness. Rather it directs the beam of consciousness.

[7] The model of Edelman and Tononi (2000) understands consciousness in a more flexible manner. They view it as the synchronous firing of an ever-changing *dynamic core* formed from reentrant corticocortico and corticothalamic connections. This core, which is internally integrated, as well as differentiated from all other states, is backed by the arousal or value system and served by encapsulated automatic routines. The potential expansiveness of the dynamic core could help account for the sense of general epistemic expansion that sometimes accompanies/characterizes higher-level intuition.

A number of observations of potential relevance to intuition suggest that attention has a much more global role in the ecology of mind than orienting the beam of consciousness**.** For example, conscious attention can influence the depth of processing of unreportable stimuli (Kanai et al., 2006). Also invisible stimuli that register on the primary visual cortex under low attentional load may not under high attentional load (Bahrami et al., 2007). Moreover the potential value of an invisible stimulus is a critical variable in the *unconscious attention* it receives. This in turn likely helps determine whether it is recorded by the primary visual cortex (see Freeman, 1998), its depth of processing, and influence on subsequent conscious mental activity. One study, for example, shows that images of naked people that remain invisible can attract (or even repel) the subsequent placement of conscious attention, based on erotic preference (Jiang et al., 2006).

As intimated above, attention, emotion, and motivation are all entwined and can function below awareness. Working together they can lead to novel connection-making outside of consciousness. A recent report shows that *subliminal clues* arbitrarily associated with monetary gain or loss can lead to instrumental conditioning (Pessiglione et al., 2008), which should not happen according to Workspace Theory. A newer study even shows that *subliminal perceptual discrimination* is enhanced in response to drops of water delivered through a tube to thirsty subjects who are unaware of performing a learning task (Steitz et al., 2009). Moreover the work of Damasio, Bechara, and colleagues (reviewed in Damasio 1994) demonstrates that subliminal, anticipatory, body-based emotional signals grounded in past experience of punishment can speed learning *below awareness* of complex novel patterns that make certain choices risky. This hidden

emotion/knowledge directs decision-making advantageously from below awareness and also speeds the eventual appearance of the pattern in awareness.

2.3.2 *Conscious inattention, learning, and creativity:* The workspace model perspective is open to question from a related perspective. Hoping to sidestep the controversial problem of determining when there is *no* conscious contribution to human learning, Baars proposes instead that the more novel and difficult the material to be learned, the more conscious attention is required.

> The more novelty we must absorb, the more conscious experience we need. The evidence for this claim seems to be widespread and noncontroversial: The more words that need to be memorized, the longer we must pay attention. The more difficult and novel some material is, the more time we must spend being conscious of all its details and implications….(Baars, 1988, p. 218)

Elsewhere he asserts that skill with language depends on paying *conscious* attention to sounds and meanings (Baars, 1997, p. 17). Yet as indicated above, information that does not come to awareness may nevertheless undergo great depth of processing.

Although e*xplicit* learning of novel, difficult material may correlate with the amount of conscious attention paid to it, the opposite tends to be true with *implicit* learning. As early studies with artificial grammar learning revealed (reviewed in Reber, 1993), the more difficult the underlying pattern, the more implicit learning occurs if subjects *don't* try to capture the pattern at a conscious level. A recent sequence learning study titled, "On the Benefits of Not Trying…" documented that looking for a difficult, noisy pattern

at an explicit level interfered with the progressive changes in brain activity that occurred with implicit learning of the same pattern (Fletcher et al., 2005). In contrast looking for an easier pattern did not inhibit its implicit learning.

Another study extended this principle to the realm of practical decision-making (Dijksterhuis et al., 2006). It suggests that decisions requiring the integration of a large array of factors---such as which car or apartment satisfies multiple requirements---are better after four minutes of distraction than four minutes considering the problem consciously (but see Acker, 2008). With many fewer requirements this advantage is not evident.

A recent study using the remote association triad test described earlier suggests that conscious *inattention* can also enhance the ability to make the kinds of creative or remote connections below awareness (Zhong et al., 2008) so important to intuition. With particularly difficult triads, *the unconscious accessibility* of the solution---measured by its priming ability---was stronger for subjects who spent four minutes performing a demanding distracting task than for subjects who spent four minutes consciously looking for the answer. (Both groups came up with same number of right answers.) A third group of subjects were told they would go to a new task after the four minutes of distraction, instead of going back to the problem. They had less unconscious

accessibility to the solution than the other two groups, supporting a role for non-focal and/or unconscious attention in unconscious accessibility.[8]

Other reports also suggest that conscious inattention to a task can lead to the activation of more remote associations. When asked to name places beginning with a given letter, subjects who were distracted came up with more small towns and villages than those attending consciously to the problem. In contrast, when asked to name cities, this difference did not appear or was reversed. Moreover when asked to come up with new names for products, subjects who were distracted generated names more unlike the examples than subjects who thought about the task for the same amount of time (Dijksterhuis and Meurs, 2006).

These observations, along with many others I have noted, are more readily explained by the existence of two parallel modes or pathway for forging *novel* connections. In one they appear to be made consciously and in the other they are forged largely below awareness by associative or parallel interactive processing.

At the same time these studies suggest we have two strategies or modes of conscious attention for meeting underlying goals, which likely correspond to two sides of a continuum. They selectively enhance alternative pathways for making novel connections. In one conscious attention is highly focused on the problem and appears to

[8] With only moderately difficult problems, in contrast, both distraction and conscious attention to the solution led to similar levels of unconscious accessibility. In this case, however, those who attended to the problem came up with more right answers.

function as a spotlight, as described by Baars. In the other---the one generally associated with intuition---it is more diffuse, or otherwise occupied. As a consequence it enhances novel goal-related processing outside of awareness. The results may influence cognition from below awareness, appear as an insight, or presumably become part of a larger intuition. The alternate strategy is more effective with *certain kinds* of difficult and/or messy patterns or problem than the limited-capacity spotlight strategy.

The two pathways for novel connection-making---at least as they relate to creative (verbal) connections---may well correlate with processing approaches dominated by the left and right hemisphere. Using priming, Jung-Beeman and Bowden (2000) assessed over 15 seconds the unconscious accessibility in each hemisphere of the solution to remote association triads too difficult to solve. Both hemispheres initially activated weaker, more remote associations. However the left quickly limited its focus to the most prominent associations. Neuroimaging studies also show that insight in the remote association test is characterized by several signals unique to the right hemisphere (Jung-Beeman et al., 2004).

2.4 Holism---Cognition: In contrast to conscious intelligence, unconscious intelligence can record many different elements at once at an implicit level, since it does not have the same memory limitations. It can also maintain many more different representations activated as long as they are at least remotely related to the topic of interest (or, putatively, when associated with the right hemisphere, which will be largely my focus in

this section). It can therefore track many different contingencies over long periods of times, even if these are not yet of interest to the conscious mind.

Instead of abstracting the object of study from its real world context and reducing it to its parts or principal component(s), unconscious intelligence excels at the opposite. It can comprehend a system it is interested in by following the patterns it makes in many, if not all, the myriad different contexts or conditions it appears in over time. Guided by selective attention that functions at many different levels below awareness, unconscious intelligence builds from its matrix of temporal and spatial associations, or parallel interactive connections, subtle understanding of objects of potential adaptive importance. This messiness, the underbelly of wholeness, includes complex patterns that the more reductive aspects of intelligence cannot detect. The unconscious mind uses this subtle knowledge to interest the conscious mind in the next level of the mystery.

Models of intelligence that allow bidirectional connections between every level (for example connectionists models such as McClelland et al., 1986; Maia and Cleeremans, 2006 or dynamical models such as Freeman, 1998; Spivey, 2007) allow the whole brain potentially to influence each moment of experience. One of the things this means is that intimations of future intuitions can sometimes be found in current awareness or in its fringe. This is especially likely when conscious attention is diffuse or apparently undirected.[9] Some of the purposes and triggers that drive novel sophisticated cognition

[9] Waking states of decreased attention to the external world may correspond to enhanced internal intentionality. The brain's default or 'resting' network generally becomes more active when external task demands decrease and conversely its executive network becomes more active when they increase (Mason et al., 2007). Yet studies measuring brain activity both before and as subjects solve problems with insight

may not (or not yet) be available to awareness, just as some of the purposes and triggers of pancreatic digestive enzyme secretion may not yet be clear.

According to intuition-friendly views of cognition, all meaning-making may occur largely below awareness. For example, in Walter Freeman's dynamical model of cognition (1998), different events compete, not for consciousness, but rather for unconscious perception, which marks their meaning, or importance, with respect to underlying goals and needs. These meaning are highly constrained by past experience yet also very sensitive to novelty.[10] As the next section illustrates, unconscious meaning-making can sometimes be much richer than the conscious mind can immediately comprehend.

2.4.1 An illustration of the cognitive potential of the unconscious mind: Before considering the last pair of thematic presuppositions, I will present a personal observation followed by an illustration of the cognitive potential of unconscious cognition. I felt drawn to the Equilibrium Model, as I tried to verbalize from time to time as a graduate student, because the traditional view seems to reflect the top-down way we humans would go about designing a transportation/distribution system---for proteins or for

---

as opposed to conscious thought demonstrate a co-operation between default and executive regions (Jung-Beeman et al., 2004; Kounios et al., 2006; Christoff et al., 2009). Intriguing recent observations moreover suggest that 'mind wandering,' during an external attention-requiring task leads to enhanced activity in both the brain's default network and its executive network (Christoff et al., 2009). The effect is particularly pronounced when subjects are not even aware that their mind has wandered.

[10] In Freeman's model, the sensory modules are largely isolated from each other. However in contrast to Workspace Theory, competition occurs at a number of different levels below awareness. Attentional/motivational factors, generated by the limbic, or value system, and carried in part by anticipatory signals, unify the different modules and different levels in line with a series of nested goals. Consciousness provides an additional layer of integration and constraint on top of unconscious meaning-making.

anything else. I sensed then and still feel we have something to learn from our cells. Even though the dizzying array of intersecting fluxes inherent to the Equilibrium Model and everything that remained unknown about it sometimes frustrated my conscious mind, at a more profound level, this pregnant complexity and all that remained unknown were the very things that drew me. I now recognize that it is much more compatible with my cognitive style, which is heavily weighted towards intuition, than the established model because it inherently leads beyond itself into mysterious terrain.

Intuitions, as I mentioned before, sometimes arrive in awareness as fanciful images that encode multiple deeper insights, which only emerge into consciousness only over time. A noteworthy experience of this occurred to me in 1994 when I had just started thinking about intuition (Isenman, 1997). At lunch one day a friend asked me for a definition of intuition. Nothing came to mind when I searched consciously for an answer, so instinctively I quieted my conscious mind and turned my attention inward perhaps as completely as I ever have. After a bit the phrase a "blink of the eye" popped into mind (Isenman, 1997; Gladwell, 2005). I reported this silly-sounding answer to my friend, but then checked inside again. This time a signal going down and then up on an oscilloscope popped into mind, accompanied by a feeling of increasing and then decreasing tension in my body.

The additional images made no sense either, yet some fringe aspect of my mind recognized that all three shared a similar pattern of motion. This vouched for their consistency and thus validated them, even as my usual consciousness was flabbergasted

at this certainty. I told my friend that my answer to her question was indeed "a blink of the eye"

Only several months later did I *begin* to unpack this unusual experience. Among other things, I glimpsed that the image of a signal going down and then up on an oscilloscope encoded my first real experiment as a biologist---which in turn suggested the analogy I have been exploring between my graduate work on digestive enzyme secretion and my then new interest in intuition. Since that time this complex encounter with intuition, so far outside my normal way of thinking and experiencing, has continued to reveal layer upon layer of understanding.

The experience illustrates that very sophisticated intuition can occur, to a greater or lesser extent, without conscious insight---in the sense of conscious understanding. In looking inside the way I did, I cleared my awareness and allowed my unconscious mind---with its ability to encode tacit knowledge in imaginative images---free reign.[11] The experience also illustrates how subtle metacognitive signals in the fringe of awareness can report on the validity of knowledge the conscious mind can at best only dimly grasp. In addition, the three widely divergent images interconnected by a common spatial/activity pattern that popped into mind help highlight the underlying holism of the meaning-making mind.

[11] Like distraction or diffuse attention, consciously clearing the workspace allows the unconscious mind to deal with pressing problems that are better served by unconscious intelligence unhindered by the approach of the conscious mind and/or it allows better access to the results of unconscious information processing. See Stewart (2006) for a discussion about the "unloaded" workspace and intuition.

3. SIMPLICITY VS. COMPLEXITY

The goal of those who approach phenomena through the lens of discreteness and reduction is often elegant simplicity and/or control.[12] They tend to envision a static well-structured world, like the clockwork universe envisioned by Newton. In contrast, the goal of those who view phenomena through the lens of continuity and holism is more likely to be the elucidation of the complex dynamics that account for the behavior of globally interconnected, self-organizing, and potentially evolving systems. They tend to favor observations highlighting the *embeddedness* of an object or organism in its environment and the complex interwoven nature of the whole. Instead of a well-organized world in which all novel connections are made consciously and only one *unambiguous* message is broadcast at a time, they see a world full of hidden possibility, undergoing constant adaptation, and characterized by unexpected transformation in response to small changes.

Western scientific culture in the past has largely been associated with the discreteness/reductive/simplicity worldview. For short I will call this perspective *the simplicity view*. The opposite worldview, the continuum/holism/complexity---or *the complexity worldview* for short---has also played a role, yet relatively speaking a minor one. The fixed one-way pathway for digestive enzymes secretion dedicated to getting

[12] In contrast to the use of *simplicity* in the companion paper as a heuristic for deciding between competing theories, here it refers to systems whose organizational structure remains constant over time---as opposed to complex or dynamical systems whose organizational structure can change.

these molecules to the gut envisioned by the traditional model has had strong appeal. Likewise views that limit sophisticated and novel intelligence to consciousness, our apparent window on the world, also have had strong appeal.

In contrast the more complex Equilibrium Model in which digestive enzyme seems to move in every different direction at once has had much less appeal. Similarly the view of cognition in which the unconscious mind can produce novel and sophisticated cognition in response to multiple simultaneous purposes, some of which may never have been conscious, has had limited appeal. The difficulty of characterizing these highly interconnected non-linear systems in which everything tends to affect everything else is incompatible with ordinary notions of a well-ordered, clearly messaged world. In the words of Gertrude Stein, "there is no there there."

What these systems lack in simplicity and clearly discernible purposefulness they make up for in their adaptability. The brain/mind is more and more seen as a complex adaptive system (for example, see Freeman, 1998; Spivey, 2007; Edelman and Tononi 2000; Maia and Cleeremans, 2006). Researcher Walter Freeman (1991) analogizes the complexity of the mind/brain's ordinary perceptual functioning to the apparent bedlam of a large train station at rush hour. People seem to be moving in every which way. However when a train is announced, there is a clearly discernible movement towards one track for a short time. The apparently disorder in the 'down time' allows the system to be prepared for a variety of different possible patterns of response.

Freeman's analogy is also apt for digestive enzyme secretion as seen through the lens of the Equilibrium Model. In the resting state the concentration of digestive enzyme in the various interconnected compartments reflects a complex equilibrium or steady state (Isenman and Rothman, 1979a).[13] This leaves the system prepared to deliver a net flux of all enzymes or, alternately, certain ones to where they are required, in response to neural or endocrine stimulation. The exocrine pancreas according to the Equilibrium Model functions as a rudimentary complex adaptive system.

Other factors in addition to the cultural zeitgeist can help explain the past preference for simplicity over complexity in science. Modeling even rudimentary complex systems requires large computer power, something not readily available until relatively recently. With respect to digestive enzyme secretion, Rothman's observations and views were not taken seriously in part because he did not have a mechanism to go with the kinetic evidence suggesting protein transport through membranes. Indeed working within the reductive framework, and depending heavily on molecular genetics, scientists have elucidated the details of a number of mechanisms that allow proteins to go through membranes. Likewise increasingly sophisticated brain imaging techniques are now allowing researchers to explore the potential intellectual prowess of the unconscious mind.

[13] Digestive enzyme secretion into the duct continues because fluid continuously renews the concentration gradient across the duct membrane (Isenman and Rothman, 1979a).

4. CONCLUSION

The simplicity view tends to be self-limiting. In seeking to reduce and explain the world, it often leaves outside its frame what does not fit as well as what is not known. In physics for example, the ascendancy of this worldview has resulted in a theory that can account for all the mass and energy in the universe----except the 95% that represents dark matter and energy (Panek, 2007). Likewise molecular biologists have sequenced the human genome---except the 97% that represents non-coding regions. We now know that these non-coding regions previously thought to be junk DNA contain conserved regions that have important regulatory functions (Bejerano et al., 2004). Recent evidence even calls into question the long held view that all neurotransmitter release in neurons necessarily occurs only at synapses (Kukley et al., 2007).

I would like to suggest that another essential and related element the simplicity view leaves out is the observer and their unconscious as well as conscious perceptual framing. By adding back the investigator and their act of reduction, the simplicity worldview becomes not something about the cosmos, but rather a powerful human technique to understand the small but ever enlarging part of the cosmos that we can now know. Instead we too often assume that the line we have drawn in the sand will remain.

The next larger frame, which might not appear for several generations, would no doubt change our view. Whether the universe is static or dynamic and evolving, our views of it

are dynamic at least in the long-term. As Goethe said, "We might venture this statement that the history of science is science itself." (quoted in Bortorf, 1996, p. XI)

The complexity worldview with its focus on holism and continuity appears to be gaining in stature. Indeed it must if we are to cope with some of the most critical current and coming challenges. For instance, managing global climate change, as well as balancing increasing technological skill at genetic engineering with the long-term effect of particular manipulations and combinations of manipulations, requires careful consideration of the potential interaction of multiple factors over time. In such a milieu, complexity-based, holistic models of cell function as well as of the potential of higher-level unconscious activity may well become the norm. Yet the simplicity worldview is unlikely to retreat significantly because it has proved too successful. For example it has given rise to those genetic engineering skills that are bringing us to the threshold of a brave new world---with all its potential benefits as well as reasons for concern.

The simplicity world view, built around discreteness and reduction, is more aligned with the way the conscious mind goes about understanding the world. The complexity worldview built around the continuum and holism is more aligned with what we think of as intuition. The unconscious mind tracks the space/time interconnections the conscious mind must ignore to function in the present and comes up with imaginative theories that incorporate these patterns. Thus effective reduction, like all theory building, begins with human intuition. What often goes unrecognized is that it is a point in time reduction

for/by the conscious mind of the underlying complexity of an ever-enlarging unconscious world.

References

Acker, F. (2008). New findings on unconscious versus conscious thought in decision making: additional empirical data and meta-analysis. *Judgment and Decision Making, 3,* 292–303

Baars, B. (1988). *A cognitive theory of consciousness.* (Cambridge: Cambridge University Press)

Baars, B. (1997). In the theater of consciousness: Global workspace theory, a rigorous scientific theory of consciousness. *Journal of Consciousness Studies, 4*, 292-309.

Baars, B. (1999). In the theater of consciousness: The Workspace of the Mind. (New York: Oxford University Press)

Baars, B. (2002). The conscious access hypothesis: Origins in recent evidence. *Trends in Cognitive Sciences, 6,* 47-52

Bahrami, B., Lavie, N., & Rees, G. (2007). Attentional load modulates responses of human primary visual cortex to invisible stimuli. *Current Biology, 17,* 509-513

Bejerano, B., Pheasant, M., Makunin I., Stephen, S., Kent, W.J., Mattick, J.S. & Haussler, D. (2004). Ultraconserved elements in the human genome. *PNAS, 103,* 5676-5681

Block, N. (1990). Consciousness and accessibility. *Behavioral and Brain Sciences, 13,* 596–98

Bolte, A., & Goschke, T. (2005). On the speed of intuition: Intuitive judgments of semantic coherence under different response deadlines. *Memory and Cognition, 33*, 1248-1255

Bortorf, H. (1996). *The wholeness of nature: Goethe's way towards a science of conscious participation in nature.* (Hudson, NY: Lindisfarne Press)

Bowers, K.S., Regehr, G., Balthazard, C., & Parker, K. (1990). Intuition in the context of discovery. *Cognitive Psychology 22*, 72-110.

Budinger, E., Heil, P., Hess, A. & Scheich, H. (2006). Multisensory processing via early cortical stages: Connections of the primary auditory cortical field with other sensory systems. *Neuroscience, 143*, 1065-1083

Caro, L.C. & Palade, G.E. (1964). Protein synthesis, storage and discharge in the pancreatic acinar cell. *Journal of Cell Biology, 20,* 473-495

Christoff, K., Gordon, A.M., Smallwood, J., Smith, R., & Schooler, J. W. (2009). Experience sampling during FMRI reveals default network and executive system contributions to mind wandering. *Proceedings of the National Academy of Sciences, 106,* 8719-8724

Cleeremans, A. & Jiménez, L., (2002). Implicit learning and consciousness: A graded, dynamic perspective. (In French, M. & Cleeremans, A. (Eds.), *Implicit learning and consciousness: An empirical, philosophical and computational consensus in the making*. (pp 1-40). New York: Psychology Press)

Cleeremans, A. (2008). Consciousness: The radical plasticity thesis. *Progress in Brain Science, 168*, 19-33.

Crawley, S.F. French, C.C. & Yesson, S.A. (2002). Evidence for transliminality from a subliminal card-guessing task. *Perception, 31,* 887-892

Damasio, A.R. (1994). *Descartes' error: Emotion, reason, and the human brain.* (New York: G. P. Putnam's Sons)

Dehaene, S., Naccache, L., Le Clec, H. G., Koechlin, E., Mueller, M., Dehaene-Lambertz, G., van de Moortele, P. F., & Le Bihan, D. (1998). Imaging unconscious semantic priming. *Nature 395*, 597-600

Dehaene, S., Sergeant, C., & Changeux, J. (2003). A neuronal network model linking subjective reports an objective physiological data during conscious perception. *Proc. Natl. Acad. Sci. U. S. A., 100,* 8520-8525

Dehaene, S. Changeux, J., Naccache, L., Sackur, J. & Sergent, C. (2006). Conscious, preconscious and subliminal processing: a testable taxonomy. *Trends in Cognitive Sciences, 10,* 204-211

Destrebecqz, A. & Cleeremans, A. (2003). Temporal effects in sequence learning. (In L. Jiménez (Ed.) *Attention and Implicit learning*. (Amsterdam: John Benjamins, (pp. 180-213)

Dienes, Z. & Perner, Z. (2003). Unifying consciousness with explicit knowledge. (In A. Cleeremans (Ed.) The unity of consciousness: Binding integration and dissociation. (pp. 214-232). Oxford: Oxford University Press)

Dienes, Z. & Scott, R. (2005). Measuring unconscious knowledge: Distinguishing structural knowledge and judgment knowledge. *Psychological Research, 69*, 338-351

Dijksterhuis, A., & Meurs, T. (2006). Where creativity resides: The generative power of unconscious thought. *Consciousness and Cognition, 15,* 135-146

Dijksterhuis, A., Bos, M.W. Nordgren, L.F. & van Baaren, R.B. (2006). On making the right choice: The deliberation-without-attention effect. *Science, 311,* 1005-1007

Driver, J. & Noesselt, T. (2008). Multisensory interplay reveals crossmodal influences on 'sensory-specific' brain regions, neural responses, and judgments. *Neuron, 57,* 11-23

Edelman, G.M. & Tononi, G. (2000). *A universe of consciousness: How matter became imagination.* (New York: Basic Books)

Elman, J., Bates, J., Johnson, M., Karmiloff-Smith, A., Parisi. D. & Plunkett, K. (1996). *Rethinking innateness: A connectionist perspective on development* (Cambridge MA: MIT Press)

Fleck, J., Green, D., Stevenson, J., Payne, L., Bowden, E., Jung-Beeman, M. & Kunios, J. (2008). The transliminal brain at rest: Baseline EEG, unusual experiences, and access to unconscious mental activity. *Cortex, 44,* 1353-1363

Fletcher, P.C., Zafiris, O., Frith, C.D., Honey, R.A.E., Corlett, P.R., Zilles, K. & Fink, G.R. (2007). On the benefits of not trying: Brain activity and connectivity reflecting the interactions of explicit and implicit sequence learning. *Cerebral Cortex, 15,* 1002-1015

Freeman, W.J. (1991). The physiology of perception. *Scientific American, 264*, 78-85

Freeman, W.J. (1998). *How brains make up their minds.* (London: Weidenfeld & Nicolson)

Fu, Q., Fu, X. & Dienes, Z. (2008). Implicit sequence learning and conscious awareness. *Consciousness and Cognition 17,* 185-202

Gaillard, R., Cohen, L., Adam, C., Clemenceau, S., Hasboun, D., Baulac, M., Willer, J., Dehaene, S. & Naccache, L. (2007). Subliminal words durably affect neuronal activity. *NeuroReport, 18,* 1527-1531.

Gaillard, R., Del Cul, A., Naccache, L., Vinckier, F., Cohen, L. & Dehaene, S. (2006). Nonconscious semantic processing of emotional words modulates conscious access. *Proceedings of the National Academy of Sciences, U.S.A., 103,* 7524-7529

Gladwell, M., (2005) Blink: The power of thinking without thinking. (New York, Little Brown)

Goncz, K.K. & Rothman, S.S. (1995). A transmembrane pore can account for protein movement across zymogen granule membrane. *Biochimica Biophysica Acta, 1238,* 91-93

Gumbart, J. & Schulten K. (2006). Molecular dynamics studies of the archaeal translocon. *Biophysical Journal, 90*, 2356-2367

Holton*, G.* (1973). *Thematic origins of scientific thought: Kepler to Einstein.* (Cambridge MA: Harvard Univ. Press)

Holton, G. (1998). *The Scientific imagination.* (Cambridge MA: Harvard Univ. Press)

Isenman, L., Liebow, C., & Rothman, S. (1995). Protein transport across membranes: A paradigm in transition. *Biochimica Biophysica Acta*, *1241*, 341-370

Isenman, L. D., Liebow, C., & Rothman, S. S. (1995). Protein transport across membranes: A paradigm in transition. *Biochimica Biophysica Acta, 1241*, 341–370

Isenman, L.D. & Rothman, S.S. (1977). Transport of alpha-amylase across the basolateral membrane of the pancreatic acinar cell. *Proceedings of the National Academy of Sciences, U.S.A., 74*, 4068-4072

Isenman, L.D. & Rothman, S.S. (1979a). Diffusion-like processes can account for protein secretion by the pancreas. *Science, 204*, 1212-1215

Isenman, L.D. & Rothman, S.S. (1979b). Transpancreatic transport of digestive enzymes. *Biochimica, Biophysica, Acta, 585,* 321-332

Isenman, L.D. (1980) Digestive enzyme transport and secretion in the Pancreas. Dissertation, University of California

Isenman, L.D. (1997). Towards an understanding of intuition and its importance in scientific endeavor. *Perspectives in Biology and Medicine, 40*, 395-403

Isenman, L. (2009). Trusting your gut, among other things: digestive enzyme secretion, intuition, and the history of science. *Foundations of Science, 14,* DOI 10.1007/s10699-009-9164-0

Isenman, L. (forthcoming). *Understanding intuition: A sense of the whole*.

Jackendoff, R. (1987). *Consciousness and the Computational Mind*. (Cambridge, MA; MIT Press)

Jiang, Y., Costello, P., Fang, F., Huang, M. & He, S. (2006). A gender- and sexual orientation-dependent spatial attentional effect of invisible images. *Proceedings of the National Academy of Sciences, U.S.A., 103,* 17048-17052

Joliot, A. & Prochiantz, A. (2005). Transduction peptides: From technology to physiology. *Nature Cell Biology,* 6, 189-196

Jung-Beeman, M. & Bowen, E.M. (2000). The right hemisphere maintains solution-related activation for yet-to-be-solved problems. *Memory and Cognition, 28,* 1231-1241

Jung-Beeman, M., Bowden, E.M. Haberman, J., Frymiare, J.L., Aerameel-Liu, S., Greenblatt, R., Reber, P.J. & Kounios, J. (2004). Neural activity when people solve verbal problems with insight. *PLoS Biology, 2,* 0500-0510

Kanai, R., Tsuchiya, N. & Verstraten, F.A.J. (2006). The scope and limits of top-down attention in unconscious visual processing. *Current Biology, 16,* 2332-2336

Kelly, R., (1985). Pathways of protein secretion in eukaryotes. *Science, 230*, 25-32

Kounios, J., Frymiare, J.L., Bowden, E.M., Fleck, J.I., Subramaniam, K., Parrish, T.B. & Jung-Beeman, M.J. (2006). The prepared mind: Neural activity prior to problem presentation predicts subsequent solution by sudden insight. *Psychological Science 17,* 882-890

Kukley, M, Capetillo-Zarante, E., & Dietrich, D. (2007). Vesicular glutamate release from axons in white matter. *Nature Neuroscience., 10(3),* 311-320

Lau, H. & Passingham, R. (2006). Relative blindsight in normal observers and the neural correlates of visual consciousness. *Proceedings of the National Academy of Sciences, U.S.A., 103,* 18736-18768

Lau, H. & Passingham, R. (2007). Unconscious activation of the cognitive control system in the human prefrontal cortex. *Journal of Neuroscience, 27,* 5805-5811

Lee, P.A., Tullman-Ercek, D., & Georgiou, G. (2006). Bacterial twin-arginine translocation pathway. *Annual Review of Microbiology, 60*, 373-95

Liebow, C., & Rothman, S.S. (1975). Enteropancreatic circulation of digestive enzymes. *Science, 189,* 472-474

Liebow, C., & Rothman, S.S. (1976). Equilibration of pancreatic digestive enzymes across zymogen granule membranes. *Biochimica Biophys*ica *Acta, 455,* 241-253.

Maia, T. & Cleeremans, A. (2006). Consciousness: Converging insights from connectionist modeling and neuroscience. *Trends in Cognitive Science, 9,* 397-404

Mangan, B. (1993). Taking phenomenology seriously: The "fringe" and its implications for cognitive research. *Consciousness and Cognition, 2*, 89-108

Mangan, B. (2001). Sensations ghost: The non-sensory “fringe” of consciousness. *PSYCHE 7* (http//:psyche.cs.monash.edu.au/v7/psyche-7-18-mangan.html)

Mason, M. Norton, M.I., Van Horn, J., Wegner, D.M., Grafton, S., & Macrae, C.M. (2007). Wandering minds: The default network and stimulus-independent thought. *Science, 315,* 393-395

McClelland, J.L, Rumelhart D.E. & the PDP Research Group. (1986). Parallel distributed processing: Explorations in the microstructure of cognition. (Cambridge: MIT Press)

Metcalfe, J. (2000) Feelings and judgments of knowing: Is there a special noetic state? *Consciousness and Cognition 9,* 179-186

Miller, G.A. (1956). The magical number seven, plus or minus two: Some limits on our capacity for processing information. *The Psychological Review 63,* 81-97

Mulvenna, C.M. & Walsh, V. (2006). Synesthesia: Supernormal integration? *Trends in Cognitive Sciences, 10,* 350-352

Naccache, L. & Dehaene, S. (2001). Unconscious semantic priming extends to novel unseen stimuli. *Cognition 80*, 215-29

Nakamura, K., Dehaene, S., Jobert, A., Le Bihan, D., & Kouider, S. (2005). Subliminal convergence of Kanji and Kana words: Further evidence for functional parcellation of the posterior temporal cortex in visual word perception (2005). *Journal of Cognitive Neuroscience, 17,* 954-968

Nakamura, K., Hara, N., Kouider, S., Takayama, Y., Hanajima, R., Sakai, K. & Ugawa, Y. (2006). Task-guided selection on dual neural pathways for reading. *Neuron, 52,* 557-564

Norman, E., Price, M.C. & Duff, S.C. (2006). Fringe consciousness in sequence learning: The influence of individual differences. *Consciousness and Cognition, 15,* 723-760

Norman, E., Price, M.C., Duff S.C. & Mentzoni, R.A. (2007). Gradations of awareness in a modified sequence learning task. *Consciousness and Cognition, 16,* 809-837

Palade, G.E, Siekevitz, P. & Cara, L.G. (1962). Structure, chemistry and function of the pancreatic exocrine cell. (In A. DeReuck & N. Cameron (Eds.), *Ciba Foundation symposium on the exocrine pancreas: Normal and abnormal functions* (pp. 23-39). London: Churchill LTD.)

Palade, G.E. (1975). Intracellular aspects of the process of protein synthesis. *Science, 189*, 347-358

Panek, P. (2007, April 11). Out there. *New York Times*

Pessiglione, M., Petrovic, P., Daunizeau, J., Palminteri, S., Dolan, R.J. & Frith, C.D. (2008). Subliminal instrumental conditioning demonstrated in the human brain. *Neuron*, 59, 561-567

Reber, A.S. (1996). *Implicit learning and tacit knowledge.* (New York: Oxford University Press)

Rothman, S.S. & Isenman, L.D. (1974). The secretion of digestive enzyme derived from two parallel intracellular pools. *American Journal of Physiology, 226*, 1082-1087

Rothman, S.S. (1967). Non-parallel transport of enzyme protein by the pancreas. *Nature, 213*, 460-462

Rothman, S.S. (1975). Protein transport by the pancreas. *Science, 190,* 747-753.

Rothman, S.S. (1976). The digestive enzymes of the pancreas: A mixture of inconstant proportions. *Annual Review of Physiology, 39*, 373-389

Rothman, S.S. (1980). The passage of proteins through membranes---old assumptions and new perspectives. *American Journal of Physiology 238,* G391-G402

Rothman, S.S. (2002). *Lessons from the living cell: The limits of reductionism.* (New York, McGraw-Hill)

Sagiv, N., & Ward, J. (2006). Cross modal interactions: Lessons from synesthesia. *Progress in Brain Research, 155,* 259-271

Schleghecken, F., Klapp, S.T. & Maylor, A. (2009). Either or neither, but not both: Locating the effects of masked primes. *Proceedings of the Royal Society B, 276,* 515-521

Spivey, J.M. (2007). *The continuity of mind*. (New York: Oxford University Press)

Seitz, A.R., Kim, D., & Watanebe, T. (2009). Rewards evoke learning of unconsciously processed visual stimuli in adult humans. *Neuron, 61,* 700-707

Stewart, J. (2007). The future evolution of consciusness. *Journal of Consciousness Studies, 14,* 58-92

van Gaal, S., Ridderinkhof, K.R., van den Wildenberg, W.P.M. & Lamme, V.A.F. (2008). Dissociating Consciousness from inhibitory control: Evidence for unconsciously triggered response inhibition in stop-signal task. *Journal of Experimental Psychology: Human Perception and Performance, 28,* 8053-8062.

Volz, G. & Yves von Cramon, D. (2006). What neuroscience can tell about intuitive processes in the context of perceptual discovery. *Journal of Cognitive Neuroscience, 18,* 2077-2087

Wickner, W., & Schekman, R. (2005). Protein translocation across biological membranes. *Science, 310*, 1452–1456

Wu , Z., Jakes, K., Samelson-Jones, B., Lai, B., Zhao, Z., London, E. & Finkelstein, A. (2006). Protein translocation by bacterial toxin channels: A comparison of diphtheria toxin and colicin. *Biophys. J., 91,* 3249–3256

Zhong, C., Dijksterhuis, A. & Galinsky, A.D. (2008). The merits of unconscious thought in creativity. *Psychological Science, 19,* 912-918