Running Title: Digestive Enzyme Secretion and Intuition

Trusting Your Gut, Among Other Things:

Digestive Enzyme Secretion, Intuition, and the History of Science

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ABSTRACT: The role of intuition in scientific endeavor is examined through the lens of three philosophers/historians of science---Karl Popper, Thomas Kuhn, and Gerald Holton. All three attribute an important role to imagination/intuition in scientific endeavor. As a case study, the article examines the controversy between the generally accepted Vesicular Sequestration/Exocytosis Model of pancreatic digestive enzyme secretion and an alternative view called the Equilibrium Model. It highlights the intertwining of intuition and reason in the genesis of the Equilibrium Model developed in response to findings that could not readily be explained by the consensus view. It suggests that tacit knowledge/understanding works in conjunction with philosophical and aesthetic presuppositions that function to a greater or lesser extent below awareness. Together they guide judgments about whether falsification has occurred and help frame alternative theories.

Keywords:

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History of science
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Unconscious cognition

Biography: Lois Isenman received her Ph.D. in Cell Physiology at the University of California at San Francisco. Her dissertation focused on the transport and secretion of digestive enzymes from the pancreas. For many years she studied the release of proteins and peptides across lysosomal membranes at Tufts University School of Medicine. As a 1995 Science Scholar at the Bunting Institute of Radcliffe College, she spent part of her time exploring intuition and its role in science. In 1997 she published a paper in the journal *Perspectives in Biology and Medicine*, entitled "Towards an Understanding of Intuition and Its Importance in Scientific Endeavor," (http://people.brandeis.edu/~lisenman/Perspectives.pdf). For the last number of years she has been working full-time on intuition at the Women's Studies Research Center of Brandeis University. She examines the likely cognitive and physiological mechanisms as well as the phenomenology of this important human mental capacity that is increasingly the focus of scientific inquiry. She is writing a book tentatively entitled, *Understanding Intuition: A Sense of the Whole.*

1. INTRODUCTION

At evocative analogy exists between intuition, that most elusive mental process, and the digestion of the food we ingest. These apparently unlikely bedfellows are both essential for the automatic breakdown and assimilation of *food* from the environment---one physical *food* and the other mental *food*.[1] Just as digestive enzymes are required in the gut for the automatic digestion and assimilation of ingested food into the body, intuition is necessary for the automatic digestion and assimilation of information from the environment into the brain/mind.

As a Ph.D. student in Cell Physiology, I worked in a laboratory that proposed a controversial theory about how digestive enzymes are secreted from the cells in the pancreas in which they are produced. After a number of years working as a biologist, I realized that my cognitive style was unusually intuitive and became intrigued both by understanding how intuition works at a mechanistic level and the role it plays in scientific endeavor. Eventually I turned my full attention to exploring intuition, never imagining---at least at a conscious level---the strong echoes of my old work in my new interest.

Both intuition and the specific view of protein secretion I studied are also once radical views that gradually have become scientifically acceptable---however only in a circumscribed sense. Unconscious cognition and aspects of intuition have gained

[1] I first became aware of the analogy in the context of an unusual experience. Early in my study of intuition, when asked "What is intuition?" one of the several images that unexpectedly came to mind was a signal going down and then up on a graph (Isenman, 1997, p. 395). Eventually I realized this was the pattern of the data in my first significant experiment as a biologist.

considerable visibility in Cognitive Science in the last number of years---in fact they are now the focus of intensive scientific interest. Yet many researchers still feel that novel and sophisticated intellectual activity occurs only in consciousness. Likewise the alternative view of protein secretion has gained acceptance in a number of other systems, but still not in the pancreas—--the most copious protein secreting organ of the body. The two also share a number of more intrinsic correspondences, which I will explore in the companion paper.

I will define intuition in terms of its three not entirely separable components or facets. The first is its *source component,* which specifies intuition's grounding largely in unconscious pattern creation/recognition, or more generally in unconscious information processing. The second is its *experiential component*, which may take the form of significant and novel content grounded in unconscious knowledge and unconscious information processing that appears awareness. The third is its *evaluative component*, which largely measures the coherence of mental contents, both conscious and unconscious, and functions both below awareness and at its fringe (Polanyi, 1969; Mangan, 1993; 2001; Isenman, 1997).

In what follows I will consider the work of three eminent 20th century philosophers/historians of science as it relates to the influence of intuition on scientific endeavor. Together their work begins to capture the influence of intuition on scientific investigation. I will entwine their views with a number of observations about the controversy over digestive enzyme secretion, my experience working with the alternative theory, and some recent findings in Cognitive Science. The interwoven organization I am using for both papers, which brings together a variety of different but interrelated strands, mirrors the underlying structure of intuition. It also mirrors the organization of pancreatic digestive enzyme secretion as viewed by the Equilibrium Model.

2. KARL POPPER: THEORY PRECEDES FACT

Karl Popper (1902-1994) was concerned with the problem of induction, how we go from apparently factual observations to theory. For the logical positivists who had dominated the philosophy of science previously, the essence of science depended on what could be positively verified by observation and analysis. Popper stressed that facts do not lead to theories. To the contrary facts get their meaning and context from theories, which he understood as "free inventions of the human mind," informed by intuition.[2]

Popper pointed out that it is relatively easy to find evidence consistent with a theory. More critical is the outcome of efforts to disprove it. Verification and falsification are asymmetrical; falsification has more weight. In contrast to the positivists, Popper saw the essence of science---what defines an empirical system as well as an empirical statement--

[2] Popper (1963, p. 180) evoked a similar analogy between intuition and digestion. Writing approvingly of Kant's views of Newtonian science, he wrote, "It is not these sense-data, but our own intellect, the organization of the digestive system of our mind, which is responsible for our theories. Nature as we know it, with its order and with its laws, is thus largely a product of the assimilating and ordering activities of our mind….We must give up the view that we are passive observers waiting for nature to impress its regularities upon us. Instead we must adopt the view that in digesting our sense-data we actively impress the order and the laws of our intellect upon them. The Cosmos bears the imprint of our minds." However Popper, who was strongly influenced by Einstein's work, disagreed with Kant over whether the laws the mind imposes on nature, no matter how powerful, are *a priori* correct and thus the last word.

-as the susceptibility to revision. He saw scientific revolution as continual and he understood the scientist's job as challenging the scientific status quo.

> The empirical basis of objective science has thus nothing 'absolute' about it. Science does not rest upon rock-bottom. The bold structure of its theories rises, as it were, above a swamp. It is like a building erected on piles. The piles are driven down from above into the swamp, but not down to any natural or 'given' base; and when we cease our attempts to drive our piles into a deeper layer, it is not because we have reached firm ground. We simply stop when we are satisfied that they are firm enough to carry the structure, at least for the time being. (Popper, 1959, p. 111)

Popper decried the common practice of adding *ad hoc* assumptions to a theory, such as the epicycles added to the Ptolemaic earth-centered system, so it can encompass contrary observations. Above all he valued the changing and developing character of scientific understanding.

3. UNDERSTANDING PANCREATIC DIGESTIVE ENZYME SECRETION: A CASE STUDY

In the 19th Century, Rudolf Heidenhain studied digestion in dog. Using the light microscope, he observed large granules within exocrine pancreatic cells, which accumulated between meals and decreased in both number and size after meals. He was also able to correlate the amount of digestive enzymes released into the gut with the disappearance of the granules. Heindenhain named them *zymogen granules* for the Greek word for *ferment*.

Digestive enzymes, like most proteins, because they have many charges on their surface essential to their various specific functions, are hydrophilic or water-loving. Yet membranes are made primarily of long chain hydrocarbons, which are oil-like molecules, and as everyone knows oil and water do not mix. Until relatively recently biologists thought that large charged protein molecules could not cross membranes. (In contrast they thought small molecules could either diffuse through the membrane or go through hypothesized water pores.) Yet some proteins, such as digestive enzymes, function outside the cells in which they are made. Called *secretory proteins,* they would seem to have to cross at least one membrane to get out of the cell.

The cells that secrete pancreatic digestive enzyme lie like grapes or berries on their stem. (They are called *acinar* cells, for the Latin word for *berry*.) This configuration allows each exocrine pancreatic cell to share a membrane with a tiny branch of the larger common secretory duct that eventually leads to the gut where the digestive enzymes do their work (Figure 1). Physiologists hypothesized the granules were extruded whole---membrane and all---from the cells into the secretory duct.

The advent of the electron microscope in the 1950s opened a new era in the study of biological organisms---the age of *Cell Biology*. The electron microscope, an outgrowth of the war effort, allowed biologists to peer into cells and describe their sub-cellular organelles clearly. Palade and Siekavitz, pioneers in the application of this new technology, used it to develop an anatomically-grounded schema for the synthesis and secretion of pancreatic digestive enzyme. They were awarded the Nobel Prize in 1974 for their work.

The researchers and their colleagues outlined in broad strokes what has become the established view of the sequence of intercellular events leading to the secretion of digestive enzymes from the pancreas (for reviews see Palade et al., 1962; Palade 1975). Immediately upon synthesis, proteins to be exported are isolated from the watery interior of the cell in membrane enclosed vesicles. Vesicles fuse easily with one another. Via a process of *controlled* fusion, digestive enzymes pass though a set network of different vesicles.[3] The last of these, the zymogen granules first described by Heidenheim, are large enough to be visible in the light microscope. In the final step, the zymogen granule membrane fuses with the cell membrane in such a way that the protein is left topologically on the other side of the cell without having crossed its limiting membrane (Figure 2).

The model is a well accepted component of the cannon of contemporary Cell Biology. It has been extended to include the secretion of all exportable protein and peptides, including neurotransmitters and hormones. The sequence of steps it suggests may well occur, since the biochemistry of some of them have been elucidated in part. (Of course, as Popper would remind us, whether the generally accepted model is the only explanation for these observations remains uncertain.)

[3] Movement of digestive enzyme between compartments is thought to occur via small vesicles. The vesicles fuse with the near side of each membrane compartment, releasing their protein. Small vesicles also bud off from the far side of each compartment carrying a quanta of protein to next in the series.

From the late 1960's through the early 1990's Stephen Rothman, the head of the laboratory in which I did my graduate work, studied pancreatic digestive enzyme secretion. Some of his early experimental data could not easily be explained by the consensus model. When he applied various stimulants of secretion to the pancreas, he observed immediate changes in the proportion of different digestive enzymes released (Rothman, 1967, 1976). These findings were at odds with the generally accepted model in which digestive enzymes are synthesized and packaged hours before their secretion.[4] In addition the model lacked a mechanism for either the selective packaging of certain enzymes or the selective release of certain granules.

To account for these observations as well as several subsequent observations from his laboratory, Rothman offered an alternative hypothesis for digestive enzymes secretion, which he called *the Equilibrium Model*. In direct contrast to the consensus view, it holds that digestive enzymes can pass individually molecule by molecule through a variety of the pancreatic cell's membranes in both directions---including the zymogen granule membrane, the membrane leading to the duct, and the blood-facing membrane of the cell (Rothman, 1975). Equilibration across a membrane occurs when the movement of a specific kind of protein in one direction equals its movement in the other and no net change occurs. These equilibrating fluxes of digestive enzyme are all interrelated via a soluble pool of enzymes in the soup-like ground substance, or *cytosol*, of the cell. This pool serves as a final common pathway to secretion into the duct (Figure 3).

[4] Somewhat later experiments confirmed that all the enzymes are found in each granule (Bendayan et al., 1980).

During the time I was in graduate school, ideas about membrane structure began to change in a way that was consistent with the Equilibrium Model and its proposal that proteins could cross membranes. Rather than static structures, membranes were more and more viewed as dynamic entities constantly in flux, exchanging lipids and embedding many proteins. It became clear that at least some proteins could alter their configuration to fit the hydrophobic environment of the membrane, could move relatively freely within it, and be added and removed. The new view of membrane structure was called the *Fluid Mosaic Model* (Singer and Nicolson, 1972).

Even before the Fluid Mosaic Model became popular, Rothman, who had previously studied the transport of small molecules, liked to say, "If you wait long enough, even an elephant can go through a membrane." It is now well accepted that many different kinds of proteins move individually through membranes, and sometimes in both directions.[5] Nevertheless vesicular transport remains the default assumption.

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[5] For reviews of protein membrane transport see, Isenman et al., 1995; Wickner and Schekman, 2005; Joliet and Prochainz, 2005. Briefly, most protein synthesis takes place in the cytosol. This means that even proteins to be sequestered in vesicles must cross at least one membrane to get into the endoplasmic reticulum where vesicles are initially assembled. Originally all transport into the endoplasmic reticulum was thought to occur a few amino acids at a time as a protein is synthesized---what is called co-translational transport. Eventually it became clear that transport into the endoplasmic reticulum sometimes occurs after synthesis is complete---or post-translationally. Some protein transport out of the endoplasmic reticulum is also now know to occur.

Nuclear proteins enter the nucleus from the cytosol via large pores. 99% of mitochondrial proteins are synthesized in the cytosol and transferred individually via a variety of different mechanisms through the outer mitochondrial membrane, and sometimes the inner mitochondrial membrane into the mitochondrial matrix. Likewise molecule by molecule transport of proteins occurs by a variety of different mechanism into choroplasts, and it also occurs into peroxosomes. Selective protein transport has been shown *into* lysosomes as well as selective protein and peptide transport *out* of lysosomes.

Proteins cross bacterial membranes by a variety of different mechanisms.
Bacteria also secrete their protein toxins through their host cell membranes molecule by molecule. Certain bacterial peptides, called *protein insertion peptides* have been shown to transport whatever proteins they are attached to across membranes.

At one level, Rothman's claim that the consensual theory could not account for digestive enzyme secretion was a rigorous deductive statement that followed from his observations of immediate changes in the proportion of different enzymes released. In his book "*Lessons From the Living Cell*," which explores the science behind the controversy around digestive enzyme secretion, Rothman (2002) frames his understanding of science, his early observations and his laboratory's work in light of Popper's view. The job of the scientist when confronted with anomalous observations is to suggest a bold, alternative theory that can be tested against the prevailing model. Like a good *Popperian*, Rothman acknowledged that the alternative theory he proposed---just like all theory---was speculative. In doing so he implicitly acknowledged that intuition may have had a role, since intuition as unconscious knowledge informs speculation/imagination. However he stressed that *the need for a new theoretical proposal was a logical necessity* following from the inability of the generally accepted view to account for his initial findings.

Yet Rothman himself points out that even Popper was uncertain how many contrary observations were necessary to falsify a theory. In the end, Rothman, like Popper, evokes Occam's razor---saying the theory he proposed was the simpler one to account for all the data. Thus it required fewer *ad hoc* hypotheses---those mini-fixes or patches applied to theories so they don't deflate like a tire with a hole.

Molecules called *chaperons* can transiently attach to proteins prior to transport, partially unfolding them or altering their conformation to facilitate passage through the membrane. However a number of transport mechanisms do not require protein unfolding and some even transport intact multiunit proteins.

Simplicity is difficult to define. Popper considered certain characteristics that make one theory simpler than another---such as boldness, how well it can explain the existing data, as well as its potential falsification with respect to future data. Yet the working scientist gives little credence to theoretical notions about simplicity when judging the validity of a theory or assessing alternatives. Rather as Michael Polanyi (1969) pointed out, these judgments depend to a large degree on intuitive evaluative feelings. As a result, different scientists may disagree as to whether falsification has occurred and also which of two hypotheses is the simpler. For example only a few others saw it the way Rothman did.

Implicit in Popper's view is that intuition has two separable roles in scientific progress. One is indicating that an alternative theory might be warranted, and the other, the one Popper stressed, is the imaginative act of shaping the theory. It is often true, as Popper seemed to feel, that these two roles collapse into one---or function closely together. Yet they can also function separately. Thus a scientist may feel (and in opposition to most colleagues) that a new theory is necessary to account for observations, without being able to suggest one.

My understanding is that Rothman’s judgment that a new theory was necessary was indeed, as he claimed, based on reason. However as I have learned more about intuition I have come to believe that it was reason grounded in intuition---in unconscious, or tacit, understanding and knowledge. As subsequent sections will explore in more detail, we generally do not need to choose between intuition and reason, in spite of the traditional view that stresses the conflict between the two. Intuition and reason tend to work hand-in-hand and very often cannot be separated from each other. We will return to the question of whether Rothman's contrary observations falsified the generally accepted model for protein secretion and how intuition might have shaped his views after considering the work of Thomas Kuhn. Kuhn provides a broader context for falsification of scientific theory than Popper, and in so doing helps explain why few others saw the situation as Rothman did.

4. THOMAS KUHN AND NORMAL SCIENCE

Thomas Kuhn (1922-1996), 20 years Popper's junior, considered falsification and intuition with respect to scientific theory within a historical and communal framework (Kuhn, 1970, 1977). He freely acknowledged his debt to Popper---for countering the positivist’s view that scientific progress depends on a series of verifiable facts, and for suggesting that theories come first and determine which facts are sought. However his views differ from Popper’s in critical ways. Aspects of Kuhn’s thought have become well known, but this popularization has come at the cost of overlooking important nuances in his ideas, at least as they developed overtime.

Science, he argued, is not a linear endeavor that steadily deepens our theoretical understanding of the nature of reality, due to either a growing body of empirical observations, as the logical positivists claimed, or to ever changing theories, as Popper claimed it should. Rather, a scientist’s view of reality is framed by paradigms---groups of unquestioned assumptions, theories, examples, and methods all mixed up together.

Paradigms act as the filter through which the community of workers in a field view the phenomenon they study. What Kuhn called *normal science* occurs within a paradigm and expands scientific knowledge in a reasonably steady way as seen through this filter. To a very large extent normal science determines which investigators are funded and what experiments are done. In fact Kuhn, looking from a very different vantage point than Popper, saw the predominance of consensus rather than the possibility of falsification as the distinguishing feature of science---in opposition to other disciplines, such as social science or philosophy.

Over time as scientists work within the prevailing paradigm and attempt to extend it to more and more phenomena, results that are inconsistent inevitably appear. Often such challenges are discounted. When this is no longer possible, the paradigm is amended here or there to account for the anomalous observations. Yet because of the communal commitment to this view of reality, consensual paradigms are generally amended in such a way that their basic assumptions remain unchallenged. This tends to result in the *ad hoc* hypotheses Popper so detested.

Eventually enough conflicting data accumulates so that if scientific progress is to continue, the reigning paradigm must be overthrown by a scientific revolution. Generally someone from outside the field whose views of reality have not been steeped in the prevailing assumptions at the base of the paradigm will offer a countervailing view grounded in another series of assumptions that can account for the newer data the older theory cannot. Often this new view also provides a deeper theoretical understanding of the data that the older theory was developed to explain. The old paradigm may be incorporated as a special case in the radical new view of reality, as for example Newtonian Physics was enfolded in Einstein's new synthesis. Or, as happened with the Ptolemaic view of the solar system, the old view is relegated to the dustbin of history.

At one level Kuhn, like Popper, is saying that scientific understanding is grounded in intuition instead of empirical observation. Our view of reality is always filtered by paradigms, whose basic assumptions can be tested if at all only by time. Yet he often emphasized what might be considered the flip side of this perspective. Even thought these ruling paradigms sometimes touch down into the empirical world only here and there, most scientists learn their grounding assumptions in school or in the laboratory as if they were fact. Scientific education means learning the current paradigm through the study of examples and the history that apparently led to the 'now correct' views. Though in a deeper sense scientific theory is grounded in intuition, most scientists take these intuitions to be proven truth. Their task as they see it is to confirm the new paradigm by extending it to ever new phenomenon.

My own experience provides an interesting variation on this general pattern. Even before I began my graduate studies in biology, I worked in the Rothman laboratory for several years. The set of assumptions I learned about protein transport were very different from those that guided normal science. We constructed experiments based on the equilibrium hypothesis and found many different lines of evidence that conflicted with the reigning paradigm. I felt strong allegiance to this model. Yet since these assumptions were learned and consensual in our laboratory group, they constituted 'normal science' within this context.

My data clearly fit better with the Equilibrium Model (Rothman and Isenman, 1974; Isenman and Rothman, 1977, 1979a, 1979b; Isenman, 1980). Yet a skeptic by nature (and also perhaps because of the passionate allegiance I felt to this view) at another level, I felt some doubt. It is one thing to discern holes in a canonical theory and quite another thing to provide complete evidence for an alternative. Moreover the established model could be repeatedly revised to account for the data. Most importantly perhaps, an infinite number of not even yet envisioned models could no doubt also account for the facts. I remember revealing to a friend that I was not absolutely sure that the model my work championed was correct and feeling as if I had revealed an unspeakable sin. Only many years later did I fully recognize this was in accordance with a rigorous understanding of the scientific method. As Popper stressed, theories can never be rigorously accepted, only rejected.

5. ANOMOLOUS RESULTS AS PUZZLES VS. PROBLEMS

Rothman in certain ways fits the *Kuhnian* mold of the researcher from outside the field who initiates scientific revolution. He trained as a transport physiologist and had initially studied the transport of small molecules in the pancreas. Instead of the mass transit of digestive enzymes via vesicles as proposed by the consensus theory, he proposed that digestive enzymes molecules move individually through membranes as many small molecules were known to do. No doubt his past experience played an important role---at both the unconscious and conscious level---in shaping his view that even large molecules can go through membranes.

Like Rothman, Kuhn's outsider who instigates scientific revolution uses prior training, reason, and intuition to weave anomalous observations into a new theory. However the timing of the novel proposal as well as the source of the anomalies that lead to scientific revolution tend to be different. As Kuhn points out, the anomalies that successfully overturn a consensus theory generally come from within the paradigm, and only after the failure of many scientists to explain away the puzzling data in a convincing manner. (Even though Kuhn is generally associated with the idea of scientific revolution, at least in his later work, he championed a scientist's commitment to normal science and also saw scientific revolution as a rare event.)

Rothman's proposal for a new theory, in contrast, occurred after only a few anomalies appeared. His alternative model and his observations garnered significant interest. However because of their timing as well as the fact that he lacked a specific biochemical mechanism to account for protein membrane transport, this interest was passing. Eventually funding for the work stopped.

In addition to his training, one of the reasons Rothman saw his contrary observations as immediately warranting a new theory---while most others assumed that the accepted theory would eventually come around to incorporating them---is probably psychological.

Broad differences exist among individual scientists with respect to their acceptance of consensual 'authority' as it relates to their work. Rothman probably has a more skeptical or iconoclastic attitude than many scientists---more of a *Popperian* nature than a consensus building *Kuhnian* nature.[6]

As Kuhn put it, he himself viewed scientists for the most part dealing with *puzzles*---trying to understand novel phenomenon within the context of entrenched paradigm. In contrast he felt Popper saw scientists for the most part dealing with *problems*---anomalous observations that cannot be satisfactory explained within the current paradigm. According to Kuhn, most scientists are motivated primarily by the admiration of the generally small community of scientists who work within the same paradigm and share their immediate interests (Kuhn 1977, p. 290) According to Popper, instead they are, or should be, ready to pounce on any significant hint that the reigning theory might be wrong.

Rothman's skeptical and iconoclastic approach to his work was likely part of the reason he felt a new theory was necessary to account for the anomalies he observed. In contrast others---to the extent they took the contrary observation seriously---saw them instead as challenges or puzzles that the old theory would deal with in time. We now know that Rothman was right about proteins going through membranes, as a massive body of information confirms. This evidence however still comes from systems other than the one his laboratory studied, the system that gave rise to the standard model. Let's look

[6] Skepticism and intuition often go together, however they need not. Skepticism may, for example, also reflect a more general stance with respect to commonly accepted views---the stance championed by Popper.

more carefully at how intuition might have figured into the debate over protein secretion in the pancreas.

6. PUZZLES VS. PROBLEMS AND THE UNCONSCIOUS MIND

6.1 Implicit learning and tacit knowledge: We extract much more information from our experience than we might think we do. For example, as young children we learn to speak grammatically from hearing others talk and only later become aware of the rules of grammar at a conscious level. A large body of work in the field of Implicit Learning demonstrates the prodigious human ability to recognize patterns at an unconscious level. For example, studies of artificial grammar learning (Reber, 1996) and complex sequence learning (French and Cleeremans, 2002) demonstrate that humans can register surprisingly complicated patterns of underlying regularity at an unconscious level. Patterns recognized below awareness help inform subsequent perception, understanding, and behavior. Even when knowledge of these patterns becomes conscious, generally *only a portion of* the information and/or evidence on which they are based will become available to awareness.

This potentially large store of unconscious or tacit information and understanding has important implications with respect to whether apparently inconsistent evidence will be seen as a puzzle that will eventually be solved within the current paradigm or alternatively as a problem requiring a new theory. *All other things being equal,* the more tacit knowledge or insight an investigator has that calls into question the established view and/or can be explained more simply by an alternative, the more likely they will perceive inconsistent observations as a problem rather than a puzzle, and feel, like Rothman, a new theory is warranted. This unconscious information can influence the investigator's view of how many contrary conscious observations are necessary to make a theory seem in trouble and also which might be the more parsimonious of two theories.

6.2 The role of unconscious emotion in reasoning and perception: The unconscious mind, in addition to recording environmental regularities and abstracting patterns from them, has another type of activity that also might sway judgments about whether anomalies are puzzles or problems. Priming studies indicate that hidden emotional/attentional influences can join forces with more purely cognitive ones below awareness to influence perception, evaluation, and judgment (for reviews, see Bargh and Ferguson, 2000; Bargh 2006). Landmark experiments by neuroscientist Antonio Damasio and his co-workers (Bechara et al., 1997) reveal a more general mechanism for the influence of emotion on cognition. They show that unconscious body-based signals mark certain alternatives as good---to be sought---or bad---to be avoided. Without coming to awareness, these somatic feelings can influence behavior, bias decision-making, and ground reasoning. The following vignette describes a brain-damaged patient of Damasio's whose injury prevents him from bringing these adaptive unconscious emotional factors to bear on trying to decide on a date for his next appointment.

> The patient pulled out his appointment book and began consulting the calendar…. For the better part of a half hour, [he] enumerated reasons for or against each of the two dates: previous engagements, proximity to other engagements, possible meteorological conditions, virtually anything that

> one could reasonably think about concerning a simple date. [Completely calmly, he walked through] a tiresome cost-benefit analysis, an endless outlining and fruitless comparison of options and possible consequences. It took enormous discipline to listen to all this without pounding the table and telling him to stop, but finally we did tell him, quietly, that he should come the second of the alternative dates. His response was equally calm and prompt. He simply said: "That's fine."(Damasio 1994, p. 193)

The passage highlights how rudderless conscious reasoning is in the absence of these orienting intuitive signals. Intuition and reason tend to work together. Damasio (1994 p. 190) has suggested that these body-based signals so important to personal decision making in normal people also may have some role in orienting reasoning in the intellectual realm. "…[T]hey would...act covertly to highlight, in the form of an attentional mechanism, certain components over others, and to control in effect, the go, stop and turn signals necessary for some aspect of decision-making and planning in nonpersonal, nonsocial domains." A growing body of work on metacognitive feelings lends support to this view (Bowers, 1990; Mangan, 1993, 2001; Isenman, 1997; Metcalfe, 2000; Dienes and Scott, 2005; Norman et al., 2006, Fu et al., 2008).

Cognitive signals ultimately fueled by bodily feelings offer a largely unconscious attentional mechanism by which a scientist with a deep skepticism towards the current paradigm could without awareness attach more importance to some evidence, *either unconscious or conscious,* than other evidence. Specifically they could direct him or her below awareness to give more weight to evidence suggesting that anomalous findings are a problem rather than a puzzle, and/or lend support to an alternative view, than would be true for those committed to the current paradigm---and vice versa. These unconscious signals conveying salience might even influence which patterns the mind records below awareness, (or what is almost the same thing, the rate at which they are recorded[7]). Because of the conjunction between intuition and reason through unconscious attention, conclusions and implications that seem rigorous and self evident to one mind might not even register on another. Even when they do, they will not necessarily carry the same force. Gerald Holton, the third philosopher/historian of science I consider, starting in the 1970s documented the covert purposefulness that the emotional/attentional substratum to thought can impart to the work of scientists.

Popper and Kuhn helped unlock the door to the subjective nature of scientific investigation. They both stressed the role of imagination in science, but they focused on science as an institution. Gerald Holton (1973, 1998) opened the door wide. By moving his analysis of the role of imagination in scientific endeavor into the individual investigator and into their unconscious, Holton gives a finer grain analysis of the potential role of intuition in scientific investigation. He documents how certain scientists are drawn to specific preconceptions that cannot be proven yet frame their theories and thus the evidence they seek as well as how they interpret their results. In contrast, other scientists are drawn to diametrically opposed preconceptions.

[7] The experiments by Bechara et al. (1997) suggests that, at least in the personal sphere, unconscious emotion/attention enhances the *rate* of implicit learning as inferred from its influence on decision-making and also speeds its appearance in conscious. Implicit information recorded at a low rate requires much more extensive exposure to influence cognition.

7. GERALD HOLTON: SCIENCE 1 AND SCIENCE 2

Holton separated scientific endeavor into two parts, what he called *Science I* and *Science 2*. Science 2 is public science, the institution of science and its public face as recorded in the scientific literature and textbooks. Science 1 is private science---science as it is actually done. A behind the scenes look, it reveals that the scientist, just like the artist, brings his or her imagination and the intuition that informs it to the process of uncovering, interpreting, and representing reality.

For Holton, a number of *themata*, or organizing preconceptions, which have appeared again and again throughout the history of science, help link private and public science. He writes:

> …I suggest a discipline that may be called thematic analysis of science, by analogy with thematic analyses that have for so long been used to great advantage in scholarship outside the sciences. In addition to the empirical or phenomenic (x) dimension and the heuristic-analytic (y) dimension, we can define a third, or z-axis. This third dimension is the dimension of fundamental presuppositions, notions, terms, methodological judgments and decisions---in short, of themata or themes---which are themselves neither directly evolved from, nor resolvable into, objective observations on the one hand, or logical, mathematical, and other formal analytical ratiocinations on the other hand. (Holton, 1973, p. 57)

These guiding preconceptions about the nature of reality influence the theories scientists use to frame known facts and seek new ones. They help shape perception below awareness and in addition they may function consciously. They also influence judgments about whether falsification has occurred and which of two competing theories might be the simpler. Holton feels that those who most influence the course of science are particularly 'themata-prone.' Like Einstein, they have "...the necessary courage (or folly?) to make decisions on thematic grounds" (Holton, 1973, p. 62).

Holton provides a number of case studies that help illuminate the role of intuition in the contribution of pivotal scientists—--such as Kepler, Newton, Millikan, and of course Einstein. For example, by studying the original laboratory notebooks of Robert Milliken, who first showed that electric charge is quantize as opposed to continuous, Holton documented that the scientist excluded about two thirds of his experimental trials in his landmark experiment (Holton 1998, pp. 25-83).[8] In the same chapter he documents that another investigator who recalculated Milliken's data and also did a similar experiment but instead used all data points came to the erroneous conclusion that electric charge takes on a continuous range of values.

The themata come in antithetical pairs that tend to shadow-dance with each other across the historical record. Both sides of the thematic pairs are always at work. Nonetheless certain periods are more defined by one than the other. Underlying cultural factors that influence all investigators, albeit to different degrees, have an important role. At the same time, Holton's work helps illustrate how 'themata-prone' scientists can function, like artists, as both agents and harbingers of changing unconscious cultural influences.

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[8] Milliken's decisions to exclude points were made on technical grounds. However it is possible that some of these technical decisions were based on preconceptions about how the data should look.

To illustrate the role of thematic preconception with respect to the digestive enzyme controversy, rather than writing about the personal and aesthetic dimension the Equilibrium Model had for Stephen Rothman, I will instead emphasize the draw the theory had for me, a student of his. At a more profound level of my psyche than the one where I experienced the doubt I mentioned earlier, I was completely convinced of the rightness of the model and its assumptions. I was sure I would be disappointed with the universe---to the point of existential depression---if it did not turn out to be true.

I have more distance on the digestive enzyme controversy now; however I still feel it is not as settled as most believe it to be. I continue to see the Equilibrium Model as the more compelling model. It can explain the equilibrium-dependent fluxes of digestive enzymes across the various pancreatic membranes documented by the Rothman laboratory, which the traditional model cannot. Moreover its bottom-up focus on transport processes as opposed to anatomical structures or top-down organization continues to resonate with me.[9]

My cognitive style, which is heavily weighted towards intuition, as well as my subsequent career studying intuition, provides evidence for the consistency of the largely unconscious philosophical/aesthetic choices I have made in my intellectual life. In the companion paper I explore a number of thematic presuppositions shared by the Equilibrium Model and intuition-friendly views of cognition. I also examine the opposite

[9] Some might understand my position as an ideological stance rather than an intuitive bias. However it was not imposed in a rigid way on my thought. Rather it came through my unconscious mind, at least at one level of experience, as a perception about how these aspects of reality had to be. My ability to doubt it also suggests it differed from an ideological stance.

preconceptions shared by the consensus model for digestive enzyme secretion and consciousness focused views of cognition.

Rothman has always argued that the Equilibrium Model is the simpler model because it ultimately rests on first principles---the diffusion of molecules down gradients[10]---and thus it can explain the data with fewer *ad hoc* assumptions. Recently he has articulated a subtle yet (at least for some) compelling argument that gives some extra force to this view (Rothman, 2007). The generally accepted model with its orderly, irreversible movement of digestive enzyme through a series of discrete membrane-bound compartment appears to require no additional regulation other than that supplied by external nervous or hormonal factors to control the last step in the process---zymogen granule fusion with the ductal membrane. However the need for internal regulation/coordination of this complex multistep process---the untidy underbelly of the generally accepted model---is just hidden from view.

Carrying digestive enzyme through a series of perhaps seven discrete vesicular compartments to the duct would require considerable internal regulation. Complicated machinery (in addition to the transport mechanisms) of a type never before described would be required to match the average rates of total synthesis and total secretion. Likewise regulatory machinery would be required at each step to match the average rate into each compartment with the average rate out, since entrance and exit depend on different mechanisms that are not inherently coordinated with each other. In contrast, with the Equilibrium Model's interconnected concentration-dependent bidirectional

[10] Some of these gradients may be maintained by processes requiring expenditure of metabolic energy.

fluxes, all the necessary regulation/coordination comes for free (Isenman and Rothman, 1979a).

No doubt many will still find the conventional model with its focus on a higher-level organization---movement through a sub-cellular architecture easily seen as geared towards the goal of getting digestive enzyme to the gut---the simpler and more compelling theory. The preconceptions that support the Vesicular Sequestration/Exocytosis model are culturally dominant, although weakening somewhat. Because of these presuppositions and/or evidence that is salient to them, some will perceive anomalous findings and theoretical complications such as those mentioned above as puzzles rather than problems. Indeed the Equilibrium Model is not free of puzzles either.

The different digestive enzymes secreted into the gut cut most readily between different specific kinds of bonds in the food we eat. For example, the various digestive enzymes that break down proteins prefer to snip between specific types of amino acids. In this way they help determine what we assimilate and what we let go by. Likewise preconceptions are an underlying component of mental digestion. They help fractionate the overabundance of potential experience into mental food via their influence on attention, and this is true for scientists as well as everyone else. In conjunction with implicit as well as explicit observations, thematic preconceptions that may remain largely unconscious guide experimental programs, determine whether anomalous findings falsify generally accepted theories, and help shape alternative models.

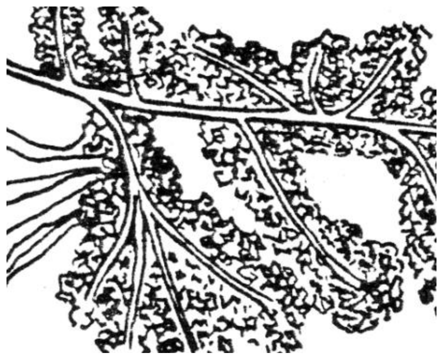
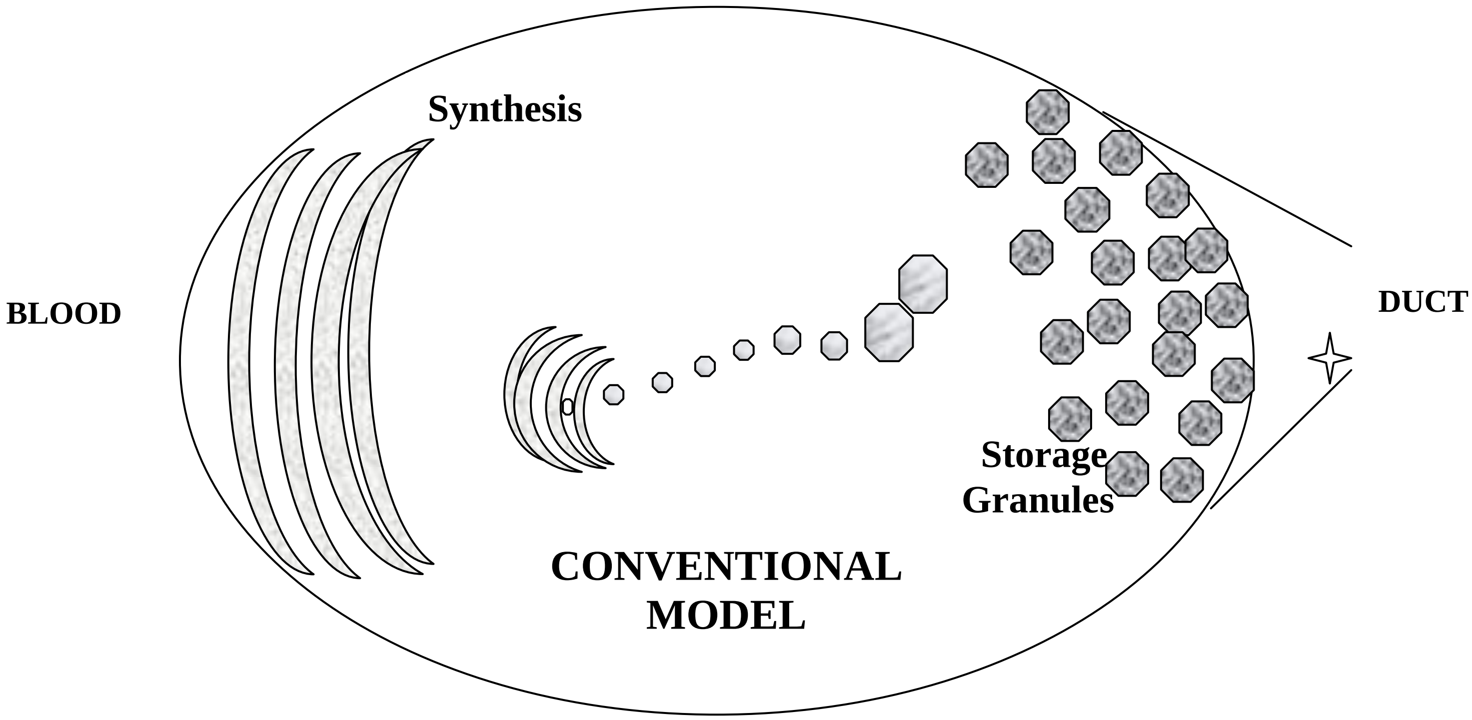
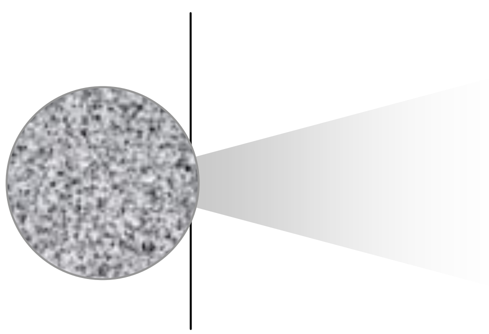


Fig 1 Pancreatic tissue (rabbit): The duct system breaks down into smaller and smaller branches. A terminal branch of the duct system shares a membrane with the secretory region of each cell.



TRANSPORT: After synthesis, digestive enzymes move via controlled fusion through a fixed sequence of vesicles to the duct-facing side of the cell.



SECRETION: An opening between the storage granule and duct membrane allows all digestive enzymes to leave the granule without having actually crossed either membrane.

Fig 2 Vesicular Sequestration/Exocytosis Model for the transport and secretion of pancreatic digestive enzymes.

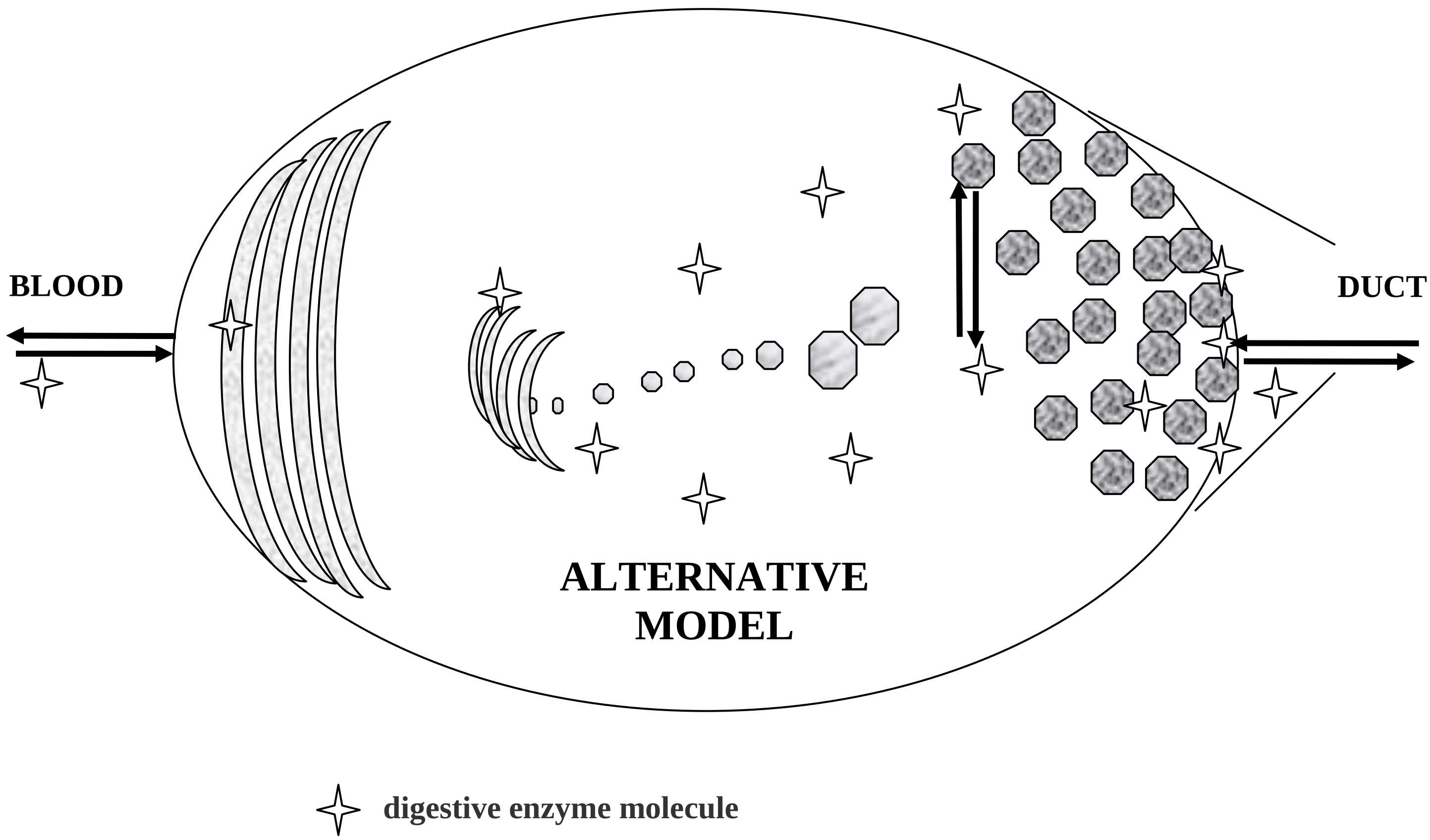


Fig 3 Equilibrium Model for the transport and secretion of pancreatic digestive enzymes. A soluble pool of digestive enzymes exists in the cytosol, or cell sap. Digestive enzymes can move individually molecule by molecule in both directions through the zymogen granule membrane, the duct-facing membrane, and the blood-facing membrane of the cell.

References

Bargh, J.A. & Ferguson, A.J. (2000). Beyond behaviorism: On the automaticity of higher mental processes. *Psychological Bulletin, 6,* 925-945

Bargh, J.A. (Ed.) (2006). Social Psychology and the Unconscious: The Automaticity of Higher Mental Processes. (New York: Psychology Press)

Bechara, A., Damasio, H., Tranel, D., & Damasio, A.R. (1997). Deciding advantageously before knowing the advantageous strategy. *Science, 275,* 1293-1295

Bendayan, M., Roth, J., Perrelet, A., & Orci, L. (1980). Pancreatic secretory proteins in subcellular compartments of the rat acinar cell. *Journal of Histochemistry and Cytochemistry, 28,* 149-160

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

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

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

French R.M., & Cleeremans, A. (Eds.) (2002). *Implicit learning and consciousness.* (New York: Psychology Press)

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

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

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. (2009). Digestive enzyme secretion, intuition, and the history of science: Part II. *Foundations of Science, 14,* DOI 10.1007/s10699-009-9163-1

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

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

Kuhn, T.S. (1970). *The structure of scientific revolution*. (Chicago, University of Chicago Press)

Kuhn, T.S. (1977). *The essential tension. Selected studies in scientific tradition and change,* (Chicago: University of Chicago Press)

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)

Metcalfe, J. (2000). Feelings and judgments of knowing. *Consciousness and Cognition 9,* 179-186

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

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

Polanyi, M. (1969). The creative imagination. *Psychological Issues,* 6, 53-70

Popper, K.R. (1959). *The logic of scientific discovery.* (New York: Basic Books)

Popper, K.R. (1963). *Conjectures and refutations.* (New York: Basic Books)

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

Rothman, S.S. (2007). The incoherence of the vesicular theory of proteins secretion. *Journal of Theoretical Biology, 245,* 150-160

Singer, S.J. & Nicolson, G.L (1972). The fluid mosaic model of the structure of cell membranes," *Science, 175*, 720-731

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