Journal of the History of Biology **35:** 149–172, 2002.
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To Err and Win a Nobel Prize: Paul Boyer, ATP Synthase and the Emergence of Bioenergetics

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Abstract. Paul Boyer shared a Nobel Prize in 1997 for his work on the mechanism of ATP synthase. His earlier work, though (which contributed indirectly to his triumph), included major errors, both experimental and theoretical. Two benchmark cases offer insight into how scientists err and how they deal with error. Boyer's work also parallels and illustrates the emergence of bioenergetics in the second half of the twentieth century, rivaling achievements in evolution and molecular biology.

Keywords: ATP synthase, bioenergetics, conformational hypothesis, error, oxidative phosphorylation, Paul Boyer, phosphohistidine

> Most of our accomplishments [in science] are the coal we mine while looking for diamonds.
>
> – Paul D. Boyer (1981, p. 232)

Introduction

Error – and recovering from error – is integral to science.[1] Nobel Prize winners are no exception.[2] Stories of error in science, however, usually focus on fraud, blatant incompetence or lapses from methodological norms. They are typically used popularly to reinforce (or challenge) the authority of science, often with a tone of amusement and/or embarassment.[3] But

[1] Darden, 1991; Allchin, 2000a, 2001. By 'error', I mean any type of mistake, from a minor experimental oversight to a major theoretical misconception or mistaken assumption, that misrepresents the phenomena being investigated. Error becomes manifest as further labor, where researchers "undo" or redo scientific *work*, whether experimental practice or theoretical reasoning (Star and Gerson, 1986). (For a typology of error, see Allchin, 2001.) In describing science (or any process of discovery) as trial and error, one inevitably expects error.

[2] Darden, 1998; Allchin, 2000a.

[3] E.g., Rousseau, 1992. The alternative, historicist method of "reverse whiggism," applied here, is articulated in Allchin (1994b, pp. 633–635; 1997, pp. 111–114).

such anecdotes reveal little about the pervasive error that results even with appropriate methodology. Moreover, they fail to capture how scientists first encounter, then characterize and remedy error. For a complete understanding, one must trace the eventual fate of discordant results and anomalies, not retrospectively as errors, but prospectively as (sometimes negative) discoveries. Here, I consider Paul Boyer, who shared the 1997 Nobel Prize in Chemistry. I focus in particular on two prominent errors in Boyer's early research on cell metabolism, using publications from 1963 and 1977 as historical benchmarks. They illustrate how a scientist can recover from error, while also deepening scientific knowledge.

Boyer's two errors, ironically perhaps, also illustrate important developments in cell metabolism. Historians of twentieth-century biology have, for the most part, neglected metabolism, focusing instead on genetics, evolution and molecular biology. One might well imagine that life is no more than genes and that biologists could not see beyond DNA. However, during the past century biologists also unraveled the mysteries of how cells process the energy that fuels life. Without energy, DNA replication and protein synthesis, for example, would cease. So, too, would sense perception, nerve signaling, hormone secretion and muscle contraction. Cells cannot function without the unit molecule of energy transfer, adenosine triphosphate – or, more simply, *ATP*. For many cell biologists and biochemists, ATP – not DNA – is "the secret of life."[4] Last century, Nobel prizes marked as many achievements in metabolism as in genetics. Boyer's was the most recent. Boyer's career, in fact, by neatly spanning the second half of the century, nicely parallels the broader history. This period is noteworthy for the development of *bioenergetics*, a new field of study that incorporated elements of biochemistry, biophysics, molecular biology and cell biology.[5] Thus, while I hope my narrative, on the one hand, deepens understanding of the general dynamics of error and scientific change, I hope also to convey episodically the emergence of bioenergetics, a major event of 20th-century biology. The larger history should both: (a) contribute to a more complete and balanced history

[4] Wang, 1973, p. 749.

[5] By "field of study," I mean here no more than a focus of cohesive research practice. That is, I do not intend to engage the extensive sociological and historiographic literature on "fields." Nevertheless, I should underscore that bioenergetics recombined elements from several well established and relatively independent fields. During this period researchers recognized that the domains of these relatively independent fields were in fact intimately connected and thus that they needed a new amalgam of expertise. This new linkage of domains and economy of expertise (reflected sociologically in patterns of communication and institutional affiliations) I am calling, for want of a better term, a "field" (echoing Boyer's [1998] Nobel lecture).

of biology, and (b) help dramatize the importance of error and recovery from error in substantive scientific achievement.

Paul Boyer, the central figure in my episodes, brought remarkable energy and frankness to his science. Born in Provo, Utah, in 1918, he was the fourth of seven children in a lineage of "hardy Mormon pioneer stock." He drifted from the religious ideas of his upbringing, yet credits the Mormon value on education for leading him into "warm social and excellent learning experiences" in high school and college. In the spirit of his family, Boyer also became "a confirmed do-it-yourselfer." With his wife he helped build two of their own homes, working as architect, contractor, plumber, electrician and finish carpenter. With similar vigor he founded the Molecular Biology Institute at UCLA in 1965 and guided dozens of graduate students over several decades. While a hard worker, Boyer has always warmly acknowledged the work of his colleagues and students. In opening his Nobel lecture, for example, he noted his "good fortune to be a spokesman for a considerable number of outstanding researchers in the field of bioenergetics."[6] Below, I hope to echo this sentiment by indicating how Boyer's benchmark errors (and the contributions that emerged from working through them) reflected larger scale developments.

Boyer devoted his career to understanding how enzymes work. Having graduating from Bringham Young University in 1939, he married and went on to graduate school in the Biochemistry Department at the University of Wisconsin. There his advisor encouraged him to pursue enzymology. He also learned about enzymes that produce ATP. In his doctoral thesis in 1943 Boyer profiled one of these, the first enzyme recognized as needing a monovalent cation [pyruvate kinase, using K^+]. After a brief foray at Stanford, Boyer joined the faculty at the University of Minnesota (in 1946), where he remained for seventeen years. While there, he learned from A. O. Nier, a developer of mass spectrometry, the "cumbersome" techniques for assaying with radioactive isotopes. Later, Boyer's most noteworthy discoveries would capitalize on these skills.[7]

In the mid-1950s, Boyer's experimental interests began to include an enzyme in the mitochondrial membrane, *ATP synthase* [then called ATPase]. Although this enzyme catalyzes an ostensibly simply reaction – forming ATP by adding a phosphate to ADP [adenosine *di*phosphate] – few enzymes could be more important. By re-energizing ATP, it is the very hub of the cell's energy pathways. Boyer studied many enzymes, but ATP synthase was certainly the most noteworthy and, ultimately, the occasion for his Nobel award. Boyer joined other biochemists who were trying to determine the final

[6] Boyer, 1981, pp. 230–234; 1998, p. 2297.
[7] Ibid.

series of energy transformations that lead to ATP: *oxidative phosphorylation* – or, in jargon familiar to biochemists, *ox phos*.[8] The problem had taken

[8] *Oxidative phosphorylation* is perhaps the central series of energy reactions in the cell, which occur in the mitochondrion, a membrane-bound organelle. "Oxidative" refers to the use of oxygen by the electron transport chain in channeling energy: this process is why we breathe oxygen. "Phosphorylation" refers to the use of this energy to add a phosphate to ADP to generate ATP. ATP is how energy becomes generally accessible in cells.

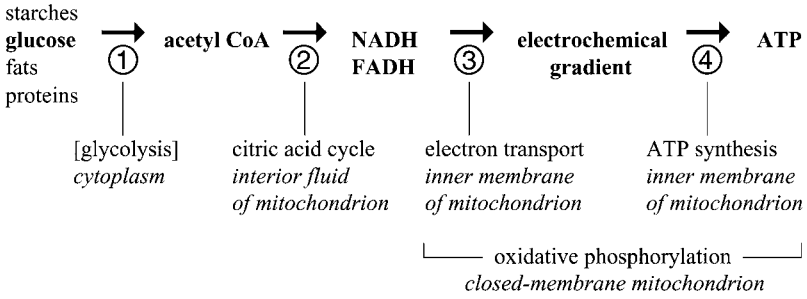

Figure A. Overview of the central energy pathway from food (*left*) to the unit of energy transfer in the cell, adenosine triphosphate, ATP (*right*). Major energy intermediates are shown in **bold**. For simplicity, many molecules involved in the reactions, such as oxygen (electron acceptor in ③), carbon dioxide (waste product in ① and ②) and phosphate (added in ④), are not shown. The form of energy varies: acetyl CoA stores energy as chemical (bond) energy, NADH and FADH as high-energy electrons, the electrochemical gradient as a pH difference (or proton potential) across a membrane, and ATP as a molecular potential (often called a "high-energy phosphate bond"). The major processes are labeled numerically; their location is given in *italics*.

Ox phos is the last process in the harvesting of food energy (Figure A). Energy is transferred along various pathways of chemical breakdown. Sugars, starches, proteins and fats are fragmented to a 2-carbon molecule, *acetyl CoA*. In many cases, this partial breakdown energizes some ATP formation directly. Acetyl CoA is then carried into the mitochondrion. Inside, a series of reactions, known as the *citric acid cycle* (also called the *Krebs cycle*), channels energy into high-energy electrons attached to two complex molecules, *NAD* (NADH) and *FAD* (FADH). The food has now been completely broken down, leaving just carbon dioxide, the familiar waste product that we exhale. The high-energy electrons of NAD and FAD release their energy stepwise via components embedded in the inner mitochondrial membrane, the *electron transport chain*. As the electrons move from molecule to molecule, they cascade down energy levels, simultaneously fueling the translocation of protons across the membrane. Eventually, the electrons join with oxygen to form water. (This is the "oxidative" part of oxidative phosphorylation.) The energy release of electron transport is ultimately *coupled* to the energized synthesis of ATP. A variety of chemicals, known appropriately as *uncouplers*, can interfere with this transfer. As a result of electron transport, energy has been stored as an electrochemical *proton gradient* across the mitochondrial membrane: an energetic imbalance of protons (alternatively viewed as hydrogen ions), measurable as a pH difference. This *chemiosmotic* gradient does not fit the image of energy as chemical bonds – and so proved exceptionally difficult to decipher historically. Describing the role of this intermediate energy state earned Peter Mitchell the Nobel Prize in 1978 (see Prebble, 2001). Finally, protons flow

center stage in enzyme biochemistry. But deciphering ox phos was proving as difficult as it was important. "Nature does not design her systems to make it easy for us to discover how they work," Boyer noted in retrospect.[9] Successive failures only seemed to amplify the importance of a solution for ox phos. A spirit of competition reigned. Thus it was in a highly charged atmosphere that Boyer published his first major error.

(*N.B.*: Readers not familiar with cell metabolism or biochemistry will find scientific background *in footnotes* throughout. See especially *note 8* above for a general introduction. This information is also available in current standard introductory college biology texts. Technical details included for completeness are found *in brackets* and are not essential to the central story for the general reader.)

Phosphohistidine, 1963

In 1963 Paul Boyer published an article in *Science* on "Phosphohistidine" – my first historical benchmark. The modest one-word title hardly hinted at the significance of his claim. For a decade biochemists had been trying to ascertain how energy from the electron transport chain is coupled to ATP synthesis. Envisioning a simple pathway of chemical reactions, they sought to isolate and identify the key compounds along the way: the hypothesized high-energy intermediate(s) of oxidative phosphorylation. Already, eight intermediates had been proposed. Each in turn proved to be experimental artifact.[10] The failure to identify the high-energy intermediates, the prime target of research, was notorious in the field. Boyer himself lamented on "the extreme lability of the phosphorylation reactions."[11] In electing to tackle the challenge, Boyer hoped to capitalize on his special skills with radioactive isotopes. Successfully so, it seemed: Boyer had apparently cracked the central problem of ox phos. He claimed that phosphohistidine was the long sought intermediate. Moreover, he described it in an *in vitro* system, free from the mitochondrial

naturally down the energy gradient, passing through the enzyme *ATP synthase* and completing a circuit across the membrane. ATP is formed by adding a phosphate to ADP and the energy from the proton flow is transferred indirectly to the energy of ATP. (This is the "phosphorylation" part of oxidative phosphorylation.) Boyer earned the Nobel prize for elucidating the complex mechanism of ATP synthase during this last step.

[9] Boyer, 1981, p. 233.

[10] Allchin, 1997. Today, biochemists would say that these chemical intermediates do not exist. Instead, the chemiosmotic membrane gradient fills the role of intermediate energy state (see Figure A, note 8). This possibility was beyond the conceptual horizon of most biochemists at the time, however.

[11] Boyer, 1963, p. 1147.

membrane, adding the prospect of greatly facilitating further experimental work.[12]

Evidence for Boyer's proposal had emerged in his lab over the previous two years. He relied on a phenomenon that would become central to his work throughout the following decades. Namely, one can track radioactively labeled atoms exchanged between molecules in a reaction. Analysis of these *exchange reactions*, as they are called, allows chemists to probe unknown reactants and products of known, but incompletely characterized reactions. Boyer had labeled inorganic phosphate (P_i^{32}). He anticipated that it would form a high-energy bond with some yet undetected ox-phos intermediate. Boyer's group fortunately found a protein that indeed bound to phosphate. They were then skilled enough to isolate it and characterize it chemically. They further showed that the newly isolated compound filled several functions of an intermediate. For example, the labeled phosphate could be further exchanged with ATP (ATP^{32}), indicating that the compound transferred its phosphate to ATP. Further, as noted above, the enzyme reaction was isolated in solution, independent of the membrane-bound electron transport chain. Through a strategy of blind search and selection Boyer and his lab had discovered, then identified and tested, phosphohistidine.[13]

Boyer's reputation certainly buoyed his claim. In particular, he had developed expertise with the technically demanding radioactive tracers. This had enabled several small but significant findings on ATP synthesis [discovering the $P_i \rightleftharpoons ATP$ exchange in 1954, and identifying phosphate as the source of water in ATP dehydration in 1958]. Other biochemists respected Boyer's experimental work, as expressed in the 1955 American Chemical Society Award in Enzyme Chemistry. Boyer also earned credibility through a small textbook, *The Enzymes* (1959). The second edition appeared, coincidentally, the same year as his phosphohistidine paper.

Despite Boyer's stature, the failures of earlier pronouncements on ox-phos intermediates had significantly raised standards of proof. Hence, before publishing, anyone implicitly needed to check for and rule out certain past mistakes, experimental as well as conceptual. That is, biochemists were

[12] Both the electron transport chain and ATP synthase are embedded in the mitochondrial membrane, whereas the citric acid cycle and earlier steps in energy processing occur in solution (see note 8). The chemistries are quite different: membranes are basically composed of lipids (oil-like molecules), while the internal medium is primarily water. As the saying goes, oil and water do not mix. Chemists were adept at working with aqueous ("soluble") systems, but unsuccessful in extracting membrane-bound enzymes and reconstituting them *in vitro*. Here, Boyer's method for isolating an intermediate and its enzyme in a soluble enzyme system – free from such troubles – would be greatly prized for experimental reasons.

[13] Suelter et al., 1961; Boyer et al., 1962; Peter and Boyer, 1963; Peter et al., 1963.

developing an *error repertoire*.[14] Boyer filled an impressive seven pages in *Science*, addressing many, by then, standard concerns. For example, he showed that the energy balance was reasonable, decreasing the likelihood that energy entered from some undocumented source.[15] All the cross-checks deepened the warrant of the initial inferences. Ultimately, exemplifying a common rethorical style of science, Boyer hedged his many claims about "convincing evidence." "Interpretations and projections ... must remain tenuous," he cautioned.[16] Disclaimers notwithstanding, the implications were not lost on any informed reader. Boyer's careful, detailed exposition, his strong suggestiveness and the prestige of *Science* all concurred: phosphohistidine was the elusive intermediate – or so it seemed. Moreover, Boyer seemed to have surmounted the technical problem of isolating the enzymes, which had hitherto stymied investigations. Biochemists were primed to celebrate. One might well have imagined that the achievement here would surely garner Boyer a Nobel prize.

The triumph of phosphohistidine as the recalcitrant high-energy intermediate was short-lived, however. "I was wrong," Boyer put it bluntly in 1981.[17] One of Boyer's students, Larry Butler, noted that the results were unusually sensitive to the amount of succinate, a molecule in the citric acid, or Krebs, cycle (not ox-phos). They needed to reevaluate Boyer's claim. The experiments had not adequately discriminated between reactions in the internal fluid (where the citric acid cycle occurs) and those embedded in the inner membrane (where ox phos occurs). With further fractionation, Boyer's lab found the earlier interpretation mistaken. Butler and two other post-docs, Gunther Kriel and Robert Mitchell, traced the histidine to a part of an enzyme, succinyl CoA synthetase, that transfers energy from succinate, one of the substrates of the citric acid cycle.[18] Kriel soon found phosphohistidine in *E. coli*, as well.[19] Bacteria have no mitochondria, however, and hence no ox-phos reactions. But they do share the same succinate reactions. This helped confirm the origin of the phosphohistidine "signal." Phosphohistidine was not part of ox phos, after all, but other energy reactions in the cell. Boyer's lab had indeed discovered something, albeit not the prestigious high-energy intermediate of ox phos. The resulting disappointment was not just personal.

[14] Mayo, 1996, pp. 5, 18, 452.

[15] Other possible errors that Boyer addressed included: theories of bonding mechanisms, data on inhibitors and uncouplers, exchange reactions and the relative rates of reactions they indicated.

[16] Boyer, 1963, pp. 1153, 1147.

[17] Boyer, 1981, p. 233.

[18] Mitchell, Butler and Boyer, 1964; Bieber and Boyer, 1966; Boyer, 1981.

[19] Kriel and Boyer, 1964.

The lost hopes cascaded through the ox-phos community. Subsequent reports of the error in reviews conveyed a tone of mourning.

How had Boyer erred in 1963? Simply put, he missed a critical control. He thereby misframed his observation of the intended phenomenon. That is, he was able to mistake other mitochondrial reactions involving ATP for ox phos. He needed an additional separation process to resolve the inherent uncertainty and to securely attribute the results to ox phos specifically. This was certainly not clear at the outset (the error was not due merely to lack of experimental expertise). Boyer's lab only *noticed* the possible alternative with further (and in this case, somewhat "chance") observation. *Ascertaining* the error then involved further experimental work. Errors, too, must be confirmed.[20] In the end, while Boyer had erred, he also detected and isolated the mistake: one more error for the error repertoire, at least. Indeed, Boyer had caught a similar, even if less severe error earlier in the same phosphate-labeling search when he "discovered" – or rather, rediscovered – another substrate [carbamyl phosphate].[21]

Some results, one might claim, should surely have alerted Boyer earlier. [For example, in retrospect, an informed biochemist might note that Boyer himself reported that the exchange reactions were not sensitive to uncouplers or inhibitors, as one might have expected in context. The apparent need to adjust well established P/O ratios was puzzling, as well.[22]] One might well be tempted to imagine that Boyer just missed obvious signals of his error. In this case, however, the status of several anomalous results depended on perspective. Boyer could easily accommodate the observations by modestly varying standard explanations. Striving to make sense of all the incomplete results, Boyer certainly exercised judgment. But Boyer's interpretation was not methodologically flawed. Like any scientist, he could not escape all potential error.

Yet Boyer did exhibit an important, perhaps underappreciated element of scientific practice: finding the error and then recovering from it. Here, detection emerged from a combination of chance and effort to amplify the initial findings. Further interaction with the experimental system exposed an unusual aspect of the pattern they had already documented. Boyer perceived how all the results could fit another pattern, or explanatory scheme, and then collected additional data to show how the phenomenon fit one and not the other. He had to both recognize the oddity as significant and be able to imagine and appreciate an alternative explanation. Boyer demonstrated these skills again several years later in helping to expose the error in another

[20] Allchin, 2000b.

[21] Boyer, 1963, p. 1147; 1981, p. 233.

[22] Peter and Boyer, 1963; Boyer, 1963, p. 1152.

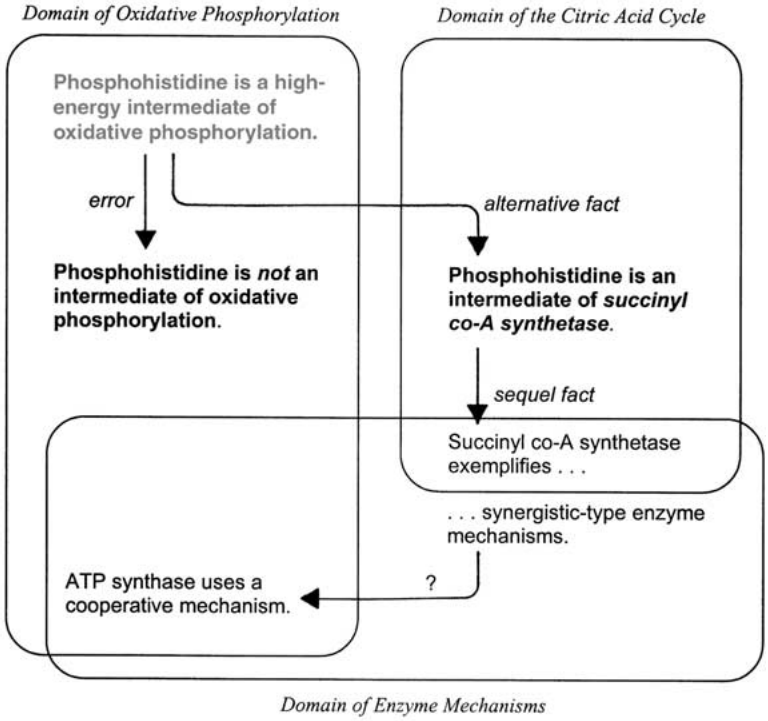

Figure 1. The ultimate status of Boyer's 1963 discovery of phosphohistidine depended on what domain was relevant. First, in the prominent domain of ox phos, it was an error: it was not the long-sought high-energy intermediate. At the same time, however, in the domain of the citric acid cycle, it was an important new fact: phosphohistidine *was* an intermediate of succinyl CoA synthetase. Moreover, it exemplified an enzyme mechanism suggestive of how ATP synthase works.

intermediate claim – this time, more happily for him, from someone else's lab.[23]

Profiling phosphohistidine as error conveys only half the story, however. Boyer's error in ox phos constituted a discovery in another domain of phenomena. Granted, phosphohistidine did not participate in ox phos. From the perspective of that domain, it was an artifact – namely, an unintended consequence of the lab procedure not related to what was being studied, but which could be mistaken as such. Phosphohistidine did participate, however, in synthesizing ATP directly from the citric acid cycle. In this other domain, phosphohistidine was a discovery: a new fact, not an artifact.

Moreover, Boyer introduced a method for isolating and studying its enzyme experimentally. The lab later found that the mere presence of

[23] Cross and Boyer, 1973; Allchin, 1997, pp. 99–101.

different reactants promoted the reactions of others [substrate synergism].[24] This, in turn, indicated how multisubstrate enzymes might work – as Boyer himself would later appreciate (see below). Further results also indicated another aspect of how enzymes work: the substrates induced a change in the shape, or *conformation*, of the enzyme. This result fit comfortably with emerging conceptions of enzyme function. It, too, would be particularly relevant in Boyer's ensuing work. Phosphohistidine, paradoxically perhaps, was *both* an error in one domain and a substantive ("positive") contribution in another (Figure 1).[25]

Boyer's encounter with phosphohistidine (my first historical benchmark) reflected the efforts of the cellular chemistry community more broadly. Boyer was not the first – nor the last – to propose a high-energy intermediate. No claim was ever fully substantiated, however. Textbooks can report now that such intermediates do not exist. Still, the search for them spanned two decades. They ranked high on the research agenda of the major contributors in the field in the 1950s and 60s, which included Britton Chance, Lars Ernster, David Green, Efraim Racker and E.C. Slater. Boyer's case exemplifies how biochemists nevertheless accumulated knowledge piecemeal in local contexts without solving the central problem. In 1963, the study of energy in the cell needed a persuasive large-scale framework for organizing – or perhaps reorganizing – its fragmentary facts and for guiding research into fruitful new areas.

The Conformational Hypothesis of Ox-Phos, 1977

New theoretical frameworks for ox phos emerged in the early and mid-1960s, provoking a contentious debate that brewed for more than a decade.[26] Boyer himself proposed and promoted a major new hypothesis, although ultimately not accepted as fully correct. One early version appeared in 1965. He profiled his new concept of ox phos most prominently, however, in a 1977 review – my second historical benchmark error.[27] Biochemists already knew that the shape, or *conformation*, of a protein altered when energized.[28] Then,

[24] Bridger, Millen and Boyer, 1968.

[25] Also see Allchin, 1997, pp. 104–106.

[26] Allchin, 1990, 1992, 1994a, 1996, 1997.

[27] Boyer, 1965, 1974, 1977.

[28] The original conception of enzyme function was described as "lock and key:" the surface "geography" of the protein provided a specific shape (lock) that fit the substrates (key), thereby catalyzing the reaction between them. Biochemists later found that the conformation (that is, shape) of proteins, such as hemoglobin, actually changed, leading them to a conception of "induced fit." A change in protein shape, associated with a shift in energy level, would actively

somewhat like a wound spring, it released its energy again as it reverted to its original state. Boyer conceived that the conformational energy might be transferred from one protein to another by direct contact. Thus, he proposed, the energy of the electron transport proteins might be channeled to ATP synthase through *conformational coupling*, rather than through successive chemical reactions.[29] The induced conformational change of ATP synthase would fuel ATP synthesis. This concept, Boyer noted, was "not a logical consequence of the chemistry and biochemistry which has given us a splendid understanding of many chemical events on energy metabolism."[30] Rather, it involved thinking about protein structure. This was why, Boyer presumed, it had escaped the notice of earlier biochemists: in tracing reaction pathways, they had largely treated enzymes as black boxes. Boyer's earlier findings on succinyl CoA synthetase, while not introducing the conformational view to Boyer, certainly gave it additional currency. Work arising from the phosphohistidine error, then, likely contributed indirectly to Boyer's major reconceptualization of ox phos.

In advocating the new conformational hypothesis of ox-phos coupling, Boyer's theoretical orientation had shifted dramatically from what had motivated and shaped his phosphohistidine research. For example, Boyer now acknowledged that the membrane housing the electron transport chain and ATP synthase was critical, whereas in 1963 he had pined about being encumbered by "the diffusion barriers and complexity of the mitochondria."[31] In its new role, the membrane would stabilize the "interlocking protein matrix." Boyer could also now explain an additional fact, why physical membrane damage and certain chemicals could disrupt energy transfer: they would destroy the sensitive structural arrangement of the proteins.[32] An experimental nuisance – the membrane – became transformed into a relevant theoretical concept. Boyer profiled the conformational hypothesis as an alternative that could remedy the errors of the *chemical coupling hypothesis* he himself had once endorsed. Ironcially perhaps, he had shifted from one error to another.

The conformational hypothesis explained many results and guided further investigation of ATP formation. One new result, in particular, shaped Boyer's

help cleave substrate molecules nestled in the surface or possibly bring two substrates closer together to react. A standard example of conformational change is the ATP-induced movement of myosin, through which muscles contract. Boyer would expand this concept by considering how two proteins might interact directly with each other through conformational change.

[29] Conformational coupling was an alternative to chemical coupling. Now, both these conceptions have given way to chemiosmotic coupling, as described in note 8.

[30] Boyer, 1977, p. 957.

[31] Boyer 1963, p. 1147.

[32] Boyer, 1974, pp. 289, 293.

thinking about the conformational hypothesis. Using an exchange reaction transferring labeled oxygen between phosphate and water, Boyer's lab discovered that ATP could form at the enzyme's catalytic site even when no energy was transferred [in the presence of uncouplers].[33] That is, the "high-energy" phosphate bond of ATP could form without energy input at all. Contrary to all precedent, bond formation was not the energy-requiring step. How, then, was the bond formed? – And how was the energy from ox-phos used? According to Boyer, energy was used to release ATP, already formed, from the enzyme. Further, he noted that it was "difficult to imagine a simple mechanism other than change in protein conformation to cause the release of tightly-bound ATP."[34] Conformational change now seemed intimately linked to the energy-requiring step of ATP synthase. Boyer's claim about the enzyme's unusual mechanism would hold, of course, only if no one had erred interpreting the results experimentally. Here, unlike the phosphohistidine case, Boyer's lab work withstood the scrutiny prompted by such a provocative conclusion.

Boyer presented his hypothesis from a position of some authority. The phosphohistidine episode, for example, had not damaged his credibility at all. Indeed, Boyer's stature had grown as he adopted many leadership roles. As Director of the Molecular Biology Institute at the University of California at Berkeley, he secured funding for a major new research building, which opened in 1977. He had edited the *Annual Review of Biochemistry* from 1965 to 1971, then served as Associate Editor (a role he filled through 1988). Since 1969 he had also edited *Biochemical and Biophysical Research Communications* (and would do so for two more years). Boyer had been elected to the National Academy of Science. And he admitted exercising his privilege there to publish a key paper on the conformational hypothesis after another journal had rejected it.[35]

Still, Boyer's hypothesis was ultimately not adopted. In the next few years it, too, was gently set aside as error: why? Boyer's 1977 paper was part of a remarkable multi-authored review by six major contributors in the field, representing all perspectives in the controversy that had raged now for over a decade. In retrospect, the review became a convenient landmark for the closing of the debate (though some personal animosities and conceptual dissent certainly lingered). The authors each recognized that the intermediate energy state of ox phos was a proton gradient, as first proposed by Peter Mitchell in 1961 and dubbed the "chemiosmotic hypothesis." The electron transport chain drives protons (hydrogen ions) across the mito-

[33] Boyer, Cross and Momsen, 1973; Boyer 1974, p. 292; 1977, p. 962.
[34] Boyer, 1974, pp. 291, 292.
[35] Boyer, Cross and Momsen, 1973; Boyer, 1981, p. 235.

chondrial membrane. Later, they move back across the membrane, down their concentration gradient, fueling the phosphorylation of ATP. Mitchell received the Nobel prize the following year, in 1978, ostensibly validating the reviewers' somewhat shaky consensus. The central coupling in ox phos was not a high-energy chemical intermediate, as proposed by E. C. Slater in 1953 and pursued by Boyer through the early 1960s. Nor was it a conformational change, as advocated by Boyer through the mid-1970s.

While Boyer erred, his claims were not wholly invalidated. Again, mapping the history in terms of a single outcome or lineage is misleading.[36] Boyer erred in seeing – and promoting – his conclusions about the ATP enzyme as applying to the whole energy-coupling process. Ultimately, they accurately described only the very last step, the enzymatic mechanism of ATP synthesis. That is, their domain (scope) became qualified – and significantly narrowed. Boyer had already (in 1975) entertained a role for protons in conformational change. Eventually he would incorporate them fully into his schemes. In 1977, however, he refrained from giving protons an exclusive or even central role. He framed conformational and chemiosmotic hypotheses as explicit rivals, and portrayed his own ideas as discounting Mitchell's. His posture was that conformational coupling was essential and primary for explaining ox phos as a whole.

Characterizing the conformational hypothesis as error may be somewhat unfair. Boyer clearly eschewed theoretical debate in favor of appraising "specific molecular events."[37] Moreover, Boyer generally regarded theories more as heuristics, or guides to discovery, than as well formed final models. On many occasions he espoused pluralism, urging others to keep alternatives open to enrich experimentation. In many ways, he epitomized one philosophical model of researchers as diffident to top-down theory-testing. Still, the tone of Boyer's 1977 review was strong and he repeatedly aimed to discredit other major hypotheses of ox phos. His bravado in claiming the relevance of conformational concepts to ox phos was perhaps nowhere more evident than in the 1977 review, ironically considered a signal of final acceptance of the chemisomotic hypothesis. Although the review was ostensibly organized to document consensus in the field, it exhibited the strains of a collaboration partly enforced upon fierce competitors. Boyer's contribution was no exception. On the very first page he acknowledged a role for protons. But in the remainder he equivocated. Sometimes he profiled as equally likely the movement of protons within the membrane (as proposed

[36] See Allchin, 1994a, on winner-take-all models of science. Also see Allchin, 1997, "Postscript," on reverse Whiggism.

[37] Boyer, 1977, p. 94.

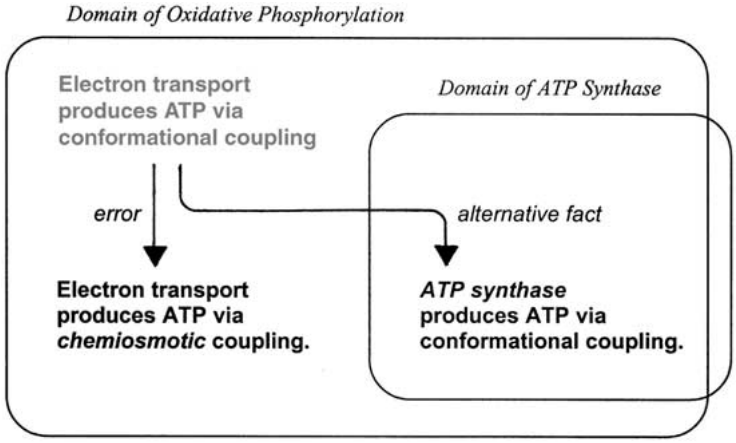

Figure 2. Boyer's conformational hypothesis, like his earlier error, fit two roles. First, in the domain of oxidative phosphorylation, it was an error: electron transport was coupled to ATP synthesis via membrane gradients, as described by the chemiosmotic hypothesis. Still, in a narrower domain, conformational change did explain the mechanism of ATP synthase – the basis of Boyer's 1997 Nobel prize.

by R.J.P. Williams) or his own protein conformational coupling.[38] Elsewhere, he suggested that proton movements were an incidental by-product.[39] He certainly portrayed Mitchell's claims as limited: "evidence must be regarded as mostly consistent, but not proving" the transmembrane potential.[40] Boyer had many sympathizers. Even so, few agreed with him on this grand scale. Boyer's error was thus not so much the local interpretation of the experimental evidence, as the reach of his claims.

How had Boyer erred, here, in 1977? First, he overgeneralized. He gave his conclusions more scope than the evidence could sustain. That is, his broad interpretation of results – appropriate for guiding research, perhaps – was too broad. The sum of local claims about ATP synthesis did not warrant the global claim about ox phos. Ultimately, as Boyer himself would recognize, chemiosmotic concepts did not exclude a role for conformational ones. The two hypotheses could "coexist," once their respective domains were differentiated (see Figure 2).[41]

Of course, Boyer originally rejected chemiosmotic ideas – and vigorously so. One might be inclined to credit the stormy competition of the controversy. After all, everybody in ox phos knew what was at stake. This

[38] Ibid., pp. 958, 960, 961.
[39] Ibid., pp. 959–960.
[40] Ibid., p. 960.
[41] Allchin, 1990, 1994a, 1997, pp. 107–109.

scenario explains possible motivation. At the same time, it does not account for Boyer's specific critcisms, nor why (or how) he would later accept certain chemiosmotic concepts. While Boyer exhibited strong distaste for Mitchell's ideas, his disdain had identifiable scholarly roots.

As noted above, Boyer's interest throughout his mature career was how enzymes work. In particular, how is ATP formed? Ox phos, in many ways, was just background. It reflected only one-third of his publications. Boyer had investigated the mechanisms of other enzymes (such as succinyl CoA synthetase, above). These all became context for later explaining ATP synthase, "one of the most beautiful as well as one of the most unusual and important" enzymes.[42] Boyer's *focal point* in ox-phos research was thus ATP synthase. Like many scientists, he adopted theoretical perspectives and experimental methods as tools. They were lenses and filters to bring a phenomenon into clear focus. These lenses and filters could also leave blindspots and incomplete interpretations. Here, the aims of research also set implicit standards for an appropriate solution. Boyer was quite explicit: "A satisfying explanation of how ATP is made must include a mechanism for synthesis."[43] From Boyer's particular *standpoint*[44] in the experimental landscape, the substantive element in the chemiosmotic hypothesis was how Mitchell explained ATP phosphorylation.[45] (Mitchell's own posture did not help vitiate this perception.) Mitchell had proposed a direct role for protons (hydrogen ions) at the catalytic site. The scheme was ingenious but, Boyer well knew, it did not fit the data on exchange reactions. No wonder, then, that Boyer targeted primarily this flaw in Mitchell's ideas. But when Boyer rejected this particular account,[46] he also tended to dismiss all ideas under the chemiosmotic label. The second element of Boyer's error, then, was inadequately differentiating Mitchell's claims. He did not treat the multiple levels of chemiosmotic concepts independently.[47]

How did Boyer actually recover from his theoretical error? To adopt the general chemiosmotic hypothesis as commensurate with his own approaches, Boyer had first to unravel *Mitchell's* mistakes. This was not easy. Mitchell's

[42] Boyer, 1997, p. 718.

[43] Boyer, 1977, p. 961.

[44] I use this term deliberately, intending to resonate fully with standpoint theory as discussed in various feminist and Marxist critiques of science (e.g., Harding, 1991). I assume that no one can escape a standpoint, although a creative individual might imaginatively adopt and compare alternative standpoints. In particular, philosophers and historians must eschew ideals of transcendental positions in interpreting error and the corresponding discourse among scientists.

[45] E.g., Boyer, 1974, pp. 293–294; 1975.

[46] Boyer, 1977, pp. 961–965.

[47] Weber, 1991.

ideas were complex. Many of them changed. Mitchell was not an articulate spokesman. He asked a slightly different set of questions. He framed problems using different categories.[48] Worse, Mitchell had erred about ATP synthesis. Boyer had to disentangle these errors from his other claims about membrane gradients. (Boyer was hardly alone among his collaegues on this score.) Ultimately, Boyer found, chemiosmotic and conformational concepts were complementary.

Boyer could take in stride the demise of the conformational hypothesis *of ox-phos coupling* (broader scope version). His work had always been primarily experimental and focused keenly on elucidating the mechanism of ATP synthase. In its now more circumscribed domain, the conformational hypothesis *of ATP synthase* was still vividly relevant and still guided research (Figure 2).

By "retreating" to claims with narrower scope, Boyer reflected what he had been doing for decades. Nevertheless, the retreat allowed him to connect his ongoing research with other experimental achievements (in the domain of membrane potentials) that were best interpreted through chemiosmotic models.[49] Boyer gained scientifically by redefining the scope of the conformational hypothesis (from ox phos to ATP synthase). The error, paradoxically perhaps, was not a loss at all.

ATP Synthase, 1997: Marking the Development of Bioenergetics

The fate of Boyer's conformational hypothesis reflects, once again, the larger story of the community investigating energetic processes in the cell. The 1977 multi-authored review, like Boyer's individual contribution to it, documented the ox-phos field finally recovering from a collective theoretical error. Researchers had largely abandoned the notion of high-energy chemical intermediates, as originally profiled by E.C. Slater in 1953.[50] They appreciated more deeply the causal relevance of membranes, gradients and protein structure. They were coming to terms with Mitchell's revolutionary perspective. As a result, formerly isolated areas of study became connected. New channels of discourse opened. Efforts became coordinated in new ways. Institutional changes ensued. The reorganized constellation of ideas, methods and social structures became known as bioenergetics.

[48] In these respects, the ox-phos episode exemplified a clash between incommensurable Kuhnian paradigms (as elaborated in Allchin, 1990, 1992, 1994; also see Weber, forthcoming). Here, I merely highlight narrowly the Kuhnian overtones of how participants in the debate found themselves talking at cross-purposes.

[49] E.g., Boyer, 1997, p. 743.

[50] See Allchin, 1997.

The reorientation from chemical to chemiosmotic frameworks reflected a major problem shift,[51] involving important new investigative strategies and techniques, as well as new concepts. Boyer's error certainly epitomized the extraordinary difficulty of the transition. But Boyer also contributed to the change. Although exchange reactions emerged from a purely "chemical" approach of diagnosing reaction pathways, Boyer applied them in a new way to interpret how enzymes worked. He did not just add another layer of detail. Rather, he added a new relevant dimension, protein conformation, to understanding energy transformations. One and the same method helped lead Boyer into error in 1963 and break new ground in the 1970s.

Boyer's new focus on protein structure marked one important shift in assembling the new field. Other researchers, each working through their own errors, contributed other elements. Efraim Racker, for example, concentrated on reconstructing ox phos *in vitro*. For years, he had tried to extract a system of enzymes in solution, free of membranes. Like Boyer, he too had once proposed a high-energy intermediate.[52] Eventually, adopting chemiosmotic interpretations, he shifted his effort to reconstituting the components of the electron transport chain in small membraned vesicles – with prompt success. From Racker's standpoint,[53] the closed membrane became critical. He showed how each molecular component of ox phos isolated in a membrane vesicle could function independently of the others. Then he constructed a "chimeric" vesicle, demonstrating that even elements taken from divergent evolutionary lineages [ATP synthase from beef heart, membrane lipids from plants, and bacteriorhodopsin from purple-membraned bacteria] could function as an ensemble. These dramatic chimeric vesicles, as a capstone, helped persuade the community of the importance of membrane gradients. Equally important, however, Racker had demonstrated how research could proceed fruitfully with new techniques for artificial *in vitro* systems.[54]

Vladimir Skulachev contributed in yet another way. From his standpoint as an ardent follower of Mitchell, measuring membrane gradients was central. Doing so reliably had proven unexpectedly problematic. Conceptually simple measurements – which might have easily helped pinpoint errors – became mired in confusion. Skulachev developed complex synthetic ions [ionophores, such as tetraphenyl boron and trinitrophenol] that could permeate membranes. The movement of these charged particles – unrelated to any natural enzymatic mechanism – allowed biochemists to measure just the elec-

[51] Kuhn, 1972, pp. 108–110, 141; also see note 48.
[52] See Allchin, 1997.
[53] See note 44.
[54] Allchin, 1996; Weber, forthcoming.

tric potential of the membrane. This cleared the way for basic measurements [calculating energy equilibria, for example].

Peter Mitchell, of course, had introduced the central chemiosmotic concepts. For example, he developed the notion of vectorial chemistry: chemical reactions were not just "scalar" (having magnitude), but also had direction as well, like vectors.[55] Mitchell viewed an ion moving across a membrane as a chemical reaction. Standard chemical equations, for example, could be misleading: they noted only what molecules were involved, not any movement of those molecules in space. In biological systems – particularly with membranes – such movement could be important. In addition, membrane gradients, as a form of energy, could be "part of the equation." Mitchell also developed concepts of "symports" and "antiports" to describe how the movement of different ions could be paired energetically. All these concepts helped link problems of metabolism to problems of membrane transport. Both involved energetic processes, but had previously been investigated by distinct sets of researchers. Mitchell's conceptual scaffolding helped unify once distinct research lineages.[56]

Thus, bioenergetics was pioneered piecemeal by different researchers distributed across newly intersecting fields. Boyer's error on the scope of the conformational hypothesis epitomizes how domains were being reshaped and reorganized. Boyer's work was thus one piece in a grand mosaic, a new conceptual and experimental gestalt. Consolidating all the new strategies and techniques into a coherent approach in the decades following his 1977 benchmark error established bioenergetics as a coherent field of study.

The development of bioenergetics involved redrawing many disciplinary boundaries. The new gestalt was evident in several ways, including new textbooks and journals. For example, the *Journal of Bioenergetics* was founded in 1970. Later, in 1976, exemplifying the scope of the maturing area of study, the title was extended to include "*and Biomembranes*." New textbooks on bioenergetics indicated that the suite of concerns was substantial and prominent enough to warrant teaching on its own. Albert Szent-Györgyi, a 1937 Nobel recipient, used the term to label his 1957 book. It was then echoed in 1965 text titles by both Albert Lehninger and Efraim Racker. These early volumes were specialized and in their revised editions (in 1971 and 1976, respectively), they began to express more fully an appreciation of the complexities of organization and new methods noted above. Later David Nicholls (1982) and Franklin Harold (1986) were able to organize their texts explicitly using chemiosmotic principles. Harold's volume, in particular, made the link to bacterial systems (also treated in an evolutionary monograph

[55] Prebble, 2001.
[56] Ibid.; also Weber, 1991.

by E. Broda in 1985). Finally, Skulachev's 1988 text, *Membrane Bioenergetics*, again marked the new extended focus on membranes. From these, more texts proliferated.

The 1997 Nobel Prize in Chemistry signaled the achievements of bioenergetics as a fully formed field of study (see note 5), just as Mitchell's 1978 award had marked its baptism. Boyer had elucidated several features of ATP synthase in the wake of his 1977 error. For example, he had identified three reaction sites on the enzyme. There were also three distinct steps in ATP synthesis: one bringing ADP and phosphate together, one forming the bond, another (as he had discerned in 1974) releasing ATP from the enzyme. The three steps occurred successively at each site, through conformational changes as the enzyme rotated. Equally importantly, Boyer had linked the rotation to the flow of protons across the mitochondrial membrane. The 1997 award also celebrated collateral achievements by John Walker and Jens Skou. Walker had begun working on ATP synthase only in the wake of the acceptance of Mitchell's concepts. He determined the sequence of the protein and, by collaborating with x-ray crystallographers, its three-dimensional structure. His physical data confirmed Boyer's model, derived biochemically. Walker's inclusion in the prize underscored the centrality, as Boyer had noted in 1977, of protein structure in understanding energetics. Skou, by contrast, did not study ATP synthase at all. Rather, he investigated an enzyme that uses ATP to transport sodium and potassium ions across the cell membrane [Na^+, K^+-ATPase], best known for its role in nerve cells. Coupling recognition of Skou's work to Boyer's, the award citation noted that "both enzymes are bound to membranes in the cell and linked with the transport of ions through these – but for different reasons."[57] In describing Skou's work they also cited other transport enzymes that use ATP. Boyer's, Waler's and Skou's award was thus a vivid emblem of the maturity and fruitfulness of bioenergetics in integrating energy transformations, membranes and protein structure at the end of the century.[58]

The 1997 award also measured the field's distance from 1953, when Fritz Lipmann was honored for discovering the significance of ATP (which he

[57] The Royal Swedish Academy of Sciences, "The 1997 Nobel Prize in Chemistry" [press release], URL: www.nobel.se/chemistry/laureates/1997/press.html (updated June 28, 2000; accessed December 31, 2000).

[58] Saraste (1999) reviewed the status of oxidative phosphorylation at the "*fin de siècle*," noting especially the emerging understanding of how individual components of the electron transport chain generate a proton gradient. In the 1970s Racker had demonstrated membrane gradients using bacteriorhodopsin, a protonmotive pigment in archaebacteria. By 1999, Luecke et al. (1999) could trace the pathway of a single proton through the molecule, from amino acid to amino acid, as it traversed the membrane. Walker's lab had also continued to elucidate how protons powered the ATP "rotor" (Stock, Leslie and Walker, 1999).

characterized simply in terms of an energy-rich phosphate bond) and Hans Krebs for articulating the reactions of the citric acid cycle. That was also the year Boyer first turned to the synthesis of ATP. His subsequent career, punctuated by the benchmarks described above, epitomizes the half-century trajectory of change. His 1963 error with phosphohistidine emerged from a research tradition modeled on the successes of Otto Warburg, Krebs and others. Indeed, in helping to detail the fate of succinate via phosphohistidine Boyer contributed further to that tradition. The scope of the problem of oxidative phosphorylation, however, was unpredictably different. Solving it involved crossing old conceptual, as well as institutional, boundaries. Boyer was not alone in working through his errors. His benchmark error on conformational coupling represented one effort among many to find that new gestalt. Ultimately, it was only one piece of the puzzle. However, it did help sensitize others to the significance of protein structure in understanding energetics. The larger framework of bioenergetics to which this contributed then guided his later successes on ATP synthase. "Most of our accomplishments are the coal we mine while looking for diamonds," Boyer once remarked.[59] If so, then Boyer found, in addition to his errors and their sequelae, a diamond when he elucidated the mechanism of ATP synthase.

Conclusion: Learning from Error

Through a complete micro-history of Boyer's benchmark errors along with the parallel macro-history of the emergence of bioenergetics, I hope to have portrayed a vivid sample of how scientists learn from error. In particular, I hope to have a complete account informed by following the errors through their "remedy" to subsequent findings, rather than by casting them merely as "wasted" effort in a lineage defined by certain later conclusions.[60] In Boyer's cases, two features are prominent.

First, both cases involved *articulating domain*. In this process, a researcher identifies the scope of a concept, interpretation or method. Alternatively, one may say that the investigator probes the extent of phenomena that can be considered "similar" for the sake of reasoning by analogy or via an abstract concept. Articulating domain contrasts with "testing," in the sense that one's primary objective is not merely to accept or reject (or even revise) a given hypothesis or explanation. Rather, the question is about when (or where) it applies. In the case of phosphohistidine, Boyer did not invalidate ("reject") his experimental results. Rather, he learned that they mapped onto

[59] Boyer, 1981, p. 232.

[60] See note 3 on the method of "reverse Whiggism."

a different domain than he originally thought (Figure 1). Domain *shifted*, significantly so. (That is, the methods Boyer outlined in his 1963 paper gave genuine results. But he learned that they should be associated with other experimental results about succinyl CoA synthetase, not ox phos.) In the case of the conformational hypothesis, Boyer learned that the scope of his concept was much narrower than he first postulated (Figure 2). Domain was *reduced*, again significantly so. In both cases, the product was a more informative picture of cell metabolism. In fact, the post-1977 reduction of domain corresponded to accepting Mitchell's chemiosmotic interpretation of the same domain of ox phos (Figure 2, left). Hence, it reflects the history of the field more broadly. The emergence of bioenergetics, as noted above, was about *redrawing* domain boundaries – most notably, to incorporate membranes, gradients and vectorial chemistry as relevant to metabolism.[61] Boyer's cases demonstrate the importance of articulating domains – here, marking the difference between fact and error. Errors in science may also be important occasions whereby researchers recognize a need to define – or, perhaps, redefine – domains.

Second, Boyer's work on the two benchmark errors involved *resolving closely related claims*.[62] Resolution refers to the degree of detail or specificity one achieves. Vague, unresolved results may not differentiate between two alternative conclusions. Error can result, of course, when one is mistaken for the other. Particulars can be critical in separating – that is, "resolving" – apparently similar conclusions or lines of reasoning. In the case of phosphohistidine, Boyer learned to resolve two ATP phosphorylation reactions: one related to the citric acid cycle, the other related to ox phos. Although both occur in mitochondrial cell extracts and both incorporate phosphate when added (etc.), phosphohistidine applies to the first, but not the second. Boyer needed to differentiate them experimentally. He designed an appropriate controlled experiment: parallel conditions differing by one telltale variable. In the case of the conformational change of ATP synthase, Boyer learned to resolve ox phos *temporally* into distinct stages: first, intermediate energy storage, and second, ATP synthesis. Although both steps involve energy that eventually yields ATP, conformational concepts apply to the second, but not the first. Chemiosmotic concepts, by comparison, apply to intermediate energy storage, but not (directly) to ATP synthesis. Boyer also learned to resolve two features of an enzymatic reaction: the formation of a bond and the use of energy. In all precedents, these events occurred together. ATP synthase was a surprise exception. The exchange reaction had revealed experimentally that bond formation sometimes occurred without energy input. Resolution

[61] Allchin, 1992, 1996, 1997.
[62] Allchin, 2000b.

leads to a sharper, more fine-grained picture of the domain of investigation. It may well clarify formerly conflated claims, as Boyer's errors show. Indeed, errors may expose when a concept needs further resolution. They may signal the need to reassess phenomena once regarded as equivalent and to search for means to resolve them experimentally.

Experimental methods are essential for effective resolution. Many major achievements of intermediary metabolism in the last century were fueled by such research tools [such as cell fractionation procedures, techniques to isolate (or "resolve") the individual components of the electron transport chain or the sub-units of ATP synthase, increased resolving power of protein crystallography, etc.]. Walker's sharing the Nobel prize underscores this point. Confirming Boyer's model of ATP synthase required details of the enzyme's three-dimensional structure. One needed to discern the placement of individual atoms. A "fuzzy" image would not suffice. Central to Walker's achievement was an x-ray image with a fine enough *resolution*. Here, image resolution is also an apt analogy for this one dimension of knowledge development.

Through these two processes, then – articulating domains and resolving closely related claims (at least) – scientists may learn from error. Although errors entail further work, they do not necessarily become worthless scientific residue. When probed, errors can guide researchers to deeper knowledge. Errors may be a source of discovery, as they were on at least two occasions for Paul Boyer. So, too, for other biologists in the second half of the twentieth century. In recovering from similar errors they found new ways to configure concepts, methods and institutional boundaries. These changes coalesced into an important new field of study, bioenergetics. Boyer's Nobel Prize can thus mark the significance of learning from error, both individually and collectively.

Acknowledgements

My appreciation to Paul D. Boyer for corresponding, confirming interpretations and clarifying details. The author enjoyed support from a National Endowment for the Humanities summer seminar under the direction of Deborah Mayo (NEH grant #FS-23146).

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