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Conceptual Aspects of Theory Appraisal: Some Biochemical Examples

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Abstract: This paper considers papers on conceptual analysis by Laudan (1981) and Whitt (1989) and relates them to three biochemical episodes: (1) the modern 'biochemical explanation' of acupuncture; (2) the chemio-osmotic hypothesis of oxidative phosphorylation; (3) the theory of the complete digestion of proteins in the gut. The advantages of including philosophical debate in chemical/biochemical undergraduate courses is then discussed.

Keywords: *amino-acids, chemi-osmotic, consiliense, problem solving, teleology, chemical education, biochemical education*.

Introduction

Despite Dirac's famous statement 'A theory with mathematical beauty is more likely to be correct than an ugly one that fits some experimental data' (cited by Hovis/Kragh 1993), conceptual analysis of scientific theories as an aspect of appraisal has received scant attention from philosophers of science. Laudan (1981) made a start, and this was followed by criticism plus an improved (?) model from Whitt (1989).

Laudan (1981) proposed a 'Problem Solving Model' for scientific progress, encapsulating both empirical and conceptual problem solving abilities of theories. The empirical problem solving approach has been criticized elsewhere (Akeroyd 1993), but his approach to conceptual analysis is certainly meritorious. Laudan's four types of conceptual problem characterized for a theory T are:

(1) T is internally inconsistent or contains ambiguous postulates,

(2) T makes assumptions about the world which run counter to other theories or prevailing metaphysical assumptions,

(3) T violates a principle of the research tradition,

(4) T fails to utilize concepts from other, more general, theories to which it should be logically subordinate.

Whitt, in an 'accentuate the positive' approach did not perceive the absence or minimization of problems as evidence of increase of conceptual merit but instead proposed that theories achieve conceptual growth through:

(a) fine tuning of their own concepts,

(b) achievement of *consiliense* (absorbing new facts from another domain),[1]

(c) appropriation (without *ad hoc* enhancement) of the conceptual resources of other domains.

I assume that what Laudan claimed in (2) is virtually equivalent to Whitt's (b) and (c), i.e., that 'other theories' of (2) refers to *unrelated* domains while in (4) 'other theories' refers to the *same* or a *closely related* domain. But Whitt would no doubt claim that her introduction of the Whewellian concept of *consiliense* had resolved this potential ambiguity.

An important modern example of the need for a precise classificatory system has been the absorption (since 1980) of the phenomenon of Eastern acupuncture into Western biochemistry, since evidence has accumulated that the stimulation of peripheral nerve fibres can lead to the release of naturally occurring opiates which then activate brainstem inhibitory nuclei and reduce the intensity of persistent pain (see Chung/Dickenson 1980, Allchin 1996). On Laudan's system this is an example of the solution of an *anomalous empirical problem for Western biochemistry*; on Whitt's it could be the achievement of consiliense only if acupuncture was regarded as being practiced in *another domain*. Is this realistic?

Laudan (1989) rebutted several of Whitt's claims but did not comment on one interesting criticism: In the hypothetical case where a theory achieves Whitt's (c) but its conceptual problem solving ability remains constant under Laudan's terminology (weighted sum of old problems solved minus weighted sum of new problems taken on board = 0) then the fact that old problems have been solved should indicate a measure of conceptual growth. I think an interesting practical example occurred in the development of Peter Mitchell's Chemio-Osmotic Hypothesis 1961-1980.

The Chemio-Osmotic Hypothesis

Food molecules are broken down in the cell into two-carbon fragments and passed on to an oxalo-acetic carrier molecule in the 'Krebs Cycle'. This fragment, in the presence of various enzymes, loses pairs of hydrogen atoms from *adjacent* carbon atoms, adds on a water molecule across the developed double bond, repeats the process, and then eliminates a molecule of *carbon dioxide*. No atmospheric oxygen is involved in attacking the foodstuff molecule. The hydrogen atoms, in the form of protons and associated electrons, are passed down a chain of enzymes known as the ETS (Electron transport System), ultimately reacting with atmospheric oxygen. The whole process releases energy which is then available to perform useful work. If the energy is not immediately required it is used to drive the reaction

$$ADP + P_i \leftrightarrow ATP$$

to the right. (ATP = Adenosine Triose Phosphate, ADP = Adenosine Diose Phosphate, P_i = inorganic phosphate)

In the early theory, by analogy with non-mitochondrial ATP synthesis involving 3-phospho glyceryl dehydrogenase, it was considered that one or more of the reduced enzymes in the ETS react with a *chemical intermediate* to form a high energy compound which then reacts directly with ADP to form ATP:

$$AH_2 + B + C \leftrightarrow A{\sim}C + BH_2$$

$$A{\sim}C + ADP + P_i \leftrightarrow A + C + ATP$$

A *conceptual* problem occurred when these proposed intermediates proved to be elusive. Mitchell's theory dispensed with the need for these intermediates: the energy from the ETS could be used to drive protons across the membrane creating a potential gradient, and later they could flow inwards at another site producing useful work, i.e. ATP synthesis or solute transport. This became known as the *chemio-osmotic hypothesis*. Mitchell (1961) wrote in the concluding philosophical paragraph of his seminal paper in *Nature*:

> In the exact sciences, cause and effect are no more than events linked in a sequence. Biochemists now generally accept the idea that metabolism is the cause of membrane transport. The underlying thesis of the hypothesis put forward here is that if the processes we call metabolism and transport represent events in a sequence, not only can metabolism be the cause of transport but also transport can be the cause of metabolism. Thus, we might be inclined to recognise that transport and metabolism, as usually understood by biochemists, may be conceived advantageously as different aspects of the same process of vectorial metabolism.

Mitchell received a substantial inheritance which allowed him to leave academia and fund a private laboratory in Cornwall, UK. The road of this heroic voyage of discovery has been traced by Robinson (1984). Initial interest was naturally low from established academics, but "by 1975 most investigators in the field had become convinced that Mitchell was right in principle if not in detail". (Malmstrom 1993) Many of Mitchell's initial auxiliary hypotheses had to be modified in the light of experimental results which exposed him to the conceptual argument of introducing *ad hoc* hypotheses, but his overall concept achieved great consiliense. The model applied to plant photo phosphorylation as well as to animal mitochondrial phosphorylation also achieved appropriation. Concepts from physical chemistry known to apply in related domains in the cell (water and solute transport) could be used to elegantly explain other phenomena taking place in a geographically close location.

As Mitchell's flexible model achieved empirical successes, solving problems but exposing itself to new ones, many of the opposition scientists *did* keep a 'score' (see, for example, Racker 1970, 1972) and used a Laudan style accounting methodology outlined above. Others, who switched allegiance, obviously followed a Whitt style accounting methodology, assigning greater weight to the number of recently solved problems as opposed to the number of successor problems. Both groups of scientists were therefore using rational conceptual arguments to justify their theoretical position.

Unfortunately Mitchell's model could not explain *all* the facts satisfactorily and in 1975 he addressed criticism from E.C. Slater over the weakest part of his hypothesis: its relationship with the cytochrome b-c_1 region of the respiratory chain. To do this Mitchell (1975, 1976) appropriated not just concepts from another domain: they were derived from the domain of rival theory! A chemical intermediates 'Q-Cycle' mechanism was proposed, involving alternate hydrogenation and dehydrogenation of quinone, analogous to the Krebs Cycle in involving a 'carrier molecule', *but the carrier molecule was an as yet undetected highly reactive free radical species!* However he made no specific predictions.

Some were impressed by Mitchell's latest essay in inventiveness: Slater just lost interest. Other scientists modified Mitchell's idea and came up with specific predictions. Improving experimental techniques meant that it was possible to detect short-lived free radicals in biological systems, and six years later Slater's group (de Vries et al. 1981) detected the presence of free radicals in the cytochrome *c* region of the respiratory chain.

This recent episode seems to show that scientists do take into account conceptual problems as well as empirical evidence in theory choice, and that the point made by Whitt that if the current score difference between the rivals is zero (or even approximately zero, FMA) then there is an historical element taken into consideration reflecting the number of old problems solved per unit time. In the case of the 'Q-Cycle', although it could be argued that Mitchell's concession to invoking unobserved entities had produced a zero sum situation, it could be also argued that the rival 'Chemical Intermediates' programme had had twenty years to come up with experimental evidence for its conventional proposed molecules which should occur in detectable quantities. Mitchell's proposed intermediate was so unlikely and necessarily occurred in such minute quantities that it was quite natural that conventional chemical analysis had thrown out no evidence for or against its existence. Therefore by Whitt's criteria it still retained a conceptual plus, so the chemio-osmotic hypothesis was still worth pursuing. Obviously on reading Mitchell's papers on the 'Q-Cycle' some scientists followed Laudan's criteria, some followed Whitt's.

The complete digestion of proteins in the gut

A theory which was criticized on Laudan Type (2) conceptual grounds in the 1870's was the theory of the complete digestion of proteins to their constituent amino acids prior to reassembly rather than to intermediate products ('peptones') which were then reconstituted into body protein without any further cleavage. Beef protein contains several sections with the amino acids in the same sequence as sections of human body protein. Fruton (1972) quotes C. Bunge (1887) as follows:

> It may be *a priori* doubted on teleological grounds, whether under normal circumstances the amount of amido-acids (*sic*) formed in the intestine is a large one. It would be a waste of chemical potential energy, which would serve no purpose when converted into kinetic energy by their decomposition, and a reunion of the products of such a profound decomposition is highly improbable.

and Fruton then continues:

> A powerful blow to the teleologically attractive view upheld by Hoppe-Seyler, Hofmeister and Bunge (among others) was delivered by Otto Loewi (1902) who fed an extensively digested 'biuret-free' autolysate of pancreatic protein to dogs, and concluded that "... the sum of biuret free end products (amino acids FMA) replaces food protein.” [...] By 1910, therefore, it was clear that proteins are nearly completely digested in the intestine to amino acids, that these amino acids can replace intact dietary proteins, and that attention had to be paid to the 'quality' of a dietary protein and not merely its nitrogen content ...

The conceptual problems that troubled Hoppe-Seyler, Hofmeister and Bunge (all leaders in the field) in the 1870's were put, by myself, to catering management students undergoing a course of nutrition in the 1980's. They had no problem in believing in the theory of complete digestion: it was the peptone theory which possessed conceptual problems. In an age of mass consumption and recycling, where complete disassembly usually precedes reassembly, the complete digestion theory fitted in with prevailing real world metaphysics of business economics.

No doubt a blacksmith in the early 19th century, breaking up a damaged vehicle for spare parts, probably would retain undamaged sections of the vehicle (by analogy 'peptones') which might be useful in future, and *not* automatically completely disassemble the vehicle (by analogy 'break down to amino-acids') while pursuing a rigid algorithm.

It is my suggestion that the rapid industrialization of Germany post 1870 had the effect of convincing the younger German biochemists of that period that the teleological arguments for partial digestion belonged to the world view of a pre-industrial society and therefore the teleological arguments belonging to a mature industrial society pointed in the *opposite* direction. There may be other examples where current social, political and industrial structures affect a scientist's apparatus for evaluating a theory's conceptual status.

Conclusions

Science undergraduates often ask: "What is the use of philosophy? After months and years of debate no consensus appears to emerge." It is true that no philosopher can report, as Malmstrom (1993) reported of Mitchell: "By 1975 investigators had become convinced that Popper (or any other philosopher) was right in principle". However philosophical debate is fascinating and develops skills in communication, logic, presentation, rhetoric and receptivity to new ideas. Undergraduates philosophizing or kittens playing with balls of wool are both following the same survival strategies: playing a 'game' which matures and co-ordinates neural patterns and prepares for life in a competitive society. Lovell (1992) has argued that philosophy of chemistry courses are of value for chemistry undergraduates seeking careers in management. Research Biochemists of the stature of Eccles, Monod, Medawar and Mitchell have paid tribute to the philosophical ideas of Popper. Let us see how this relates to the topics discussed in this paper.

Mitchell's philosophical reflections on the nature of cause and effect enabled him to make the conceptual jump that maybe transport affected metabolism, the reverse of the conventional thinking.

Some Western biochemists were troubled by the fact that in some areas Eastern traditional medicine could achieve more successful results using theoretical concepts incommensurable with Western biochemical hypotheses. They therefore kept an open mind, realizing that the conventional system was to some extent inadequate due to lack of *consiliense*, and a weather eye open for any pointers in unexpected recent results which could resolve the paradox.

Uncritical philosophical assumptions can often hinder intellectual progress (cf. Popper cited by Magee (1973)). I suggest that such a philosophical assumption hindered the rapid uptake of the theory of the complete digestion of protein in the gut.

Note

1. A *domain* is an area of scientific activity initially thought to require its 'own' theoretical concepts to deal with its empirical problems. The classic example of *consiliense* is the use of Newton's theory (initially designed for the domain of Celestial and Classical Mechanics) in the domain of Tidal Theory.

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