2 A possible history of the field

Although in this book we aim to obtain general conclusions about scientific discourse, most of the data we shall be drawing upon come from the interviews that we carried out with scientists working on bioenergetics, and from their research papers and other literary products. This chapter outlines the recent history of bioenergetic research, and at the same time provides an overview of the scientific issues involved. These should help in understanding the material with which we shall be illustrating our later discussion.

Biochemists study the chemistry of living matter; bioenergetics, a research specialty of biochemistry, deals with the organic processes that create, transport and store chemical and other kinds of energy. The scientists with whom we shall be concerned are particularly interested in the formation of a complex molecule called ATP (adenosine triphosphate), which plants, animals and bacteria use as a means of moving and temporarily storing energy within the cell. The process whereby this molecule is formed in animals and bacteria is called oxidative phosphorylation (often abbreviated in informal speech to 'ox phos'); in plants, the process is somewhat different and is known as photo-phosphorylation.

ATP is created within the cell from the combination of ADP (adenosine diphosphate) and inorganic phosphate in conjunction with an enzyme, ATPase, a process which requires an input of energy. The reaction may alternatively proceed in the reverse direction, yielding ADP and inorganic phosphate from ATP, with the production of energy that can be used for other cellular processes. Since the late 1940s, it has been known that the creation of ATP in animals takes place in small particles called mitochondria. These are located within the cell protoplasm. The mitochondria appear as bodies enclosed by two membranes, the inner one of which is highly convoluted. It is now widely accepted that it is the inner of the two membranes that is essential for the formation of ATP by oxidative phosphorylation.

During the late 1940s and early 1950s, evidence accumulated to show that a series of chemical oxidation and reduction reactions linked together components of the inner mitochondrial membrane into a chain. The

operation of this 'respiratory chain' (often called the 'electron chain' by our respondents) seemed to be coupled to the formation of ATP. Nevertheless, the details of the components of the chain, the reactions which took place in it, and the precise relationship between these reactions and the formation of ATP were not then clear. However, the biochemical details had previously been established with reasonable confidence for another ATP-forming reaction, 'substrate level phosphorylation', and it seemed that analogies might reasonably be drawn between this well-understood reaction and oxidative phosphorylation.

This chapter will mainly be devoted to relating how bioenergeticists, over the course of three decades, came to understand in finer detail the mechanism of oxidative phosphorylation. The material we shall be drawing on to tell this history consists principally of the interviews we conducted in 1979 and 1980 with 34 bioenergeticists. This sample constituted approximately 50 per cent of those British and American scientists who have published more than one or a few occasional papers in the area. The scientists were interviewed, usually in their laboratories, for on average between 2 1/2 and 3 hours. The interviews were tape-recorded and transcribed in full. We then read through the transcripts and copied those pages which included material relating to the topics which interested us. The passages from the interviews concerning each topic were placed together in 'topic files', so that we had convenient access to all the material on, for instance, consensus or diagrams and pictorial representations.[1] We aimed to make each file as inclusive as possible so that no passage which could be read as dealing with a particular topic was omitted from its file.

Other materials we drew on for the work reported in this book include a collection of letters circulated privately amongst the major figures in the field, a listing of research papers obtained from the Science Citation Index of those co-citation clusters[2] which we identified as relating most closely to bioenergetics, a collection of some 400 articles from the bioenergetics research literature (including all the review articles published between 1960 and 1980), copies of the relevant portions of around 30 biochemistry textbooks, and curricula vitae obtained from our interviewees.

In this chapter, we intend to present only an outline of the history of bioenergetics. Working at this high level of generality, it is relatively easy to piece together, from what the participants told us, an apparently coherent and plausible history of scientific developments. But, as we shall note at intervals, this coherence is a fragile construction, obtained at the expense of ignoring the variations and inconsistencies in the accounts we were offered. As we have suggested in the first chapter, and will go on to demonstrate in some detail in later chapters, there is a very considerable degree of variability in the accounts we obtained. For the purposes of this

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introductory history, we have chosen to ignore or suppress most of this variability. In doing so, we have probably followed the procedures used in most other studies of science, and by the participants themselves, in resolving potential conflicts of evidence by appeal to common-sense notions of what was most likely, or most easily understandable. We have adopted this strategy for this chapter alone because our main intention here is not to provide an analysis of the scientists' discourse, as it is in the rest of the book, but to provide the necessary background for an appreciation of the talk of our bioenergeticist respondents. Towards the end of the chapter we shall make some brief comments about the kinds of variability in the accounts we have drawn on, though this will be a topic we shall explore in much greater detail in later chapters.

Before beginning to relate this history, we must deal with two preliminary issues of nomenclature. We have reluctantly adopted the convention of referring throughout to scientists as 'he', partly because the phrase 'he or she' becomes clumsy on repetition, but also because all the scientists we interviewed for the study were male. We have also adopted the sociological convention of using pseudonyms to refer to our respondents. In general, we have applied these pseudonyms consistently throughout the text, so that the scientist called Barton in this chapter will also be called Barton elsewhere in the book. There are, however, some exceptions. Wherever it has seemed to us at all possible that a participant's real name could be discovered by a persistent detective - for example, where the author of a traceable research paper is mentioned in the text or where speakers' names appear in a diagram which is well known to participants and which is publicly available, then new pseudonyms have been introduced for the relevant passages.

In one case, however, it has proved to be impossible to maintain a participant's anonymity. The dominant theory in this area of research, the chemiosmotic theory, is very closely associated with one particular scientist whom we have called Spencer. Because this scientist is so central to the field, because he is mentioned so frequently in our material and because his name is used eponymously for the chemiosmotic theory, it would have been immensely confusing if we had tried to vary his name in order to cover his tracks. We have, therefore, used the pseudonym of Spencer consistently throughout the book. As a result, there can be no doubt that those already familiar with the field will know who Spencer is. But this is not a mere pretence of anonymity, for most of our readers will not be biochemists, they will not be familiar with the field, and, we suspect, few will want to know Spencer's real name. Thus, there is nothing to be gained by abandoning the convention of using a false name in the case of Spencer. Moreover, the systematic use of pseudonyms in the text helps to

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emphasise in a formal manner our contention that the passages of discourse we examine in subsequent chapters are not of interest as statements by Barton or Spencer or any other specific scientist, but as instances of generic interpretative procedures which are regularly used by scientists.

A version of the history of research on oxidative phosphorylation

Although forebears of the research area are traced by some back to the 1920s and 30s, most commentators see discoveries made in the 1940s as first opening up the field. One respondent, for example, began his account of the origins of work on oxidative phosphorylation by referring to research on pyrophosphates, a generic name for compounds like ADP and ATP.

> 2A
> Early in the 40s, a Russian and Lippmann in America had shown there was a general form in which energy was used and that was a molecule called pyrophosphate. It's called ATP, adenosine triphosphate, and triphosphate means just that phosphates are linked together in a chain . . If you put two phosphates together, those two phosphates have to be forced together by energy, so the energy currency running the system was going to be this pyrophosphate ... [Jennings, 13]

Also in the 1940s, Keilin in Cambridge had isolated the respiratory chain and some of its components, and American biochemists had discovered the mitochondrion within animal cells' protoplasm. Grant, then a young scientist who had been involved in the discovery of the mitochondrion, had had the opportunity to establish a new research laboratory:

> 2B
> I decided that this was my life's work - the mitochondrion. Here is the system that made

ATP and fatty acid oxidation. You name it, the mitochondrion did it! And this was a worthy subject for a lifetime's effort. So we were very fortunate. Rockefeller gave us lots of money. We set up a beautiful laboratory - everything you want, large-scale isolation facilities. It turned out mitochondria by the bucket. And then there was a golden period of twenty years, where we just did all the basic work, isolated it, tore it apart, separated out the complexes, studied the citric acid cycle, the fatty acid oxidation cycle, oxidative phosphorylation, all the goodies, everything the mitochondrion did was systematically explored. [Grant, 6]

The feeling of heady excitement conveyed by this respondent was

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accompanied by confidence that any problems in laying bare the details of oxidative phosphorylation would soon be overcome.

2C

It started when [Fennell] was a post-doctoral fellow and we ate lunch together every day. I had been working on an enzyme which was called glyceraldehyde phosphate dehydrogenase. That is, on substrate-level phosphorylation, it's a key enzyme in fermentation, which results in ATP, and I worked for a time on that enzyme. I showed that there was an intermediate, an oxidised intermediate, a thioester intermediate, which is formed during the action of the enzyme.

Fennell, who was working on oxidative phosphorylation, said immediately, 'Well, why is that not also the mechanism of oxidative phosphorylation?', and so the model was built according to something which biochemists knew about and it was what we were used to. [Merrifield, 3]

Fennell formulated a theory to explain oxidative phosphorylation in terms of an unidentified 'high energy chemical intermediate' which, it was hypothesised, played an analogous role in oxidative phosphorylation to glyceraldehyde-3-phosphate dehydrogenase in substrate level phosphorylation. The latter enzyme was known to provide the chemical link between the oxidative and the phosphorylating reactions in substrate level phosphorylation, thus 'coupling' them together. Researchers turned to the search for the intermediate of oxidative phosphorylation.

2D

They were quite convinced that electron transport was going to be just as easy a thing to sort out as glycolysis in solution. You had to have a series of carriers. Admittedly these things were not readily purified. But it became apparent that they reacted in an orderly sequence in the membrane. The game was - spot the missing factor. Everybody was convinced that you would just find the missing Fennell factor which would enable you to mimic all these effects in solution. [Whitehead, 5]

Unexpectedly, the search proved to be frustratingly difficult. The missing factor did not reveal itself.

2E

I had the feeling that if you are a good boy, and do your homework, and study all the different parts of the mitochondrion, then in the end everything will fall into place, and all the mysteries will be resolved. It didn't turn out that way. . . We had some very exciting times, isolating these systems and proving the chemistry of it. But when it came to mechanism, a leap forward to the strategy of the structure, how was the mitochondrion designed - total failure, nobody succeeded. We were no better than anybody else. It was a great shock to me. [Pugh, 6]

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2F

What I always say to undergraduates is: [Fennell's chemical intermediate hypothesis] looked very nice and you could forgive all of us working in this field for not finding [a chemical formula for the unknown intermediate], because that's rather like looking through a haystack for something without knowing what it is. A rather tall order. [Ashwood, 18]

Nevertheless, a succession of claims to have found the missing intermediate were made at intervals during the early 60s. In each case, the claims were eventually shown to be false.

One perspective on the state of research at that time is given in the following account by a scientist who was then a post-doctoral student at a prominent laboratory.

2G

I think at that time the general view in the field was that you could make ATP in a soluble system, so all you had to do was throw in ... some cytochrome C [a component of the respiratory chain], take ADP and phosphate and then take [a proposed intermediate] enzyme, which made ATP. And at that time Perry had just isolated ATPase from beef heart mitochondria and Milner's lab had just isolated what they call an ADP/ATP exchange enzyme. And there were many papers, if you go back in that era, even showing that you could add this enzyme back to particles that were deficient in it and you could reconstitute ATP synthesis.

And so I worked on that system for the better part of three years . . . And the net result is that we could never really show any specificity of the enzyme in terms of its interaction with cytochrome C. Some other people had shown that it was specific for cytochrome C. And then Smith and Pugh and his collaborators had even indicated that they could take cytochrome C and basically the same enzyme and they would add ADP and phosphate and get reconstitution of oxidative phosphorylation. You had Milner's laboratory who wanted to do the same thing, and Perry's too as well . . .

It never occurred to me that people could say things like this, very important people, and turn out to be completely wrong, or perhaps had fabricated the whole thing. And I remember Perry went to Pugh's laboratory and tried to reproduce Smith's results, or even see the data, but apparently they couldn't come up with the data and it was learned that Smith had apparently fabricated the whole thing...

I thought well, the field is really screwed up. . . and I didn't believe half the stuff that was published, because I saw that we were dealing in this field with people who had very strong egos, who were trying to get an answer very rapidly, and who weren't cautious about what they were trying to do. [Carless, 4-6]

The incident with Smith was recalled by many of our respondents. The

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story goes that Smith had told his laboratory director that he had performed experiments which successfully identified an intermediate. The director announced this finding publicly at a conference, but later retracted the claim since Smith was unable to reproduce his results when the experiments were repeated under supervision.

It was during this period that Spencer formulated an alternative proposal which came to be known as the 'chemiosmotic hypothesis'. The first paper outlining his ideas in relation to oxidative phosphorylation was published in 1961, and this was followed by a series of publications developing the theory and providing some experimental support for it. The central ideas of the chemiosmotic hypothesis are that the creation of ATP takes place in the mitochondrial membrane; that the respiratory chain is located in the membrane and operates to divide hydrogen into electrons and protons; that specifiable numbers of protons are in effect transported across the membrane, thereby creating a gradient of protons and an electrical potential across the membrane; and that this proton gradient and difference in electrical potential, funnelled back across the membrane, provides the energy necessary to bind together ADP and phosphate.

Later, some researchers began to refer to parts of the respiratory chain as 'proton pumps' to emphasise their role in transporting protons across the membrane to create a proton gradient and electrical potential, although Spencer himself never seems to have used this term. Spencer's hypothesis avoided the need to postulate an unknown chemical intermediate, and explained why none had been discovered. But it was a somewhat unusual theory in the context of biochemistry at that time, because the proposed mechanism necessarily involved a membrane across which the proton and electron potential gradients were developed, and because Spencer's explanation drew on irreversible thermodynamics, a field in which most biochemists were not knowledgeable.

The initial reactions to Spencer's theory were not encouraging.

> 2H
> When Spencer's paper first came out it was given very little attention really. There had been similar ideas in the literature before then -Robertson, and going back to Lundegardh, and so the field was familiar with the general idea that electron transport chains could act as proton pumps. Spencer did two new things: he suggested that... hydration and dehydration could lead to the pumping of protons... And his other new idea was to suggest that the sort of pump which Lundegardh had originally suggested . .. could be improved if you had an electron transport chain which is folded across the membrane with alternate hydrogen and electron carrier loops. That idea wasn't too clear in his first

> paper, but it certainly became the dominant idea in his later papers . . .
> I think the major laboratories in the field were just not disposed to think of Spencer's hypothesis at all - I think that almost certainly someone in all those labs read the paper and put it to one side. . . I think that Spencer's paper was regarded as interesting but eccentric. [Richardson, 6-7]

Indeed, during the early 60s, his work was all but ignored, except by one British group of researchers who were interested in an issue which at that time seemed to be rather peripheral to the study of oxidative phosphorylation. These researchers were studying the action of 'uncouplers'. Oxidative phosphorylation involves two coupled reactions: respiration and the production of ATP. Normally these proceed hand in hand, with the energy produced by respiration consumed by ATP formation. However, certain reagents appear to uncouple them, so that, for instance, respiration continues rapidly, but without any accompanying formation of ATP. Many of the uncouplers were also known to be capable of transporting ions across the membrane. According to members of this group, researchers who were working from the basis of the chemical intermediate theory found it difficult to formulate convincing theories to explain why the uncouplers had an effect on oxidative phosphorylation.

The British researchers working on this topic picked up Spencer's work and used it to develop what they considered to be more adequate theories of uncoupler action. One of the members of this group related how he

> 2I
> first heard about the chemiosmotic theory as one always does these things, by word of mouth. A man with whom I was collaborating at the time . . . had met Spencer. Spencer had got a new theory, respiratory chain phosphorylation, and he's sitting there watching a pH meter needle move. He said, 'I can't see it move, but [Spencer] says it does', and he told me about him, and had a good laugh and decided Spencer was a bit mad; then the paper came out and I don't think at that stage it was taken very seriously. Now one of the problems is that we don't read enough outside our field and all Spencer's previous work had been in things like the *Journal of General Microbiology* and so on, and I don't think I'd ever read anything he'd written beforehand, and so I was not familiar in the least with his thinking. But we really only started to take things seriously when we started work on ion transport and then it became increasingly obvious that there was an economy in the chemiosmotic hypothesis describing what was going on which went right across the range of what we were doing. . so that one became convinced that this really was more likely than the other thing [the chemical intermediate theory]. [Burridge, 9]

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In the United States, however, the chemical intermediate theory still dominated the field:

> 2J
> A lot of experimental results and valuable information was gained by the supposition that there were chemical entities in the respiratory chain [i.e. chemical intermediates] that were generated as electrons passed through
> - this led to Gowan's masterful analysis of the components of the respiratory chain, the cross-points and the change in the redox balance between carriers when you added ATP - all this was generated by the chemical theory, so they had no grounds for abandoning it. They regarded with some hostility any attempts to cut this from under their feet, they found it good and solid and their careers were based on it. [Roberts, 14]

Although this speaker suggests that the chemical intermediate theory was proving to have continuing value, and was generating 'masterful' analyses, other respondents painted a different picture of the situation in the United States at the time:

> 2K
> The big Smith thing undermined a lot of confidence, not only in Smith and Pugh, but really in themselves. And I think there was a very big temptation at that time for people to get more slapdash rather than less because they were just desperate. They had to make the breakthrough and they were looking for shortcuts... You had people like me with no great ambitions to win Nobel prizes who were just prepared to work at it and just see what came out. You had the established people who in most cases were getting desperate, because they had committed, because they had made too big an investment. They were like in a game of poker where they had got all their money in the pot. They just had to keep upping the ante. And then there were a lot of very arrogant people who were coming in from other fields and saying, 'You chaps don't know a thing, I am a chemist, I

> don't think there is a problem at all'. . . And we had physicists coming in and saying the same thing and within about three years they were in just as bad a position as the old established people. So at that stage, well, it was exciting but also a bit of a mess. [Harding, 7-8]

An American scientist who was using the chemical intermediate framework at that time recalled his reactions to the chemiosmotic theory:

> 2L
> You see the problem is that at first sight most people look at what he says and they just say, 'God, you can't understand it!', that's the first thing, especially in the late 60s, early 70s, you just didn't know what he was talking about. It was so much to buy, that here was this respiratory chain squirting out protons and making this magic electro-chemical proton. A biochemist is someone who is trained to purify, characterise and

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> crystallise. Nobody is going to purify, characterise and crystallise an electron gradient. [Cookson, 17]

Spencer travelled to the United States several times during the mid- to late 60s to speak at conferences. A senior US biochemist remarked that:

> 2M
> American biochemists working on oxidative phosphorylation until late in the 1960s were very much committed to the chemical coupling hypothesis. Their whole outlook was that way ... On three occasions [Spencer] came over. He didn't come over very well at first in this country at all . . . I still remember, and I had occasion not long ago to compare notes with other people who were present at that time, apart from a very few people he was greeted with complete disbelief and that even by some extremely intelligent people in this country. People just weren't thinking in those terms at all then among the American biochemical fraternity. And we'd had this period in which Pugh would every year or two make a pronouncement, 'Well, next year we'll have the problem all solved', and it never did get solved. [Milner, 9-10]

The British scientists working on uncouplers, who had already accepted chemiosmosis, also visited the States, and found the researchers there to be relatively ignorant about Spencer's ideas. A scientist who at the time was a student attached to that group said,

> 2N
> I went over to work with Gowan... for a month. That was at the end of my first year as a research student. In [the laboratory he visited] there were quite a few people who were at the forefront of Oxidative Phosphorylation... I had to give a seminar there and that was really quite difficult because I had only done one year of my PhD, but actually I felt quite cocky about it, about half-way through the seminar, because I realised then that the people at this institute were lagging behind on these new ideas. And I was fairly confident saying, 'You are wrong here', and 'You are wrong here.' I was able to say that standing up in front of them because they hadn't given sufficient thought to Spencer's ideas. [Crosskey, 4-5]

In part as a response to these visits, and to the evidence produced both by Spencer himself and by his British supporters, some American scientists published work reporting results of experiments which, they argued, cast doubt on the chemiosmotic hypothesis. However, the supporters of chemiosmosis thought little of the quality of these experiments.

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There were a lot of experiments that were coming out at the time which were saying, 'This disproves the chemiosmotic hypothesis because . . .' and then giving some stupid reason. [Crosskey, 3]

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2P

Until the 70s, at least in some of the major labs in the field, nobody had made the effort to understand the chemiosmotic hypothesis. It's pretty obvious from the kind of things that they were saying at conferences or in papers, and the number of people who 'disproved' the chemiosmotic hypothesis that they were just making trivial physical-chemical mistakes, this sort of thing, or were interpreting experiments in a way which was plausible, but not probable, in the sense that they would fail to take account of other possible effects. [Richardson, II.1]

During this same period, two other theories to explain oxidative phosphorylation were proposed by American biochemists. Watson's 'conformational coupling' hypothesis, formulated in 1964, suggested that the energy necessary for the formation of ATP was not stored as a chemical intermediate or as an electro-chemical gradient, but as changes in the conformation or shape of the molecules in the mitochondrial membrane. Pugh proposed a theory in which the coupling between the respiratory chain and ATP synthesis was conceived in terms of mechanical movements of the membrane. Neither of these theories became particularly popular, and comments made by our respondents suggested that, in retrospect, they were either dismissed entirely, or were regarded as variations on the chemiosmotic and chemical intermediate theories. The following passage from a scientist who has always thought the chemiosmotic theory to be correct, is typical of the reactions that these two theories received from many of our respondents:

2Q

[Pugh] had a chemist drafted in to prove the conformational hypothesis, which Pugh had jumped upon and used all his electron microscopes and things to 'prove'. . . He was an ace chemist. Very, very good. He went to work there for about a year. At the time they published this chemico-mechano-chemiosmotic six-stage theory or whatever. In which all you had to do was take out four stages and you could throw away the rest. This guy went and listened to Pugh and after he'd been there about six months, he came over to see me. And he said, 'Now look, I hear you know all about the chemiosmotic theory.' So we had a long chat and we talked about it. He went away again and came back three months later and said, 'I'm convinced the chemiosmotic theory is probably right', he said. 'But Pugh doesn't believe me.' So a month after that he was gone. [Barton, 15]

Meanwhile, there were continued attempts by some to find experimental proof that the chemiosmotic theory was incorrect. The following passage describes one such experiment. The chemiosmotic theory included the postulate that oxidative phosphorylation would only

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take place in closed membranes. If the membrane were ruptured, for example by exposing it to intense sound waves, the theory predicted that phosphorylation would not be observed. In the experiment described, as in many others of this kind, the membranes were in the form of artificially produced 'vesicles' rather than intact mitochondria.

> 2R
> There was a paper ... in a meeting about 1970... They'd sonicated these things for about thirty minutes - a desperate attempt. They implied, maybe they were more explicit and said that they'd got oxidative phosphorylation in open vesicles. That was the point of the experiment, anyway. I remember in [another] meeting in 1972, somebody had written an abstract saying that they had demonstrated oxidative phosphorylation in a membrane-free system derived from a bacterium. . . Normally these ten-minute papers, not many people attend. But I noticed that the room was filled, and the usual anti-chemiosmotic gang were all there like vultures. But the evidence that there were no membranes there wasn't very satisfactory. You could see them going away a little disappointed. Once again, this horse hadn't run very far. [Aldridge, 8-9]

On the other hand, two experiments, one carried out in 1966 and the other over a period of years in the late 60s, had some influence in Spencer's favour. These were Miller's 'acid-bath' experiment, and Perry's reconstitution experiment. The former produced results which were hard to explain in terms other than those of the chemiosmotic theory, but was an experiment on photo-phosphorylation in plants, rather than on oxidative phosphorylation. The second experiment involved artificially constructing a working phosphorylating system from separate components taken from a number of different sources. It was considered that if the chemical intermediate theory were true, the resulting reconstituted system would be most unlikely to form ATP, whilst the chemiosmotic theory predicted that such a system could be made to work. The experiment showed that small amounts of ATP were formed.

> 2S
> The reconstitution experiments were just beginning. I think Perry and Czigler, that is perhaps the touchstone, that is the one single experiment that people cite - you take the ATPase away from the respiratory chain and it still behaves like a proton pump and you cannot postulate some hidden lost proton pump stuck in between the respiratory chain and the ATPase which is what the chemical people were driven to. [Roberts, 17]

Gradually, however, the tide seemed to turn in favour of Spencer. A number of respondents put this movement down to the influence of younger scientists entering the field without the 'prejudices' and preconceptions of the older ones.

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> 2T
> When I came here I knew nothing. All the seminars they had here were just incomprehensible, but it was clear that everybody was against Spencer heavily at that

> time and he wasn't doing too well. There was a lot of 'evidence' against his ideas. The movement towards accepting it...was due to a lot of young people coming in. People who were very strongly involved with Spencer. The thing about [the director of the laboratory] was that in spite of his anti-dogma thoughts, he would always invite people here who opposed him and that was one of his terrific characteristics . . . and so a lot of people [came], particularly young English people, the national support club of Spencer. [Jeffery, 20]

Thus, by the early to mid-70s, the big American laboratories had begun to become more friendly to the chemiosmotic hypothesis, although there is some disagreement about the extent and timing of this shift. For instance, Spencer wrote in 1976 that, in his opinion,

> 2U
> Several of the more eminent authorities in the field of oxidative phosphorylation are reluctant to agree that coupling between the proton-translocating respiratory chain system and the proton-translocating ATPase system, plugged through the coupling membrane, is due to the proton current circulating between and vectorially through them. . . they have preferred to believe, in keeping with the traditionally scalar origins of their conception of metabolism, that coupling is achieved by some unidentified energy-rich chemical intermediates or by some direct interactions between components of the respiratory chain and reversible ATPase systems.

In contrast, Norton, speaking of the same period, noted that,

> 2V
> There was a substantial shift about the time I went to the States. [Earlier], it was unthinkable that Fennell should talk in chemiosmotic terms. And just as I was leaving [for the States], he started to. I think that made a big impression on a lot of people. Their hero, the chemical theory's hero, starting to switch positions, or at least to admit that it was very *reasonable* to talk in chemiosmotic terms. And Gowan as well, about that time, finally got worn down by the stream of British post-docs coming into his lab and telling him chemiosmotic things and thinking chemiosmotically. But the respectable way to talk about things has become chemiosmotic and the odd way non-chemiosmotic, rather than the other way round. That switch was occurring while I was there. It was surprisingly rapid, unexpectedly rapid. [Norton 34-5]

Whilst according to most respondents, the tide was clearly flowing

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towards the adoption of chemiosmosis, there was continuing controversy about some aspects of the theory. One issue that remained unresolved was that of ‘stoichiometry’. Respondents used this term to refer to the number of protons that are transplanted across the membrane as one electron passes down the respiratory chain:

2W

There's an interesting thing that has happened in the last five years and that is that five or ten years ago people were trying to show that either the energy balanced, or it didn't balance. These two numbers, delta P is the size of the proton gradient and delta Gp is the energy needed to maintain ATP. People wanted to show that delta P and delta Gp balanced and they used Spencer's numbers. Spencer predicted certain stoichiometries between the number of electrons, the number of protons and the number of ATP molecules. So, in those days we used his numbers and applied those numbers to the data and the thing roughly balanced, but there's definitely been a swing away from that in the last few years. The assumption has been that the chemiosmotic hypothesis is right and the energies will balance, but what numbers do we have to use? What stoichiometries do we have to use to get them to balance?. . . So there's a lot of argument as to whether 'n' is 2 or 3 or 4, whereas ten years ago we were assuming Spencer says 'n' is 2, we will take 2 and plug it in and roughly it balances. And any imbalance we put down to, well, a data problem, error. [Crosskey, 9]

As this speaker notes, Spencer's chemiosmotic hypothesis assumed a stoichiometry of 2. Moreover, Spencer subsequently formulated a fairly elaborate biochemical mechanism, involving proton-transporting pathways that formed so-called 'loops', based on this stoichiometry. However, in the late 70s, doubts were cast on this figure; experimental evidence was interpreted to support stoichiometries of 3 or, in some cases, 4. But to most respondents, the stoichiometry question was a 'side issue', a detail which had only become important because the overall chemiosmotic framework was no longer controversial, and because Spencer seemed to some participants to be unreasonably inflexible in refusing to accept that his numbers were not the correct ones.

At the time we interviewed our respondents, in 1978-79, the controversy over stoichiometry had not been settled. Nevertheless, in the autumn of 1978, Spencer was awarded the Nobel Prize for his contribution to the understanding of biological energy transfer. Some respondents seemed a little surprised that Spencer had been given the Nobel Prize, since they regarded his theory as still subject to doubt. Although as one speaker said,

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2X

The chemical [intermediate] theory is as relevant as phlogiston. Only in textbooks is there any discussion about conflicting theories. [The chemiosmotic theory] has taken over. [Aldridge, 29]

others were less certain that chemiosmosis, as formulated by Spencer, had 'taken over'. Most respondents accepted that the field, in general, now concurred about the existence of a pH gradient and a membrane potential that could be used to drive ATP synthesis, but few would accept that there was such general agreement about more specific details. The following is characteristic of respondents' present-day views about chemiosmosis, although different speakers emphasised different points of contention, doubt or agreement.

2Y

> Spencer's proposals can be broken down into three parts. The main hypothesis, which is that all the energy which is conserved during electron transport passes through an electro-chemical gradient on its way to different functions to drive ATP synthesis and transport. That's the idea he was awarded the Nobel Prize for, I believe. Then, how is that electro-chemical gradient, the proton gradient, formed and used. How the gradient is formed, the idea of loops, some people have subscribed to them, but more and more people seem to be thinking that there's a proton pump, rather than the actual oxidation-reduction reaction involving a hydrogen ion donor and an electron acceptor ... that's Spencer's loop idea. More and more people seem to be coming round to the pump idea . . . The mechanism of ATP synthesis, when he takes this electro-chemical gradient and says the protons on the outside can rip an oxygen molecule off phosphates so that it spontaneously combines with ATP, that is I suppose an attempt to use the gradient directly without any intermediate step or conformation step or chemical step. The idea is to try to make ATP directly from a proton gradient. It just doesn't agree with a tremendous amount of data that's in the literature, it's contradictory. [Hargreaves, 21-2]

Thus, this speaker, as soon as he begins to talk about specifics, and in particular about ATP synthesis, the area he is working on, starts to identify what he sees as serious shortcomings in Spencer's ideas. Others suggested that Spencer's theories, although previously regarded as too complicated to be worth pursuing, were in fact too simple to represent the facts correctly, and that combinations of Spencer's ideas with elements of, for instance, Watson's conformational coupling theory were likely to be needed. These scientists seemed to think that much further research to develop more detailed and refined theories was required. In contrast, a few of those we spoke to suggested that knowledge about oxidative

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phosphorylation was now so advanced that there was no longer anything interesting left for them to work on, and that they were therefore moving out of bioenergetics into other areas of biochemistry.

Any attempt to draw conclusions about the present level of agreement about the chemiosmotic hypothesis within bioenergetics is further complicated by the fact that different respondents describe the theory in quite different ways. It is far from clear, therefore, whether all those who say that they accept the hypothesis are subscribing to the same theory. For instance, compare the following rendering of the chemiosmotic hypothesis with those cited above:

> 2Z
>
> The field changed enormously because of Spencer. It was during this period of time when I came in 1964 that everybody was thinking of chemical mechanisms for how ATP would be made in a soluble system. And it was only then, at that stage of the game, that Spencer came out with his early papers in *Nature,* and then finally those two little books that he sent me, in which he emphasised that all biological systems that carry out the synthesis of ATP are membrane systems and they are all closed systems and that nobody had ever isolated a chemical intermediate before and so maybe they didn't exist. Which was a little far-fetched, because you've got to have chemical intermediates to make ATP.

> But in a way he had chemical intermediates, he was simply stating that there was a different way of making ATP than having a high-energy chemical compound of the electron transport chain. I think that was his main emphasis, to do away with any high-energy intermediate which was associated with electron transport. [Carless, 23]

The speaker describes the chemiosmotic theory here in a way which emphasises the close connection between his version of it and the fundamental ideas of the chemical intermediate theory, the theory that he had earlier espoused. He states, for example, that even Spencer's theory had chemical intermediates 'in a way'. His implication that the chemical and chemiosmotic theories are not really so very different contrasts markedly with the opinions of other respondents (such as those quoted in 2H, 2L, and 2R). We shall be returning to consider in more detail the topic of agreement and consensus in chapter six.

Alternative versions of the history

In order to give a view of the development of the field as a whole, we constructed the history of oxidative phosphorylation presented in the previous section from a patchwork of quotations from many different respondents. Overall, it is an account which we believe many participants

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would recognise and accept as a reasonable approximation to the way in which the field developed. But it would be quite misleading to suggest that this history describes 'the way things really happened'. There are several reasons for this. First, the history was created from portions extracted from interviews, in which speakers were asked to give an account of their scientific biographies, and to comment on the history of the field from their own knowledge. This means that many respondents gave us an account in which their own activities were the major focus, and which was therefore inevitably a very partial account of the development of the field as a whole. It cannot be guaranteed that even when all the speakers' accounts have been put together, every significant event will have been included. Secondly, the speakers gave us retrospective accounts, in which, to an unknown degree, the events they reported may have been 'reconstructed' in order, for instance, to fill gaps in the speaker's recollection. Thirdly, the historical events that were mentioned in each speaker's account were given meaning in relation to particular 'dramatic episodes' that varied between speakers and during the course of each interview. Thus some respondents mentioned particular events and others did not; different speakers emphasised the importance of specific events quite differently; and whilst some speakers frequently talked in general terms about the development of the area, others focused more narrowly on their own involvement in it. In short, the quotations have been taken out of their particular contexts.

These 'problems' with the data are not, however, confined to extracts from interviews. They would not be avoided by recourse to 'harder' data, such as, for example, laboratory notebooks, contemporary publications, diaries and so on. Descriptions of events from these sources would also be subject to precisely the same 'problems'. Particular examples of such data could not be expected to provide more than partial descriptions of events, thus still requiring the historian to construct a coherent, overall view from a patchwork of items of data. Furthermore, even items of written data are reconstructions of past events, produced by the author for some particular context, and oriented to that context. For example, as we shall show in the next chapter, the introductory sections of research papers, which often present reviews of prior work and which to that extent are sources of historical data, can be seen to be rather finely crafted reconstructions in which certain kinds of events and actions are systematically excluded.

Thus, although we recognise that the history we constructed is but one possible version of the history of the field, this 'weakness' cannot be remedied by relying instead on other kinds of data. Other versions of the history will remain both possible and plausible. Examples of such other versions may be found in our interview transcripts and it is to these that we shall now turn.

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From the very large variety of 'events' which *could* have been mentioned in outlining an historical sequence, our respondents inevitably chose only a small number to talk about. One of the ways in which such selections appear to be made in the course of conversation is to choose those events which, when put together, compose a dramatic story. Thus speakers, asked to describe their scientific biographies, did not merely list the papers they had published, the research problems they had worked on, or the laboratories they had worked in. Instead, they 'told the story of their lives', connecting the events into a dramatic narrative.

Examining the narratives that were offered to us, many, but not all, the respondents used a story line which could be called the 'David and Goliath' theme. This theme also enters the version of the history we have presented in the previous section. In brief, the story line runs like this: The field was dominated by three very large, very well funded US laboratories. The directors of these laboratories were arrogant, over-confident, and determined to be the first to crack the problem of oxidative phosphorylation. The competition between them was so intense that their assistants were pressurised into making fraudulent claims, bitter disputes emerged at scientific meetings, and the field as a whole began to have a bad reputation. But 'David', the scientist from Britain, launched an attack on these 'Goliaths' single-handed, and after battling for nearly twenty years against them, and resisting all their attempts to defeat him, cracked the problem and won the Nobel Prize, to the Goliaths' fury.

The following passage, rather longer than those we have previously quoted, taken from one respondent's interview transcript, will serve to illustrate how the historical accounts which we have used above are often told as a moral tale, in this instance, of David versus Goliath.

> 2AA
> The personalities in the field were very dominant. The big groups were dominated by the leaders and there you had Perry, Pugh, Gowan, and then to a lesser extent . . . Fennell, who happens to have a reasonable group, but regarded himself as a sort of grand referee in the field. So every meeting you went to, you had these personalities always pronouncing the gospel. In the US all of this was dominated by those particular groups. . . I don't know when Spencer first went and gave those Federation meeting talks, '66 or '67.1 think people at the time didn't take him very seriously, but I think he attracted a good deal of attention among, first of all, the chloroplast people because they were moving that way already. But he also attracted in the US, more particularly, support

> among the bacterial people... But still a lot of dubiousness among the mitochondrial people. Whereas over in Britain, the reverse was true. I think he was beginning to attract a strong following in Britain particularly, which overflowed to the continent, but it took time... I don't think *he* helped... People didn't

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> really believe it and he was advocating what *he* thought was a reasonable hypothesis, which wasn't going over. But he wasn't dealing with reasonable people. The opposition was in some cases quite vitriolic. . . It was the norm in the field at the time. Particularly in the 60s, the oxidative phosphorylation field had the reputation that if you went to a Federation meeting, all the meetings were crowded because everybody went along because they knew there would be a damned good fight there... I think it basically relates to the fact that progress was so slow that the points that were being discussed were so nit-picking and the field wasn't moving at all. Large, huge, effort went into it in many laboratories. People have put their lives into this field and with huge groups associated with them, it's been very disappointing in this respect. [Peck, 21-3]

In this tale, the leaders of the major US laboratories are described in critical terms as 'dominant', 'unreasonable' and 'pronouncing the gospel'. In contrast, Spencer is simply engaged in advocating what he thought was a 'reasonable hypothesis'. The opposition to Spencer is indicated to consist of 'groups', 'laboratories', or even 'huge groups' that are dominated by their leaders. In contrast, Spencer attracts a strong following among presumably independent researchers. Spencer himself is referred to throughout the passage as a single actor, a lone person without the support of great resources. He had to contend with people whose unreasoning opposition was 'vitriolic'. Yet these people were making no progress; the discussion in meetings was 'nit-picking'. Furthermore, their failure to accept Spencer's theory is contrasted with the much more ready acceptance of those working with chloroplasts and bacteria, areas which were presumably not dominated by leaders having the opprobrious attributes characteristic of US research on mitochondria.

This kind of moral tale features in a number of accounts, although not all used the same David and Goliath theme. A common, but less popular, theme was the one in which a researcher, often the speaker himself or a colleague, laboratory director or other mentor, produced a masterful theoretical or experimental advance which failed to get proper credit from other scientists. When respondents tell their story in these terms, the history of the field appears rather differently. The following passage illustrates this second theme.

> 2AB
> I happened to run into one of Pugh's papers... this was in the late 60s, I think. He was developing some ideas about what he called an electro-mechanical model. And it seemed that somebody with a training in solid state theory could *do* something there. And he was rather unique in the field, in the sense that he was trying to construct physical models where other people were not trying to do that. I read more about the field;

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> in fact I don't think I could have penetrated the field without his papers, because everything was just a giant mess and he was the one who was trying to create some order in it. . . I started reading his papers because I couldn't make head nor tail of the chaos of the mostly bio-chemical type of papers and it was his organisation of the material which allowed me to penetrate into this field. We started collaborating and evolved this model . . . The way I perceived it at the beginning was that there were several experiments for which the details were not clear, but some kind of picture *had* to emerge and as far as I could see he was the only one who tried. . . I felt at the time that he developed a model which was very sound. There was no proof for it; there was no disproof for it either . . .
>
> The chemical theory didn't seem to *say* very much. The chemiosmotic theory I always felt was weak in one respect, which was that the proton gradient develops across the membrane and there is an equilibration with the two liquid phases before the protons would transmit the energy and make ATP. Which was something that Jennings had already emphasised:
>
> he came out with the proton-in-the-membrane hypothesis about the same time as Spencer and I thought that that was a much more *reasonable* hypothesis. However, what I felt was lacking was a physical mechanism by which the energy is transmitted, and [the speaker's] theory was supposed to supply a possible mechanism for such energy transfer.
>
> But looking back on it now, I think it would have been better never to have got into [the area]. Because the time when we got into trying to develop such a model was the time when what I would call the first generation's theories came to an end . . . It is models like the chemiosmotic model, the chemical hypothesis, etc., which try to make some simple pictures, they just about ran out of usefulness at that time. We picked up on the last edition to this first generation's theories. My feeling is that just about that time, much more detailed experiments were being produced, which as far as I know have led to *no* theoretical understanding at all. But what this means to me is that it is time to keep quiet and wait for the second-generation experiments which are of greater detail and precision. I think most of these experiments are more confusing than helpful at the moment, but it also means that the precision of the theory is way behind the precision of the experiments at the moment. [Hinton, 2-3, 6]

In quotation 2Q we saw a speaker dismissing Pugh's model, formulated in the 60s, as merely a version of chemiosmosis. The present speaker, however, reports that at that time he saw this model as 'trying to create some order' from 'a giant mess'. Pugh is cited as trying, as nobody else, to construct physical models to reduce the 'chaos'. Ultimately, although the model he developed was 'very sound', he was defeated by the fact that he was at the tail end of the 'first generation' of theories. It is clear that the overall characterisation of the research field is treated quite differently by

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this speaker as compared, for instance, with the respondent quoted in the previous passage, 2AA. The chemiosmotic theory is here considered to be merely one from a number that 'try to make simple pictures', and which together constitute the 'first generation' of inevitably inadequate hypotheses. Real progress will have to await 'second-generation' experiments. There is no mention of Spencer having a heroic role in the development of the area. Moreover, Spencer's theory is not seen as having 'solved' the problems of the field; indeed, it seems to be suggested that the problems themselves are not yet clearly defined, and await clarification by 'second-generation experiments'.

The two researchers whom we have quoted in this section had both contributed to oxidative phosphorylation research. Both were describing events which occurred during the mid-60s. Both were fairly young, but were established scientists by the late 60s. Furthermore, both scientists had had close contact with the same laboratory director, whose interests and ideas had greatly influenced their subsequent research. Despite these common features in their biographies, the historical details they offered to us and the perspectives they took were so different that it is quite easy to believe at first sight that they were not describing the same research area. Many further examples of variability can be found by comparing other accounts obtained from our respondents, and as we argued in the first chapter, this variability casts considerable doubt on the worth of traditional forms of analysis that attempt to reconcile these variations.

As we showed in the previous section, however, the existence of this variability is not, in itself, a bar to the construction of a version of history by the analyst. In the main body of this chapter we have compiled our own 'folk history' of 'ox phos' in order to introduce some of the terms and issues to which participants will constantly refer in subsequent chapters. We have also illustrated the kind of recurrent variation in accounts which is a feature of our data. However, in the interests of making the scientific issues clear, we have merely pointed to, but not systematically described or analysed, such variation. In the next chapter, we start to show that a detailed examination of variations in participants' discourse reveals regularities of some sociological significance.