CLOCKWORKS, HOT POTS, HEAT MACHINES AND CHEMICAL MACHINES:

THE CONTRIVANCE ASPECT OF THE MACHINE METAPHOR

by

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ABSTRACT

From a general discussion concerning the shortcomings of the received view of scientific theories and scientific explanation I conclude that metaphorical thinking, until quite recently restricted to literary analysis, may play a significant role not only in the way theories are conceived, but also in the way that meaning is ascribed to the concepts used in science. The analysis of the literal realm of 'machine' considers three aspects that could appear in the metaphorical assimilation of organisms to machines: the contrivance aspect, which is the 'hardware'; the fact that machines exhibit purpose; finally, the integrated aspect of the machine (its harmony). The study is devoted only to the first aspect.

I offer a narrative of pivotal ideas about the workings of the biological individual, from the clockworks of the early mechanicists to modern biochemistry, not just as a succession of discoveries but also as alleged accomplishments of the 'machine metaphor' revealing its scope.

Some recognized milestones in the history of ideas about the inner workings of organisms are surveyed: the proposals of the early mechanicists during the Scientific Revolution, Lavoisier's view of respiration as combustion, Liebig's description of the human body as a chemical machine and the suggestion that the chemical accomplishments in living beings are the result of myriads of fermentation-like processes. I devote special attention to the problem of the direct conversion of chemical energy into mechanical energy using the evolution of ideas about muscular contraction as the main example.

During the period 1900-1930 the study of colloidal behavior was considered to be the right path for unraveling most of the mysteries of vital processes. I carefully describe this work particularly the proposed models for muscular contraction and enzymatic action. The dismissal of this colloidal approach after the acceptance of the existence of those particular kinds of macromolecules that exist in living organisms marks the entrance of our modern approach. One of the remarkable features of the modern approach is the incessant elaboration of the idea of 'molecular machine'. I conclude with a discussion of the problem: how literally can this metaphor be taken?

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INTRODUCTION

The title itself looks like a short introduction, but a proper one is necessary to explain it.

Since the Scientific Revolution man has been increasingly thinking of himself, and all any other living organisms as well, as various kinds of machines. Such comparison with a machine was sometimes explicitly stated -- although rarely was its scope carefully examined -- but on other occasions the metaphor was not openly expressed and to reveal it a degree of perspicacity is needed. The present essay is an attempt to uncover the pervasive presence of what I term the 'machine metaphor' behind the different views of what living organisms are and how they work.

To achieve my purpose I took some recognized milestones in the history of ideas about the inner workings of organisms: the proposals of the early mechanicists during the Scientific Revolution, Lavoisier's view of respiration as combustion, the first coherent description of the human body as a chemical machine attempted by Liebig and the suggestion that the chemical

accomplishments in living beings are the result of fermentation-
like processes.

After energy became the unifying concept of physical sciences and
machines began to be analyzed as transducers, the conversion of
chemical energy into mechanical energy turned out to be a central
issue of the treatment of an organism as a chemical machine. That
is why I devote a rather large portion of this study to analyze
the models suggested to explain the muscle, the prototype of a
chemical machine. After all, the term 'machine' is closely
associated with macroscopic movement.

The conversion of chemical energy into mechanical energy without
the intermediation of heat -- as the process was found to occur
in living organisms -- was explained for decades using models
belonging to the field of colloids. The third chapter is devoted
mainly to that period during the first decades of the present
century during which the study of colloidal behavior was
considered to be the right path to unravel most of the mysteries
of vital processes. The dismissal of the colloidal approach after
the acceptance of the existence of particular kind of
macromolecules in the cell marks the entrance of our modern
approach, which in the last chapter I describe as the period of
the molecular machine .

As can be deduced from this short summary, the undertaking of describing the 'machine metaphor' at work is confined within the contrivance aspects of the metaphor. That is, I treat the machine mostly as an apparatus, a physico-chemical arrangement of parts. Neither the purposeful feature emerging from the fact that it is a contrivance arranged to execute a task previously foreseen, nor the harmonic working of its operation, are dealt with here. Metaphors relating these two aspects -- purposefulness and harmonic operation -- with those physiological phenomena encompassed under the broad category 'homeostatic mechanisms', not to say the assimilation of the human brain to a computer, are regretfully left aside. The only reason is time.

Finally, the fact that the study is restricted to the history of ideas does not mean at all that in principle I look with indifference other aspects of the scientific endeavor. I just believe that the approach followed in this essay establishes a coherent narrative, opening wide and interesting lines of research to pursuit later. Moreover I claim that it throws insightful views on the question of the construction of meaning of scientific theories.

1. ON METAPHOR

> There is a mysterious wisdom by which
> phenomena among themselves disparate can
> be called by analogous names, just as
> divine things can be designated by
> terrestrial terms, and through equivocal
> symbols God can be called lion or leopard;
> and death can be called sword; joy, flame;
> flame, death; death, abyss; abyss,
> perdition; perdition, raving; and raving,
> passion.
>
> Umberto Eco: The Name of the Rose

1.1 INTRODUCTION

From the beginning of his existence as a conscious being man has

wondered about his most astonishing tool: language. Western

thought, from Plato's cave to Sapir and Whorf has speculated

about the limits language imposes on our ability to understand

the world.[1] Are we trapped in the logic we use to communicate our

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[1] Linguistic relativity, that is, the idea that language
determines the conceptual scheme of individuals is associated
mainly with the names of Edward Sapir and Benjamin Lee Whorf, and
the idea is commonly dubbed the Sapir-Whorf hypothesis.

ideas, or does this logic just mirror some sort of 'world's structure'? Are not we losing important insights into nature's lawfulness with our logic of communication? How can we endeavor to understand what we still do not understand using the language and theories built up out of what we already know? Are theories semantic-free, i.e., is the language used in science only a conveyor of information and theoretical statements just logical propositions, or should we adopt the view that we use language as a sort of organ of reception, not only a conveyor of information? Do the categories embedded in discourse limit the possible categories of thought? In summary, What is the relationship between language and the world?

These, or some of these, are hard questions to answer which psychologists, anthropologists, philosophers of language, philosophers of science and plain philosophers have been engaged in deep disputes. Some of these can be stated in questions involving the term 'metaphor', such as: Can metaphor be considered as a cognitive device? Is there a literal language, as compared to a metaphorical one?

Some decades ago metaphor was a subject matter only for rhetoric and literary criticism, and it was usually considered as an intentional misrepresentation of the world. On the other hand, in the philosophy of science models and analogies were considered as tools restricted to what Hans Reichenbach called the "context of

discovery". Under the program of logical empiricism, the role of philosophers of science was confined to 'cleansing' science from meaningless statements and rendering scientific theories as semantically-free logical structures. The meaning of the non-logical terms used in a scientific theory, either neologisms invented ad hoc as 'operon' or the vocabulary borrowed from everyday language should be given only by the logical web of concepts or by some sort of rules allowing for an observational interpretation.

After the advent of other strands of philosophical analysis and the critique directed against this so-called 'received view' of the logical empiricists, the attention paid to metaphor changed noticeably, and literature in the philosophy of science is nowadays flooded with references to it.[2]

In this chapter I will make explicit some fundamental points concerning the grounds for and consequences of using the notion of metaphor to clarify questions about the production, validation

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[2] As Geoffrey N. Cantor affirms, "Metaphor has during the last couple of decades become a contentious subject among philosophers" [Cantor, 1982]. In the same collection of articles, Jan V. Golinski [Golinski, 1982] mentions as landmarks in the awakening of the new interest on the language of science the work of H.G. Gadamer, Jacques Derrida and Richard Rorty in the philosophy of language, and T.S. Kuhn and M. Foucault in the history and philosophy of science. In particular disciplines, G. Canguilhelm has approached some aspects of the history of biology following a similar approach, and in Crystal, Fabrics and Fields Donna Haraway examined a crucial period for the history of modern embryology under the guide of metaphor analysis [Haraway, 1976].

and use of scientific theories. In other words, I am going to use
'metaphor' as a metaphor to account for some features of
scientific theories and explanations.

1.2 THE LITERAL AND THE METAPHORICAL

The most recognizable feature of a metaphor is the juxtaposition
of two domains: a word or phrase is used in a place (second
domain) where its literal meaning (literal in a first domain)
does not fit exactly. The "semantic anomaly" [McCormack, 1985]
originates a tension which could be used as a symptom that a
metaphor is present, were it not for the fact that a persistent
use exhausts the metaphor's unconventional feature. Phrases or
words that once were able to cause strain die as source of
tension, becoming new entries in the dictionaries.[3]

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[3] For instance, people are not aware of the large number of
anthropomorphic metaphors present in everyday language: the leg
of a table, the arms of a chair are but two examples. The
etymology of words is usually a source of information about the
societies where a word was originated, as when we know that
'school' comes from a Greek word denoting what today we call
'leisure'. Etymological exploration can also show the deep
philosophical problems behind the use of some words. In the case
of the verb 'to be', for example, Julian Jaynes tells us: "Even
such an unmetaphorical-sounding word as the verb 'to be' was
generated from a metaphor. It comes from the Sanskrit bhu, 'to
grow, or make grow', while the English forms 'am' and 'is' have
evolved from the same root as the Sanskrit asmi, 'to breathe'. It
is something of a lovely surprise that the irregular conjugation
of our most nondescriptive verb is thus a record of a time when
man had no independent word for 'existence' and could only say
that something 'grows', or that it 'breathes'" [Jaynes, 1976].
Sometimes people seem to pay more attention than is sensible to
the dormant metaphors, as when some radical feminists struggle to

Why is the second domain described in terms of the first instead of being referred to literally? One possible answer could be that in some instances the available vocabulary is insufficient and pointing or drawing are not allowed (catachresis), as in the use of the word 'orange' to denote a color. Another possible answer could be that for aesthetic reasons an author prefers an unusual term of a periphrasis to say something that he could have said directly.

Although situations in which these answers account for the use of a metaphor exist, they far from exhaust the apparent cognitive and emotional achievements of the juxtaposition of meanings in paradigmatic metaphors. Take the classical example: "Man is a wolf". "Wolf" refers literally to "any of a large group of flesh-eating doglike mammals widely distributed throughout the Northern Hemisphere" (Webster's Collegiate Dictionary) and does not map completely onto <u>Homo sapiens</u>. Which of the many anatomical, physiological or behavioral features of 'wolf' is the author aiming to ascribe to 'man' depends on the context of what is being said and especially on the set of "associated commonplaces" between the concepts 'man' and 'wolf' when taken literally in a particular culture.[4] In literary contexts the author will play

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change 'chairman' or 'mankind' for something less male-dominant.

[4] The expression "associated commonplaces" is Max Black's, in his <u>Models and Metaphors</u> [Black, 1962]. Black reminds us that in cultures where wolves are sacred animals the metaphor will

with the analogies and disanalogies to evoke in the reader some specific emotions, rarely planning to close the interpretations. Aside from suggesting similarities, the metaphor opens a universe of vagueness and assumes this as the risk of trying to say something new.°

A metaphor is an exploration of novel interpretations, of new possible meanings for already existing words and concepts, suggested by an author when he introduces an <u>intelligible anomaly</u> in literal meanings. The metaphor not only produces its effect by suggesting new perceptions about the second domain; it also has the power of affecting meanings in the first domain. In the example above, not only 'man' is exposed to reinterpretations; 'wolf' is, too. The metaphor is successful if it evokes <u>new</u> insights -- the tension is attached to the novelty -- if it awakens in the hearer or reader a net of interconnections or similarities between the two domains. The reader will say he 'understood' the author's intentions if the text is able to

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have a quite different effect. Konrad Lorenz used to tell that when two doves are confined until starvation they will fight until one eats the other, while two wolves will never behave in that way. Were this everyone's knowledge the dove as metaphor for peace would lose it appeal.

° Morse Peckham, in his Foreword to Turbayne's <u>The Myth of Metaphor</u> [Turbayne, 1970] puts metaphor in the forefront of language construction: "I was convinced that metaphor is not only a normal semantic mode but a mode essential for the existence and above all the extension of the semantic functions of language. It is the only way we have for saying something new".

produce a partial overlapping of the reader's views about both domains.

1.3 THE RECEIVED VIEW OF SCIENTIFIC THEORIES AND EXPLANATION

Are these considerations of any relevance when we analyze the way in which theories are suggested, proposed, invented and defended by scientists? Many people will agree that they are indeed, but within the context of discovery, not in the context of justification. In fact, does Kekule's dream about a snake biting its tail have any importance for understanding the benzene ring?

In the context of justification, it would be argued, we are engaged in the task of finding or arranging the evidential support for a theory. Justification would not be the realm of imagination, where the individual scientist after a trial and error procedure with analogies, extensions, generalizations, models, aesthetical considerations and so on, envisions a theory or an explanation for a phenomenon. All this can be of interest only to biographers, psychologists, or some historians of science hardheadedly stuck with the history of ideas. The judgement of a particular scientific community should barely be influenced by these things, if influenced at all.

There are, however, other circumstances in which the relevance of
metaphor-like processes is not so easily disposed of. Is the
benzene ring itself a <u>literal</u> description about a real, existing
molecule? Is the 'slippery' electron a particle, a wave,
sometimes the former and sometimes the latter, both, or only a
mathematical fiction? Are men jealous like geese, or geese
jealous like man? [6]

With their rejection of these sorts of 'unobservables', earlier
positivists ended up denying not only the existence of molecules,
but some of them even suggested that an appeal to fictions like
these in sound science was illegitimate.

As for the logical empiricists, harmonizing the unavoidable
approval of unobservables with the aim of barring from science
statements devoid of empirical content was one of their goals.
They had to acknowledge that one of the outstanding features of
scientific theories, particularly in physics, their great

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[6] It is a well documented episode in the history of science
the strong resistance against Van't Hoff's suggestion that
molecules have shape. Kolbe, the editor of the <u>Journal fur
praktische Chemie</u>, where Van't Hoff's theory of the asymmetrical
carbon appeared for the first time in German (1877), wrote about
the theory using bitter statements like the following: "'The
arrangement of atoms in space', by Messr. Van't Hoff and Hermann
... teems with fantastic trifles. A Dr. Van't Hoff who is
employed at the Veterinary School in Utrecht appears to find
exact chemical research not suited to his taste. He deems it more
convenient to mount Pegassus (evidently loaned from the
Veterinary School) and to ... proclaim how to him on the chemical
Parnassus ... the atoms appeared to be arranged in the
Universe... The prosaic chemical world found little taste in
these hallucinations" (quoted in [Van't Hoff, 1967]).

exemplar, is the fact that those very theories contain unobservables. If a theory of science is going to give an account of what science is and what scientists do, these unobservables cannot be neglected. The problem, then, was how to assign to them a precise meaning, and the solution was looked for in the relationship between unobservables and observables.

But the reduction of theoretical statements to statements in a purely observational vocabulary could not be done just by definitions. According to Carnap, "there is no way that a theoretical concept can be defined in terms of observables. We cannot give a really adequate definition of the geometrical concept of 'line' by referring to anything in nature..."

> [The] axiomatic terms -- 'electron', 'field', and so on -- [of a postulate system in physics] must be interpreted by correspondence rules that connect the terms with observable phenomena. This interpretation is necessarily incomplete. Because it is always incomplete, the system is left open to make it possible to add new rules of correspondence. Indeed, this is what continually happens in the history of physics [Carnap, 1966].

Observational vocabulary is not applicable to theoretical vocabulary. Instead, "correspondence rules" have to be formulated between theoretical terms and observable terms for some of the former, so they can be contrasted with experimental facts. For example, if t is a theoretical term we cannot say that t means 'red', because we would be defining a theoretical term with an

observable one. A statement such as "a certain wavelength is red" makes no sense; one does not say that the wave is red, but rather that it corresponds to the observable red. Correspondence rules are of the form "whenever property x (an observable property, in the example here, red) of an entity a (the radiation coming from a source) is true, then it is also true that 'ta' (the radiation coming from the source has an specified wavelength)."

In very general terms this is Carnap's view of theories as "partially interpreted axiomatic calculi". Any possible meaning for theoretical terms different from their being part of an axiomatic structure and from the meaning acquired in virtue of correspondence rules was explicitly ruled out. (See below for further precision on this point.)

The account just sketched represents what, following Hilary Putnam, has been called the 'received view' of theories. As part of logical empiricism it dominated Anglo-American philosophy of science in the 1940's and 1950's. For many years since, criticizing the received view has been the main source of self definition for many philosophers of science.

Parallel to the received view of theories, the so-called deductive-nomological, or covering-law, model of explanation was developed, mainly by Carl Hempel. According to the model all explanations in science have in common the following scheme: a

series of statements about phenomena (the <u>explanandum</u>) are said to be explained if one can logically deduce them from some singular statements (antecedent conditions) along with some general laws of nature (these two comprising the <u>explanans</u>). The explanation must comply with the following rules:

R1 The explanandum must be a logical consequence of the explanans

R2 The explanans must contain at least one general law

R3 The explanans must have empirical content

R4 The sentence constituting the explanans must be true

According to the received view, then, theories do not spring up as generalizations from experimental data. Theoretical terms could appear as the result of an intellectual process properly catalogued under 'imagination', a process belonging to the context of discovery. But what constitutes scientific knowledge are the final clean statements formalized in propositional structures. Explaining is fundamentally a logical process by which statements describing observations are obtained deductively from a set of statements containing at least one general law. In this account, we see, there seems to be no place for anything akin to metaphor. As stated in the introduction, the terms used in science -- force, attraction, particle, reaction, molecule, competition -- and the statements built with them have a meaning restricted to their use in scientific language. If the words or the images coincide with terms or statements in everyday

language, it is just an unfortunate state of affairs. Supposedly, ideology is kept out of science with this strategy.

1.4 MODELS IN THE RECEIVED VIEW

There are two ways of attaching meaning to theoretical terms. One is given by the logical web of axioms (for example, the term "molecule" appearing in a theory may be defined implicitly as "that entity satisfying such and such axioms and theorems"). The other way is by the correspondence rules correlating <u>some</u> theoretical terms with observational terms. There are then two sources of 'partialness' in Carnap's idea of "partially interpreted axiomatic calculi":

(1) Correspondence rules are not definition-like. If one had a definition for "molecule" then one would be able to replace the word with its definition and every sentence would preserve its meaning. There is no definition as such for theoretical terms because as continuous research unravels more features of the world, more correspondence rules (and hence 'more meaning') are attached to a theoretical term.[7]

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[7] Carnap asserts even that at the moment one states a definition, one has an observable term: "Eventually a point may be reached beyond which there will be no room for strengthening the interpretation of a term by new correspondence rules. Would not the rule then provide a final, explicit definition for the term? Yes, but then the term would no longer be theoretical. It would become part of the observation language" [Carnap, 1966, p.

(2) As there is not necessarily a correspondence rule for each unobservable (theoretical) term, some statements can have no meaning attached to them via a correspondence rule.

In this description of the attachment of meaning, one of the more conspicuous expressions used by scientists when they describe their work is missing: models. Rarely are scientific theories presented or used as "partially interpreted axiomatic calculi". Normally, they are presented through models. We can say that part of the content of the theory can be visually imagined, and here is where scientists appeal to models. In its more general (logical) sense a model for a theory is a set of entities and its attributes that satisfies the theory. Some authors call this an "interpretation". A model for Newton's law of gravitation could be an imaginary system of particles attracting each other according to the inverse-square law and moving according to the three laws of motion. Correspondence rules can then be established between this model and astronomical observations of the spots seen in the sky. Thus, a model for a theory plus the correspondence rules satisfies both the axioms and the rules, but can attach additional meanings for theoretical terms and can attach "meaning" to statements lacking it in a rigorous view. In this way, the model would be complementing the partial interpretation arising from considerations (1) and (2) above,

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providing at the same time candidates for new correspondence rules.

Now, is this view of model licensed in the "received view"? Some followers of logical empiricism claim that it is. Some antagonists remind them of Carnap's explicit prohibition of attaching meaning by ways different from correspondence rules and axiomatic structure.[8] To them accepting a sort of 'meaning' (Nagel writes it in quotation marks) from an interpretation in terms of a metalanguage -- in this case the natural scientific language -- would be like opening the backdoor to let in the vagueness against which the core of the logical empiricist's program had promised defense. But even if we accept that through the metalanguage the received view allowed some kind of non-observable interpretation language, undoubtedly it was very far from being sponsored.

The logical empiricist account, then, is intended to license theoretical terms in the philosophy of science. To accomplish this goal while keeping all science based on 'safe sense data', the distinction between "theoretical terms" and "observational

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[8] Nagel, for example, formulates three components of the theory: the axiomatic calculi, the correspondence rules and "an interpretation of model for the abstract calculus, which supplies some flesh for the skeletal structure in terms of more or less familiar conceptual or visualizable materials" [Nagel, 1961, p. 90]. Although Nagel can be considered an advocate of the logicist view of logical empiricism, his inclusion of models as part of the apparatus for attaching meaning is quite different from Carnap's almost complete dismissal of them.

terms" was drawn.[9] By axiomatizing scientific theories while attempting a 'logic of induction', science was thought to be put on a safe basis. Curiously enough, among all the criticism the received view and its collateral developments suffered, the ones that inflicted more severe damage were directed against the dichotomy observational – theoretical and against the claim that scientific theories are axiomatic structures.[10]

As is particularly clear in its treatment of models, logical empiricism strived to separate the context of discovery -- which in fact is more like the context in which theories are actually used -- from the context of justification, the former full of everyday experience and ordinary use of language; the latter,

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[9] The need to license terms in scientific theories is a philosophical problem. Scientists do not ask philosophers to issue any sort of licence.

[10] A Lakatosian account of the rise and fall of the logical empiricist's research program fits very well with its development. The program was born with two aims -- coinciding with its greatest anomalies. To show that scientific theories can be studied as axiomatic structures, and to allow for the presence of unobservables. To deal with the latter logical empiricism sponsored the distinction between observational and theoretical. But in spite of the fact that they were always discussed, the anomalies did not stop the research program until the program itself failed to produce results remarkable enough to diminish the significance of these anomalies. If it is claimed sometimes that inside science dismissal of a theory comes after a complex switch of view, this feature of theory change must be even more noticeable in the decline of a philosophical school. None of the individual criticisms against logical empiricism was by itself decisive enough to be the cause of its dismissal.

pure, the realm of logic.[11] That was precisely the division that made 'metaphor' an unacceptable tool to analyze the growth of science. But now, if the received view has been dismissed and theories are not anymore considered as 'partially interpreted calculi', what is left as a 'scientific theory'?

As distinct from the years of high praise for the received view, today there is more consensus about what theories are not than about what theories are. Presently, most philosophers of science claim that more attention must be paid to the way theories are used, giving up any illusion of constructing safe knowledge based in something akin to pure sense data and giving up any dream of building a logic of induction to account for theory change and development in 'logical terms'.[12] Terms in scientific theories are continually open to reinterpretation, a fact acknowledged even in the received view with the extension of meaning through

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[11] If scientific theories are there only to be falsified the idea that theories are actually used in the context of discovery more than in the context of justification is strange-looking. But theories exist at different levels, and in addition more than one is present in a particular research endeavor. For example, the 'enzyme theory' of cell processes (see Chapter 3) is _used_ to apprehend, say, data related to the oxidation of foodstuffs, and as a result a theory for this particular process will result. To some extent the 'enzyme theory' is enduring a falsifying test, but to a much greater extent it is being _used_ in a context of discovery to analyze sets of experimental data. It is supplying the 'glasses' through which a particular experiment is being observed and parametrized. The procedures to relate the results to a model pertaining to oxidation in this cases, as well as to an enzyme theory are anything but closed.

[12] Stephen Toulmin interpreted the aim of logical positivism as that of reducing 'rationality' to 'logicality' [Toulmin, 1977]

new correspondence rules. Philosophy of Science does not draw anymore a demarcation between science and non-science by barring some class of terms from the former. Scientific theories, of course, must render statements susceptible to comparison with experimental results, notwithstanding the fact that there are not straightforward rules for a decision procedure following a contradiction between experimental results and predictions coming from the theory. Having almost abandoned the task of establishing formal rules to differentiate the statements comprising scientific theories from all other statements that are the product of man's faculty of thinking, modern theories of science have ruptured their link with old claims that science offers the unique route to the _literal_ description of man and the world. The difference between science and other intellectual endeavors is clearer if we look at attitudes: some scientists struggle to close their favorite metaphors, while others strive to change the metaphors by shaking theoretical structures at the loose ends.

1.5 MODELS, METAPHORS AND PARADIGMS

Let us briefly consider some situations where the word 'model' is invoked: Faraday's lines of force, Ising's model of phase transitions, the hydraulic model of electric current, the electrical circuit model of an economic system, the scale model of an airplane, the Darwinian model for the survival of theories

in science, the covering-law model of explanation, the balls and sticks models of molecules, the Briggs-Haldane mathematical model of enzyme kinetics, the liquid drop model for the nucleus of the atom and so forth.

Models are enormously varied and taxonomies of different kinds are possible. According to its "sense", Suppe [Suppe, 1977] considered models to be either mathematical or iconic, the former ones the strictly logical, the latter referring to concrete objects. Conversely, Black mentions scale models, those icons presuming relative geometrical proportions, analogue models, reproducing some structural relationships in the original, mathematical models, sometimes just a mathematical treatment and sometimes an intended physical and/or mathematical simplification, and theoretical models, those generally describable as originating in an analogue model whose objects are idealized by stripping off the negative analogies [Black, 1962].

The favorite example of a theoretical model is Maxwell's set of equations for the electromagnetic field. Initially conceived as equations describing stress/strain relations of a really existing mechanical ether, the model was stripped of its uneasy features until the ether transmitting the waves simply disappeared. Electromagnetic waves ended up being vibrations of nothing, and each point of the space was accepted as the place of an electric field whose intensity and direction is described by the set of

equations. No reference is made anymore to the ether model. In almost all cases, the models fades away while at the same time the theory itself is more and more accepted. The waning of the original model is at the heart of the idea that there is really no model here at all and that the description is direct and literal.

A mixture of tradition and success has produced the feeling that some theories allow us to describe and explain the world as it is, in its natural categories without any models. Today everyone is at risk of waking up after a bad Lucretio-Cartesian night with the vision that everything really is just matter and motion. The most clear symptom that nowadays one particular approach has acquired a monopoly on the status of the literal is that 'finding the mechanism' and 'explaining' are often considered to be equivalent. Ingenuousness about the vocabulary being used is a direct road to becoming a victim of a metaphor instead of its user.[13] 'Finding the mechanism' is an expression whose long history should make us aware to take it with caution. But its daily and all pervasive use has transformed it into a dormant metaphor, as if it were another common element of our natural language.

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[13] One of the central ideas of Colin Turbayne's The Myth of Metaphor is that unawareness of the existence of metaphors underlying alleged literal description will turn the user of the theory into a victim of the hidden metaphor [Turbayne, 1970].

When no explicit reference is made to a model, we must suspect

the presence of categories that once were mere challengers of

other accepted classifications, but that are now so deeply rooted

that they do not seem at all to be suppressing other possible

approaches. They are the only possible approach. Max Black calls

them 'conceptual archetypes'. They are:

> systematic repertoire[s] of ideas by means of which a
> given thinker describes, by analogical extension, some
> domain to which those ideas do not immediately and
> literally apply. [Black, 1962]

Reconstructing such kinds of underground archetypes amounts to

finding "a list of key words and expressions, with statements of

their interconnections and their paradigmatic meanings in the

field from which they were originally drawn" [Black, 1962]

In order to show what he means by conceptual archetypes, Black

makes use of Stephen Pepper's penetrating effort to discover

deep-rooted constitutional metaphors. Pepper tries to make a

taxonomy of the highly variable "zoology" of suggested worldviews

in the history of philosophy.[14] By using what he named "root

metaphor theory" Pepper concluded that behind the great variety

of world hypotheses there are repeated themes, so that the

successful ones can be fitted into a small taxonomy. "The root

metaphor theory is simply a recognition of the fact that there

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[14] Pepper called these worldviews "world hypotheses", and
defined them as those "products of knowledge ... that ... cannot
reject anything as irrelevant" [Pepper, 1961].

are schools of philosophy... but philosophical imagination is not
as prolific as many claim" [Pepper, 1961, p. 328].

> The method [of world hypothesis construction from a
> root metaphor] in principle seems to be this: A man
> desiring to understand the world looks about for a clue
> to its comprehension. He pitches upon some area of
> common-sense fact and tries if he cannot understand
> other areas in terms of this one. The original area
> becomes then his basic analogy or root metaphor. He
> describes as best he can the characteristics of this
> area, or, if you will, discriminates its structure. A
> list of its structural characteristics becomes his
> basic concepts of explanation and description. We call
> them a set of categories. In terms of these categories
> he proceeds to study all other areas of fact whether
> uncriticized or previously criticized. He undertakes to
> interpret all facts in terms of these categories. As a
> result of the impact of these other facts upon his
> categories, he may qualify and readjust the categories,
> so that a set of categories commonly changes and
> develops. Since the basic analogy or root metaphor
> normally (and probably at least in part necessarily)
> arises out of common sense, a great deal of development
> and refinement of a set of categories is required if
> they are to prove adequate for a hypothesis of
> unlimited scope. Some root metaphors prove more fertile
> than others, have greater power of expansion and
> adjustment. These survive in comparison with the others
> and generate the relatively adequate world theories
> [Pepper, 1961, p. 91].

Pepper found four "adequate world theories", which he dubbed
formism, mechanism, contextualism and organicism.[15]

Although Black seems to endorse Pepper's conclusions, nonetheless
the former does not challenge the existence of a literal
descriptions in science. His suggestion to look for the

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[15] One interesting use of Pepper's "root metaphor theory"
can be found in The Vitalism of Hans Driesch, by Horst H.
Freyhofer [Freyhofer, 1982].

archetypes is limited to "[those] cases where we have, as it were, an implicit ... model" [Black, 1961, p.239]. Presumably, one is to understand by Black's reluctance to say that all theories have conceptual archetypes that he believes there are realms describable or explainable in their own terms, in contrast with some domains where certain "ideas do not immediately and literally apply" (ibid.).

This sort of literality is surely in the mind of some 'soft critics' of the use of models in science (like Braithwaite) who accept their use, but argue that "the price of [their use] is eternal vigilance". I would agree with them, but only after having obtained an answer to the question: When is eternal vigilance not necessary? I would suggest we must extend our vigilance to any theory, those with explicit models and those with implicit archetypes. In this way all scientific conceptual- ization would be covered by the call of prudence implicit in the warning that hidden assumptions, very likely originating in some kinds of metaphors, are within the citadel of science. This recognition, however, does not deny the fact that different schools may allocate the watchmen to different places.

The feeling of literality produced by these scientific theories which make no clear declaration that a model or metaphor is being used is heightened by the covering-law account of explanation. In fact, the latter's emphasis on logic pretended to circumvent any

appeal to models or analogies. Hempel deliberately contested N. R. Campbell's insistence on the crucial role of analogy when the latter wrote: "In order that a theory may be valuable it must ... display an analogy" [Campbell, 1920, p. 129]. For Campbell the analogy was far from being a mere aid in formulating a theory. The dynamical theory of gases, for example, was accepted not because it provided a general formal structure from which some experimental laws previously known could be deduced -- for Campbell producing such sort of logical structures is extremely easy -- but because the theory provided a successful analogy.

More recently, Mary Hesse, repeating Campbell, suggested that for theoretical explanations "the deductive model should be modified and supplemented by a view of theoretical explanation as metaphorical redescription of the domain of the explanandum" [Hesse, 1966, my emphasis]. In this way, she claims, some inadequacies of the covering-law model would be amended, as follows:

(1) The statement describing the fact to be explained in the observational domain is not obtained exactly from the logical deduction. What occurs is that a deduced statement is used to interpret the first domain, an interaction of meanings properly belonging to the semantic figure we have called metaphor.

(2) There is no deductive relation between the explanans and the explanandum, for there is the mediation of correspondence rules. These 'rules' would be better understood as part of a metaphorical redescription.[16]

(3) The strong sense of prediction -- extension of the theory to new domains by prediction of laws not logically contained in the theory and explicit correspondence rules -- requires additions to the correspondence rules. There is no rational method for adding new rules. They become a useless concept.

> "In the metaphoric view... since the domain of the explanandum is redescribed in terminology transferred from the secondary system, it is to be expected that the original observation language will both be shifted in meaning and extended in vocabulary..." [Hesse, 1966].

The metaphorical view, then, does not require additional consideration of the idea of correspondence rules.

There remains, of course, one important question: Does it make any sense to bring in the notion of metaphor, taking the risk of converting it into just another name for the already well discussed 'model'?

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[16] In this way, Hesse is eliminating the theoretical/observational distinction: "There is one language, the observation language, which like all natural languages is continually being extended by metaphorical uses and hence yields the terminology of the explanans" [Hesse, 1966].

The question itself reveals one of the outstanding features of metaphor-like processes. When we import the term 'metaphor', whose literal realm belongs to art, with the aim of using it in an examination of the process of constructing the meaning of categories in natural sciences, we engage ourselves in a comparison of conceptualization in science with the processes of the extension of meaning in language itself and with the creative uses of language in literature. Once we have decided to use the term 'metaphor' to study what scientists do when they look for explanations, we have to decide if we are going to take the term literally.[17] Poetry and science are not the same endeavor. The exploration of the negative analogies should show the usefulness of attempting to understand scientific theories by considering ideas in science as evolving through metaphor-like processes. If we do this -- if the metaphor has been successful -- new insights not only on how scientific theories are constructed and validated, but also on the character of metaphor in literature will be gained.

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[17] We should not feel discouraged by the fact that 'metaphor' is going to be a metaphor to account for scientific theories. The logical empiricist account, that scientific theories are pure mathematical structures, is also a metaphor [Kuhn, 1977]. I think in addition that Colin Turbayne is right when he claims that behind Newton's approach there is the idea that 'principles' such as are used in logical analysis can be used to lead us to 'natural principles' whereby to analyze nature. That is, Newton uses a metaphor in which the literal realm is the realm of logic, to try to discover in the world a logical structure.

There is an evident resemblance between model and metaphor. According to Black, a model would be a "sustained and persistent metaphor". But while in literature the interaction is usually left to commonplaces requiring for the creator only proverbial knowledge, in science the creator requires "prior control of a well-knit scientific theory if he is to do more than hang an attractive picture on an algebraic formula" [Black, 1962]. Turbayne stresses the fact that in models the analogies should be specified [Turbayne, 1970], while Hesse states that "in scientific contexts the primary and secondary systems may both be highly organized by networks of natural laws" [Hesse, 1966]. For example, if one is to apply an hydraulic model for the electric current in metals, the behavior of systems in both realms must be fairly well known. She points out two other negative analogies: "We can perhaps signal the difference by speaking in the case of scientific models of the (perhaps unattainable) aim to find a 'perfect metaphor'; in poetry, metaphors may be intentionally (often, not always) imperfect...". On the other hand, "scientific models ... may be initially unexpected, but it is not their chief aim to shock..." [Hesse, 1966].

We can see that the differences are not sharp -- "models may be", "metaphors perhaps are". There exists a kind of 'illustrated poetry' where the author consciously explores different faces of a metaphor. 'Shocking' is not necessarily an explicit purpose of a metaphor in literature -- better, we say that the 'shock' is

produced by the suggestion of a novel interpretation -- while scientific theories change in a tense environment of imprecise meanings. On the other hand, we cannot neglect the presence of root metaphors -- undoubtedly not carefully knitted -- at the base of theoretical models.

Models are metaphors in the sense that there is transfer of meaning between different domains and that they contain open and consequently imprecise analogies. The tension inherent in their use is noticeable during periods of theoretical rivalry and remains visible in the loose ends. There, logical empiricism saw a place for adding new correspondence rules to a solid, almost immovable theory, while the metaphor approach stresses the resemblance with the process of the construction of meaning pertaining to all form of knowledge. Finally, I will add that models do not pretend to have an emotive content, and that, unlike what happens in art, they are stated as speculative instruments to be taught, learned, accepted and methodically explored by successive generations.

These last features accentuate the differences due to the kind of community to which the metaphor is addressed. Inside the social processes of validation and perpetuation, scientific terms share all the uncertainties suffered by the meanings of any terms, so well described by Hesse:

> To understand the meaning of a descriptive expression
> is not only to be able to recognize its referent... but
> also to call to mind the ideas, both linguistic and
> empirical, that are commonly held to be associated with
> the referent in the given language community. [Hesse,
> 1965]

We cannot help but see Kuhn's notions of paradigm, exemplar and

conceptual shift in the metaphor approach.[18] Something having the

properties of metaphor is often called upon, states Kuhn, not

only when a new term is introduced in the vocabulary of science;

"it is also called upon when such terms -- by now established in

the common parlance of the profession -- are introduced to a new

scientific generation" [Kuhn, 1977] . Further on he states:

"However scientists apply terms like 'mass', 'electricity',

'heat', 'mixture' or 'compound' to nature, it is not ordinarily

by acquiring a list of criteria necessary and sufficient to

determine the referents of the corresponding terms"

[Kuhn, 1977].[19]

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[18] Kuhn himself explicitly acknowledged this point. After
accepting that the term ' Paradigm' had led to many
misunderstandings, he stated: "No aspect of my viewpoint has
evolved more since the book was written... We approach the
problem in the same spirit including a common conviction of the
relevance of the philosophy of language and of metaphor"

[19] An uncommonly open statement of the relevance of non-
formal meaning of scientific concepts is found in the Prologue to
Kurt Gottfried's and Victor Weisskopf's book Concepts of Particle
Physics, Vol. I: "physics has both a written and an oral
tradition. Intuitive modes of thought, inference by analogy and
other stratagems that are used in the effort to confront the
unknown are transmitted from one generation of practitioners to
the next by word of mouth. After the work of creation is over,
the results are recorded for posterity in a logically impeccable
form, but in language that is often opaque. The beginner is

The meaning of scientific terms and theories to the oncoming
generation will be captured through the exposure to shared
exemplars, not by explicit rules for attaching the theory to new
situations. Instead of correspondence rules, Kuhn suggests
"resemblances between apparently disparate problems" [Kuhn,
1979]. It appears clearly that in Kuhn's view, the kind of
openness present in the cognitive processes explicitly
acknowledged as metaphors will provide a better account for the
way theories are used than fixed theories with a changing number
of correspondence rules.

. . . .

In the following chapters I am going to trace the evolution of
ideas about the prototypical features of organic processes
occurring in the biological individual, paying attention to the
explicit and implicit references made to 'mechanisms' and
'machines'. Besides devoting attention to the open allusions to
the realm of man-made contrivances, I will also endeavor to find
hidden assumptions, that is, aspects of the undeclared use of the

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expected to absorb this written tradition, and only the survivors
of this trial-by-ordeal are admitted to circles where the oral
tradition is current.... We believe that this tradition plays an
essential role not only in the creation of physics, but also in
the search for new understanding" [Gottfield, Weisskopf, 1984, p
vii].

<u>machine metaphor</u> hiding behind the explanations suggested for particular physiological processes.

2. FROM CLOCKWORKS TO CHEMICAL MACHINES

2.1 INTRODUCTION

As one of the entries for 'mechanism' a dictionary will tell us that the term refers to a doctrine according to which all phenomena related to living beings are just manifestations of physical and chemical laws.[20] Etymologically the term comes from the greek mechane -- machine or contrivance. Apparently, the original relation of the term with machines was abandoned a long time ago and can be found, if at all, only as a relic, a curiosity, when observers interested in the evolution of ideas move among the original sins of today's traditional approaches.[21]

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[20] See, for example, Webster's New World Dictionary, The World Publishing Company, Cleveland and N. York, 1966.

[21] In her book On the nature and origin of life Hilde S. Hein, for example, remarks that the thinkers belonging to the period of the Scientific Revolution were limited by the knowledge and the simple machines then available for explanation or analogical extension to the organic realm: "The mechanism of the XVIIth and XVIIIth was dominated and limited by the character of contemporary science" [Hein, 1971, pg 81]. She is right, but I am afraid that to her XXth century scientists are neither limited by

As I shall show, open allusions to machine-like operations have been always present when the most fundamental features of living creatures are under scrutiny. But more interesting are some hidden assumptions of the reductionist approach that in differing degrees remind us either of contemporary technology or just of those everyday exemplars of evident mechanical behavior. At the same time, when hypotheses about particular physiological events were advanced under the view that those events were caused by a peculiar organization of matter moving according to knowable rules, it was not forgotten that the phenomena are parts of living creatures.

A very appropriate starting point is the so-called Scientific Revolution of the XVIIth century, when the present meaning of 'mechanism' was established, and when physiological processes began to be analyzed as mechanical interaction of the matter making up the constituent parts of organs and substances.

In later sections, after examining directly what is contained in a 'machine metaphor', I will undertake a narrative of some landmarks in the present understanding of life from the point of view of the appropriateness of various hypotheses to account for machine-like operations of living organisms.

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contemporary science nor biased by contemporary technology.

2.2 MECHANISM, OR MACHINISM?

If we rely on the main achievements of XVIIth century physiology the narrative of the scientific revolution as the "mechanization of the world picture" appears deceivingly literal.[22] Harvey's view of arteries, veins and the heart as an hydraulic system with the heart as its pump is the outstanding example. Throughout the century many mechanical approaches to the human body's economy with different degrees of success can be found. Lorenzo Bellini, disciple of Borelli and the leading iatromechanist in Italy, together with his theory of the kidney as a sievelike arrangement to separate urine from blood, advanced a theory of disease relating malfunction mainly to changes in the blood's velocity. Descartes's accounts made use of existing or conceivable contrivances of his time as well as chemical technology as sources for models. For instance, in his Treatise of Man he compared digestion with the action of an acid on an alkali, and he alluded to hydraulic machines to account for muscle changes during contraction.

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[22] The expression coincides with the title of Dijksterhuis's now classic book The Mechanization of the World Picture [Dijksterhuis, 1961], where the author claims that this was the final outcome of the scientific revolution.

However, to focus only on such examples produces a misleading interpretation of what was happening intellectually during the Scientific Revolution. Descartes's unsuccessful physiological undertakings -- he is not the starting point of any real school of physiology -- in fact illustrate most clearly the methodological meaning of 'mechanism'. Firstly, in many places Descartes warned the reader about the hypothetical status of the models he uses for particular physiological processes. Second, he was not interested in rejecting contemporary physiological accounts, as much as in showing that they could be consequences of matter in local motion.[23] For instance, his account of embryological development in his small posthumous treatise De la formation de l'animal is remarkably worthless for embryology.

> If one knew what all the parts of the semen of a
> certain species of animal are, in particular, for
> example, of man, one could deduce from this alone, by
> reasons entirely mathematical and certain, the whole
> figure and conformation of each of its members (as
> quoted in [Roe, 1981]).

Scarcely any statement an embryologist would consider useful can be found in this treatise. There is only the general statement that physiological phenomena must be understood as matter and motion alone. Indeed, Cartesian corpuscularism is the reduction of all phenomena to local motion.

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[23] Thomas S. Hall shows how the physiological explanations or models provided by Decartes in his Traite del homme were contemporarily accepted views re-stated in corpuscular terms [Hall, 1970)].

Robert Boyle also embarked on physiological experimentation.

Among others, he devised a lengthy program to research blood

[Boyle, 1772] and accomplished many experiments in respiration.[24]

However, in our attempt to find the broader meaning of

'mechanism' we can be misled by considering only his mechanico-

physiological excursions and not relying also on his

philosophical writings, such as his Of the Excellency and Grounds

of the Corpuscular or Mechanical Philosophy [Boyle, 1772, Vol.

4]. Here he argues in general terms in favor of the mechanical

philosophy against Aristotle's substantial forms and the

chymist's "principles and elements". No fewer principles than

matter and motion are necessary. They are intelligible and admit

enough variation to account for the diversity of phenomena we

observe. They even allow for the alchemist's dream of the

transmutation of metals, a mere rearrangement of compounds!!

Evidently for Boyle the "mechanical philosophy" is an approach in

which matter and motion are the only categories necessary for the

explanation of natural phenomena.

Another outstanding mechanical philosopher, the political thinker

Thomas Hobbes, discussed the physiology of perception, among

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[24] Boyle planned an experimentum crucis to decide between
his view that the mechanical motion of the lung interacting with
the spring of the air was the relevant process in respiration,
and the chemical-particulate view favored by the Oxonians; they
were to determine whether it be the supply of fresh air or the
motion of the lungs, that keeps animal alive [Frank, 1980].

other things. He did this not in the way in which a modern scientist would have, but as part of his agenda to support his political conclusions on the foundation of Galileo's law of inertia and the universality of motion. In the first chapter of Leviathan [Hobbes, 1968] he deals with various parts of the mechanism by which the human body operates.

> Neither in us that are pressed are [the sensible qualities of objects] anything else but diverse motions (for motion produces nothing but motion) [Hobbes, 1966, Vol I, p. 390)].

Sense, imagination, memory, understanding, dreams, are explained in terms of motions:

> sense in the sentient can be nothing else but motion in some of the internal parts of the sentient [ibid].

The major declared contention of the mechanical philosophers in physiological matters was not the reduction of the inner workings of animals to machine-like behavior. The contention was that phenomena must be explained as matter in motion. But, how are we to interpret the fact that when this point of view was taken to explain the functioning of living organisms it ended up alluding to clocks, springs, wheels, levers, strings and the like? When were these sorts of contrivances used to illustrate, and when were they brought in as portraits, of what is really happening in an organism?

Against contemporary criticism claiming that the laws of motion could not be valid for small motions, Boyle argued that this kind of false reasoning is similar as saying that "the laws of mechanics may take place in a town clock, but cannot in a pocket watch" [Boyle, 1772]. Here the analogy is explicitly stated but the specific reference to a clock or a watch is merely accidental. Any pair of large and small machines could suffice. In Hobbes' statements like "What is the heart but a spring, and the nerves, but so many strings, and the joints but so many wheels?" [Hobbes, 1968, p. 81], the analogies appear to be not mere analogies. The heart _is_ a spring. Finally, Haller's mechanical theory of nutrition as replacement of corpuscles in those parts of the body worn by friction [Holmes, 1975] looks like a literal account of what is happening, not an analogy at all. Thus, a whole range of degrees of literality for the use of 'mechanism' can be found in the writings of the thinkers belonging to the period.

Of course, neither the heavens nor animals are literally clock-works. Fontanelle was right:

> Do you say that beasts are machines just as watches are? Put a male dog-machine and a female dog-machine side by side, and eventually a third little machine would be the result, whereas two watches will lie side by side all their lives without ever producing a third watch (as quoted in [Roe, 1981]).

This is one side of the issue, an argument against the use of contrivances in a literal way, claiming that in the mechanical philosophy the term 'mechanical' should be understood only as a methodological attitude, namely, to give explanations in term of matter in motion. But was it possible for the mechanical philosophers completely to dissociate the idea of 'mechanism' from its original literal reference to mechanical contrivances? Can the idea of mechanism be completely divorced from all remnants of machinism?

A careful look at some assertions of Boyle in his defense of the mechanical philosophy will uncover an often overlooked assumption that in part can be traced in part to a common property of machines in Boyle's own time.

In addition to the argument in which he uses an analogy between cathedral clocks and pocket watches, Boyle argues in favor of the universality of matter and motion in a literal way. What could be more literal than his claiming that he actually has examples that the laws of mechanics are valid for the elementary corpuscles? Nature is more skillful than any human artisan, he cautioned his readers, but there is one such artisan of whom "good authors tell us [that he has managed to make] a chain of a strange tenderness and lightness, insomuch, that its divers links ... [were] fastened to a flea, and could be moved by it" [Boyle, 1772, Vol IV, p. 71]

It is not necessary to dig into any history of craftsmanship in the XVIIth century to find if the tamed flea with its fantastic chain existed. We only have to point out that Boyle insisted on continuity between the microscopic and the macroscopic. The smallness of the flea's chain is a picture of the universe of corpuscles. The grounds for intelligibility of the mechanical philosophy were precisely that operations among corpuscles were the same operations seen in the everyday experience -- and in mechanical contrivances particularly -- of solids and liquids pushing solids by contact of parts. The big difference between the 'chymist's' active principles and the mechanical philosophy is that the latter relied on a phenomenon that Boyle and other mechanists considered <u>required no explanation</u>: hard corpuscles transmitting their motion to hard corpuscles. "No motion is generated but by a body contiguous and moved". Pressure on the outermost part of the organ "is propagated through all the parts of the organs to the innermost" [Hobbes, 1966].

Action through 'hard contact' caught also the imagination of the short lived mechanical chemistry during the last years of the XVIIth century. Nicolas Lemery, author of the very influential <u>Cours de chimie</u> published in 1675, states the superiority of

mechanical explanations by way of the explanation of precipitation.

> To say merely that by the conjunction of these two
> spirits the aqua fortis is compelled to abandon the
> metal that it had dissolved, is nothing at all to the
> clearing of the question, unless a man will needs give
> an intelligence to these spirits. Wherefore we must
> still have recourse to the agitation and jostles, for
> the true reason (as quoted in [Westfall, 1971])

Acids are composed of pointed particles ("acid points"), a view that could explain not only the action of acid but also the existence of saturation effects, which would appear when all the points are in use. Microscopical points, micro-saws and the like, acting as macroscopical objects do, provide an intelligible explanation in comparison with the obscure intelligence of 'active principles', only, I repeat, if the interaction of hard corpuscles is regarded as unproblematic.

No wonder that Newton's forces between particles not in contact were so difficult for the mechanical philosophers to swallow. They strived -- as Newton had strived also, unsuccessfully -- to find a 'mechanical' account of gravity. Newton was driven to reject their unquestioned assumption of repulsive contact of hard particles and, with later Newtonians, offered an account of particle interactions in terms of attractions and repulsions, especially to account for chemical properties. Newton gives a

full account of his reasoning in the famous Query 31 to the
Optiks (published in 1705):

> The parts of all homogeneal hard Bodies which fully
> touch one another, stick together very strongly. And
> for explaining how this may be some have invented
> hooked Atoms, which is begging the Question; and others
> tell us that Bodies are glued together by rest, that
> is, by an occult Quality, or rather by nothing; and
> others, that they stick together by conspiring Motions,
> that is, by relative rest among themselves. I had
> rather infer from their Cohesion that their Particles
> attract one another by some Force [Newton, ... p. 389].

> There are ... Agents in Nature able to make the
> Particles of Bodies stick together by very strong
> attractions. And it is the Business of experimental
> Philosophy to find them out (Ibid, p. 394).

> When therefore spirit of salt precipitates silver out
> of Aqua Fortis is it not done by attracting and mixing
> with the Aqua Fortis, and not attracting, or perhaps
> repelling silver?... Salt of vitriol dissolves
> homogeneously in water, as if receding from each
> other... (Ibid, 387, my emphasis)

> As in algebra ... in mechanicks, where attraction
> ceases there a repulsive virtue ought to suceed.

It is remarkable that Newton rejected the appeal to hooks and the
like not because he considered such explanations as flights of
the imagination, but because these kinds of explanations "beg the
question". Not only what holds the parts of the hooks together,
but what makes them rigid? Although he did not abandon the
convenience of referring to hard corpuscles to account for
impenetrability, clearly he rejects the macroscopic action of
solids against solids as a full account of chemical events.

to feign pointless hypotheses in favor of achieving more limited
experimental conclusions. An outstanding member of this group was
the highly respected XVIIIth century physiologist Albrecht von
Haller.

Haller's main contribution to physiology is seen to be his
distinction between 'irritability' and 'sensibility':

> I call that part of the human body irritable, which
> becomes shorter upon being touched... I call that a
> sensible part of the human body, which upon being
> touched transmits the impression of it to the soul...
> (as quoted in [Roe, 1984]).

He considers irritability a property "of the animal gluten in the
muscular fiber... to which... it is unnecessary to assign any
cause, just as no probable cause of attraction or gravity is
assigned to matter" (ibid.).

Haller himself claimed that his method was Newtonian, a
remarkable fact considering that he worked in German-speaking
countries.[20] His 'mechanism' was not exactly that of the

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calculations but could not raise a drop of water to fifty paces
from the reservoir. Vanity of vanities! Vanity of mathematics!."

[20] A careful assessment of Haller's methodological views as
well as how he was influenced by Newtonianism can be found in
Shirley A. Roe's 'The Newtonian physiology of Albrecht von
Haller' [Roe, 1984]. Here she states: "In my opinion, Haller
consciously sought to emulate the Newtonian program in his
scientific work and to construct, in particular, a new physiology
based upon the canons of the new philosophy".

mechanical philosophers, as he added the Newtonian concept of force.

> Whoever writes physiology ... must explain the inner movements of the animal body, the functions of the organs, the changes of the fluids, and the forces through which life is sustained (Haller: <u>Elementa physiologiae</u>, as quoted in [Roe, 1984]).

But irritability does not require explanation. Irritability "is a physical cause, hidden in the intimate fabric, and discovered through experiments, which are evidence enough for demonstrating its existence, [but] which are too coarse to investigate further its cause in the fabric" (<u>ibid.</u>). It appears that the assigning of vital properties to fibers without any further explanation required played an influential role in the waning of mechanism during the XVIIIth century and was a part of the reawakening of vitalism.[27]

The staunchest advocate of mechanism was Julian Orffay de La Mettrie. He stated as conclusion of his <u>Man a Machine</u> that "man is a machine and that in the whole universe there is but a single substance differently modified" [La Mettrie, p. 148]. In arriving at this conclusion he included possible analogies for explaining physiological events, such as

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[27] The waning of mechanism in England in the XVIII is a well documented fact. "One of the most striking features of English physiology was the dramatic decline of varieties of mechanism and the rapid rise of preeminence of alternate varieties of vitalism" [Brown, 1974].

> a violin string or a harpsichord key vibrates and gives
> forth sound, so the cerebral fibres, struck by waves of
> sound are stimulated to render or repeat the words that
> strike them (ibid).

He also unavoidily took into his discussion the technical

capabilities of his time, as in the following passage:

> Even if man alone had received a share of natural law,
> would he be any less a machine for that? A few more
> wheels, a few more springs than in the most perfect
> animals... (ibid, p. 128).

A more striking example of the mechanist as a machinist could

scarcely be found.

Although it was a methodological stand trying to move away from

its origins in metaphors with mechanical contrivances, mechanism

in fact declined when they had exhausted the speculative capacity

of models taken from everyday processes and contemporary

technology. Some years later, electrical phenomena and

contrivances enriched again the possibility for speculative

conjecture about physiological events. But this corresponds to a

period that I am not going to deal with in this study.[20]

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[20]   Du Bois-Reymond launched his research activity on the
possibilities opened by electricity, an endeavor that,
notwithstanding some successes, proved to be quite difficult. The
first volume of his Untersuchungen uber thierische Elektricitat,
appeared in 1848. Twenty-five years separate the first and second
parts of the second volume, and in the second Du Bois-Reymond
wrote: "So I have at least decided, with heavy heart, to stop

2.3 MACHINES

In the last section I reviewed some episodes during the Scientific Revolution in which the machine metaphor was brought in as an explanatory device or as a speculative instrument. I will attempt now to characterize the machine itself, _i.e._, what in the first chapter I called the 'literal realm'.

There are three distinctive features of a machine:

1) The contrivance itself, that is, the hardware.

2) The purposeful character associated with an artifact that is designed with a particular objective by a machinist.

3) The implied internal harmony in its operation if any particular machine is going to do the task for which it was designed.

The Contrivance

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where I might just as well have done more than a quarter-century ago...." (as quoted in [Cranefield, 1957].

* The <u>effect</u> of the running of a machine is some kind of macroscopic motion of a solid or a fluid (usually constrained) in 3-dimensional space, in other words, a change in the geometrical configuration in the environment.

The machine itself is moving and can be described as an arrangement of parts in space. Generally a complicated <u>machine</u> can be analyzed in a combination of elementary <u>mechanisms</u>.[29] We can reserve the term machine to the more or less complex arrangements of parts, and these will prompt the analogy with everyday's tools and utensils (hammer and containers, for example) as parts of machines.

* To be properly called a machine, a contrivance must be able to work in some sort of cycle: it must be able to operate again and again, almost unchanged after each cycle. Upon finishing a cycle the machine preserves its structure, which means its parts and the geometrical relation between its parts.

This feature enables us to highlight an important difference between 'machines' and 'processes'. In the latter, the features of having parts and working in cycles are out of place. An analogy between organisms and plain 'physico-chemical processes'

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[29] This distinction was suggested by Reuleaux, who by the end of XIXth century made the first systematization of the mechanical contrivance. He distinguished inside the <u>machine</u> different <u>mechanisms</u>. The distinction is used, for example, by Georges Canguilhem [Canguilhem, 1965]

falls too short to be considered as the only feature of a machine metaphor, because it sets aside central features of a machine such as its preservation after the process.

At the end of a cycle the machine itself is essentially in the same configuration as at the beginning. This feature allows us to analyze its operation balancing input and output and disregarding the machine itself. Devices designed to transform one form of energy into another - transductors - are at the center of many thermodynamical arguments.

* The composition (that is, the 'chemistry') of the moving parts in a machine is responsible for its bulk properties, like density and 'stiffness' (encompassing elastic properties of springs, mechanical characteristics of strings as opposed to bars, etc.) , but their role in the general functioning can be accounted for mostly by the parts' profile.[30] This can be seen when the machine metaphor is carried into the living realm in the suggestion that processes inside organisms can be explained in terms of "little bits of stuff pushing each other about" [Woodger, 1929], and into molecular biochemistry as the steric factor approach. This is one of the senses in which it is said that the relation between the parts in a machine is external.

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[30] The fact that some machines, like the hydraulic press of the steam machine, includes gases or liquids will not alter in any essential way the features discussed here.

* In handiwork manufacturing 'power' is intermingled with the
manipulation itself. In its earlier versions, some modern
machinery began to separate them by transferring power to foot-
pedals, and the machinery developed during the Industrial
Revolution continued this track. Most, if not all, modern
machines have a 'power stage' geometrically or conceptually apart
from the manipulating stage, a separation whose importance grew
side by side with the advent of energy as a commodity and the
ascension of energy as a central concept in science, as well as
the view of food as combustible.

Purposefulness

The historical account given in the first section of this chapter
focused on the 'hardware' aspect of the machine. Notable features
were left aside in that approach: a machine is a man-designed
contrivance whose parts, movements and composition can be
explained making reference to the outcome obtained from them;
transmission belts are 'explained' by transmission needs and
their detailed structure depends on selected combinations of
force/displacement; gears, strings, valves, are accounted for by
referring to their role in the contrivance, to the designer's
rationale for including them, to their function towards the
fulfillment of a purpose. Nobody will dare to reject explanations
of a machine using this duality function and purpose.

This duality has always been present in biological thinking, and it is quite explicit in the traditional view of nature that the scientific revolution pretended to overcome. In Descartes's animal-machine the apparent problems arising from this aspect of the metaphor were solved by appealing to God as the supreme designer.

Machine and Harmony

Above I referred to the contrivance as a spatial arrangement of parts. Now I add time. The machine works 'in tune' over time: it can be considered as an exemplar for harmony, a fact that reminds us that cosmological visions placed the clockwork instead of the heavens as the exemplar of harmony in the XVIIth and XVIIIth centuries. At its more basic level, harmony refers in the case of a machine to an ordered succession of steps.

. . . .

The description just presented displays such a broad view of machine-based metaphors it would seem that physiological thinking could exist outside it. The discussion below points out some negative analogies.

Machines made of springs, cogs, wheels, gears, chains, strings, comply fairly well with the features explained above. Now, the permanence of the structure in machines is at the base of a clear cut separation between structure and process. But particularly in living systems we can conceive processes which create meta-stable structures -- dissipative structures in contrast with the more evident equilibrium structure -- themselves becoming the structure for other processes. That is, processes creating and re-creating structures. In fact, all the 'machinery' responsible for processes in living organisms are more or less labile structures whose molecules are continuously renewed, structures which are then outcomes of other processes, structures that sooner or later will disappear. To imagine in physiological studies these labile structures as fixed, or as quasipermanent structures, may be regarded as an approximation -- a theorist will say that it is the dismissal of some term in a differential equation due to the fact that its coefficient is quite small for the times involved -- but is also a remnant of the machine metaphor.[31] Do we not risk missing something important about life if we take Claude Bernard's assertion -- "all phenomena which

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[31] In 1929 F.G. Donnan advanced his own conclusions and speculations from A.V. Hill's experimental results working with non-medullated nerve cells and muscle: "the organized structure of these cells is a _chemodynamic_ structure, which requires oxygen, and therefore oxidation, to preserve it. The organization, the molecular structure,is always tending to run down, to approach biochemical chaos and disorganization... The life machine is therefore totally unlike our ordinary mechanical machines... Personaly I believe that ... for the first time in the history of science we begin ... to understand the difference between life and death..." [Donnan, 1929].

make their appearance in a living being obey the same laws as those outside it" -- as an invitation to study the relationship between structure and function as if the former is fixed to execute the latter, imposing the machine metaphor?

This last question throws more light on the point I am trying to stress: the structure in the 'physiological machine' -- when portrayed as one enduring the process after a cycle -- is tightly related to the idea that the structure is there again, ready to repeat the process. The technical artifact, indeed, is designed to serve some end, and its structure is the means to achieve that end. In contrast, the process in the organic 'machinery' might have to be conceived as necessary to preserve the structure itself, a vision that would make more intelligible the fact that biological structures disappear when physiological processes stop. The operations connected with 'living' are the requisites for remaining alive. As organisms, we are not alive in order to enjoy eating; we must eat to be alive. As human beings, up to now we are free to dispute this point either with a physiologist, a psychologist or our parents.

In physiological thinking energy is treated, in some instances, in a clear machine-laden view, as a pre-requisite for a process to occur, in the sense of 'necessary fuel'. This is a description of phenomena carried into science from the analysis of combustibles in machines, where some kind of externality between

the power stage and the manipulation stage applies (see below).
That is, in physiology, some energy reactions are often thought
of as suppliers of energy in order to accomplish such or such
processes.

To realize that a metaphorical transfer of meaning is present
here it is necessary to show that this is not the only way in
which we can see the process. An idea from Szent-Gyorgyi might be
the best example since it illustrates both this point about
energy as well as the previous one about fixed structures.

The flow of electrons in the respiratory chain is a very delicate
mechanism, and the enzymes responsible for it must be in very
close and precise relation. In Szent-Gyorgyi's words, "to
interact in a chain, these precisely built molecules must fit
together most precisely, as the cogwheels of a Swiss watch do"
[Szent-Giorgyi, 1969]. For him there was only one way of making
intelligible how this precise mechanism could appear as a result
of evolution -- the electrons flowing down along the respiratory
chain must also be involved in maintaining the stability of the
structure along which they run; their flux preserves the
structure. The electrons flow not like water in a pipe, but like
water in a river, so the waterfall is where the water falls. The
flow of electrons is not just producing chemical energy to be
finally stored in those adequate energy-carrying molecules --
like ATP -- needed to drive energy-requiring processes. It might

be needed to preserve and regulate the structure along which they flow. ATP itself is there not only as stored fuel, but its concentration is crucial for the direction in which some reactions may go. Fuel is external in literal machines, like the gas engine, but it is very unlikely the case in living organisms.

Therefore there are some negative analogies of the machine metaphor. These need to be understood historically. That they are now disanalogies do no preclude the possibility of later becoming positive analogies by technological innovation. Improvements of man-made contrivances may come to resemble features found in living organisms which are not present in any contemporary devices. Technology has not yet produced replicating watches to refute Fontanelle with a Popperian counterexample, but nowadays self replicating molecules can be assembled and studied inside a biochemist's retort. Thinking machines were incredible fantasies in past centuries, but now more than one computer scientist and more than one cognitive psychologist claim that they are here, on our desks: that computers are not like us, but that we are like computers. In fact, philosophers of technology and anthropologists have long been involved in discussion about what comes first, machines as material expressions of what man sees in himself, or man making himself in the image of the machines he produces.

Having examined the literal meaning of 'the machine' and some of
its metaphorical analogies and disanalogies, I will now discuss
the development of some central physiological ideas during the
XIXth century in light of the machine metaphor.

2.3 HOT POTS, HEAT MACHINES AND CHEMICAL MACHINES

According to the characterization of the machine developed above,
there is more to calling the animal body a chemical machine than
the mere recognition of the fact that chemical processes take
place in its interior. Aside from the details of the research
program launched with the suggestion of the living retort -- how
particular organs accomplish the operations assigned through an
input-output chemical analysis, or how biological replication
could be chemically explained, and so on -- other obvious general
issues should be addressed, such as: What drives the processes in
a particular direction? How is harmony guaranteed? Here I will
deal mainly with the broad features that would justify the use of
the term 'machine' as a contrivance.[32]

Are organs, cells or cellular organelles kinds of physical
compartments where chemical processes are going on as if they

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[32] It appears that it is simply the complexity of processes
inside a living organism discovered by modern research that has
made the problem of harmony a major, maybe the major, concern. Is
it just a coincidence that this concern arose precisely when the
modern archetype for a machine became the cybernetic one?

were in a test tube? Are there specific organs selecting some
substances to react in this 'test tube' while the organs
themselves remain intact (or are gradually worn out)? Or, should
the structure of any organ, cell or organelle be pictured as
chemically active, such that the machine is itself literally
consumed, or not?

2.3.1 LAVOISIER AND LIEBIG: THE HOT POT

The modern strand of thinking in terms of chemical machines can
be considered as starting from the work of Lavoisier and Laplace
which developed the analogy between respiration and combustion.
According to their interpretation of the results of their
renowned ice-calorimeter experiments, oxygen is used in the body
to burn slowly carbon and hydrogen compounds present in the blood
forming water and carbonic acid, which reaction takes place in
the lungs. The released heat is then spread out through the body
by the blood. Although their theory was a huge breakthrough in
accounting for animal heat -- itself a focal point in the debate
about the nature of living things -- physiologically it was weak.
The high temperature gradients which could be expected in the
body, particularly in the lungs, were not dwelt on by Lavoisier.
But Adair Crawford in Britain explained the absence of
perceptible differences in the temperature of the blood before
entering and just leaving the lungs by suggesting that there is a
difference between the specific heats of arterial and venous

blood. On the other hand, the additional 'latent' heat taken by arterial blood, according to Crawford, is delivered to the tissues and the blood again regains the specific heat of venous blood, accounting also for the absence of a temperature gradient in the tissues.

There are many features in common between Lavoisier's, Crawford's and Joseph Black's theories of animal heat, but chief among them there is the quite remarkable feature that animal heat did not need to be explained. It could be integrated into the animal's harmony in various ways -- for example, pointing out the advantages of having a constant and relatively high temperature for chemical reactions to occur -- but respiration was taken to be a physiological event whose direct aim was only to preserve a constant, relatively high temperature. Heat exchange was the only important issue.

> The heat developed by this combustion is transferred to
> the blood which passes through the lungs, and thence is
> transmitted throughout the animal system. Thus the air
> we breathe serves two purposes equally necessary for
> our preservation: it removes from the blood the base of
> fixed air...; and the heat which this combination
> releases in the lungs replaces the constant loss of
> heat into the atmosphere" (A. Lavoisier, as quoted in
> [Goodfield, 1960])

The analogy between respiration and combustion is, then, more than a chemical analogy: it is also an analogy with a hot pot.

The first general picture of the human body as a chemical machine was an outcome of Justus Liebig's researches, or better, proposals. But, to evaluate Liebig's views, we have to review current research that was going on about the chemical composition of plant and animal tissues.

Methods to determine the elementary constitution of organic substances began to appear by the end of XVIIIth century -- partly as a result of the order brought by Lavoisier's theories, experimental results and techniques -- and were fairly well developed by Gay-Lussac in the period 1810-1830.

But another way of analysis was also pursued: the treatment of organic substances with milder methods than those revealing elementary composition. These methods could render what later Chevreul called "immediate principles" [Fruton, 1972, p. 91] from which a classification using some shared chemical or physical properties could also be achieved. For example, coagulation of egg white, curdling of milk and clotting of blood were seen as similar processes. The substances resulting from these coagulations were termed albumin, casein and fibrin respectively and were included in the same category: "albuminous" substances. Aside from the property of suffering some kind of coagulation, they had one thing also in common from the point of view of elementary constituents: analysis revealed that all of them contained nitrogen.

Magendie in 1816 killed several dogs and cats by excluding from their diet all these nitrogen-containing substances, feeding them only sugars and fats. This fact, along with their widespread presence in living tissues, gave way to the increasingly popular view that these albuminous substances occupy a central role in living processes. They were the core of life.

The results of uniting both strands, elementary analysis and the immediate principles, spurred the imagination of more than one researcher. After the verification that most organic fluids and tissues were composed mainly of carbon, hydrogen, oxygen and nitrogen, the suggestion arose to base a taxonomy of tissues on variations in their relative presence in those tissues.

Highly inspiring for Liebig and for later versions of his 'animal chemistry' were the results obtained by the Dutch chemist Gerardus Johannes Mulder during the years 1838-9. Mulder claimed to have found some striking resemblances in the elementary chemical composition of animal and plant tissues. Although they differed in the content of sulfur and phosphorus, they appeared remarkably similar in the proportion of carbon, hydrogen, oxygen and nitrogen. From these results he inferred that these tissues

were formed by some kind of aggregation of a common "radical".[33]

Following Berzelius' suggestion Mulder called it "protein":

> The word protein that I propose to you for the organic oxide of fibrin and albumin, I would wish to derive from _proteios,_ because it appears to be the primitive or principal substance of animal nutrition that plants prepare for the herbivores, and which the latter then furnish to the carnivores" (as quoted in [Fruton, 1972, p. 96)

Mulder found an empirical formula for the 'protein' radical – $C_{40}H_{62}N_{10}O_{12}$ – and claimed that combinations of different numbers of these radicals with phosphorus and sulfur accounted for the differences in composition between this or that animal or plant tissue.

Liebig did not follow Mulder completely –– in fact, he repudiated the protein radical by 1846 –– but his general picture of the body's workings were well in line with the pattern of thought of a chemistry dominated by an interest in the study of nutritive requirements. After making considerable improvements in

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[33] By this time organic chemistry was being further developed by leading chemists such as Berzelius, Liebig and Dumas as the chemistry of compound radicals, in distinction to inorganic chemistry whose aim was to investigate the chemistry of simple radicals, where a "radical" is understood to be a simple or complex aggregate of chemical atoms. This is a good place to notice how variable a chemical-machine view of living beings and processes must have been in a conceptual environment as giddy as chemistry was. In a period of 50 years, challenging new ideas were suggested by workers like Dalton, Avogadro, Cannizaro, Berzelius, Faraday, Thomsen, Van't Hoff, Kekule, _and_ their opponents. Every few years came a new proposal which altered or challenged all that had been held before.

the methods of analysis he had learned under Gay-Lussac in France, Liebig with his students in the laboratory at Giessen undertook the task of determining the precise composition of foodstuffs, animal tissues and fluids, and excreta. By 1842, in the Preface of his epoch-making <u>Animal Chemistry, or Organic Chemistry in its Application to Physiology and Pathology</u> [Liebig, 1843] (published both in German and in English in 1842), Liebig presented his chemical tenet:

> every physical and mental action of an animal is the result of chemical changes occurring within its structure or substance" [Liebig, 1843].[34]

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[34] He dismisses many possibilities here, as he is taking the risk of claiming that he could explain how a hammer works by its chemical changes during hammering! I don't know if at some time in his long scientific life Liebig had to tackle any objection along this line. On the other hand, to say that Liebig inferred "the physiological role of the various organs from the chemical properties of the elements which made up their substance", as June Goodfield does [Goodfield, 1960], is not, in my opinion, an accurate view of his chemical project. His research was not what later came to be called physiological chemistry, but animal chemistry, well centered in conclusions obtained from elementary analysis. With his nutrition-laden view, he was explaining chemically the evident chemical changes undergone by substances in the organism. This particular chemical way of dealing with physiological questions was popular enough to generate comments among its critics like the one related on several occasions by Szent-Gyorgyi (and attributed by him to earlier Victorian scientists, probably Tyndall): "If you would ask a chemist to find out for you what an electric motor is and does, the first thing he would do is to dissolve it in hydrochloric acid" [Szent Gyorgyi, 1962]. Liebig had a chemical formula for flesh ($C_{48}NH_{39}O_{15}$), which is like having a chemical formula for electric motors; In 1864, Oskar Liebrich, Professor of Pharmacology at the University of Berlin, suggested, along the same line, that 'protagon' -- $C_{116}H_{241}N_4PO_{22}$ -- comprised the main part of 'cerebral matter'(Noel).

The book offered a coherent picture -- albeit strongly conjectural, to say the least -- of physiological processes in chemical terms. It contains three parts and two appendixes. The first part, without a title of its own, deals with questions of heat and nutritional requirements. The second part is entitled "The metamorphosis of tissues" and deals extensively with the bile's composition and its role in the animal economy. The third part, with no title, deals with 'motion' and Liebig's highly controversial "living force".

Liebig stipulated that carbohydrates and fats do not enter into the formation of animal tissues; they are only for combustion. Protein radicals transported by the blood to different parts of the body are assimilated by the tissues, in whose interior no synthesis is accomplished, only growth [Goodfield, 1960, p.119]. In the muscles, however, the tissues suffer 'metamorphosis' during exercise, as a result of which different nitrogen compounds appear, particularly urea, that are later excreted in the urine. The carbon compounds remaining after this process are brought by blood to the liver and converted there to "choleic acid" -- according to Liebig, the main component of the bile -- and returned to the digestive tract to be oxidized in the capillaries just like other carbon-hydrogen compounds (fats, sugar, starch and gum). Depending on the demands for heat, more or less of these oxidative processes take place, the excess carbohydrates being excreted.

This is, in short, the general scheme under which Liebig
suggested that chemical changes occur in the organism. Two main
categories of chemical changes occur in the human body in
Liebig's view: those generating heat to replenish heat losses,
and those related to tissue metamorphosis. Liebig thus agrees
with Magendie's result that sugars and fats cannot sustain life,
although Liebig added his own conception that the human body is
not able to synthesize the protein radical and that only
carbohydrates and fats are burnt in respiration. As for this
process of burning, Liebig remarks:

> To make use of a familiar but not on that account a
> less just illustration, the animal body acts, in this
> respect, as a furnace, which we supply by fuel... In
> order to keep up in the furnace a constant temperature
> we must vary the supply of fuel according to the
> external temperature... [Liebig, 1843, p. 21]

Liebig, as I interpret him, is not only accounting for the animal
heat in chemical terms -- his explicit aim in this passage -- but
is also pointing out, as Lavoisier and others had done before,
that oxidation of foodstuffs (more precisely, carbohydrates) is
accomplished in the organism for the sake of heating it.

> In whatever way carbon may combine with oxygen the act
> of combination cannot take place without the
> disengagement of heat. It is a matter of indifference
> whether the combination take place rapidly or slowly,
> at a high or at a low temperature; the amount of heat
> liberated is a constant quantity [Liebig, 1843, 29]

Liebig's indifference to intermediary steps expresses first his

adherence to a sort of conservation of heat.[38] Secondly, it

reveals also his understanding that the intermediary steps might

be irrelevant physiologically -- after all, the process is just

combustion. With respect to combustion, then, Liebig repeats

Lavoisier's theme: the furnace.

Claude Bernard's dissatisfaction with Lavoisier's description of

respiration as combustion focused on this point. Maintaining that

the process is going on in the blood itself, either in the

capillaries of the lungs or tissues, as Liebig had contended, is

like seeing it as a combustion process -- chemicals are degraded

only for the sake of heat. But this is not exactly the case, said

Bernard. Bernard showed that homeothermy is a complex regulatory

mechanism that in some circumstances is quite different from

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[38] This is not a version of what later became known as Hess's Law, but a commonly held mistake prior to the general acceptance of the conservation of energy. We now know, first, that the heat "disengaged" (a word which suggests the caloric view of heat) when carbon reacts with oxygen is not indifferent to the conditions of the reaction (recall the differences between Q_p and Q_v). Secondly, the heat evolved is not indifferent to the chemical environment. For example, consider the independent evaluation of Lavoisier's theory by Dulong and Despretz in 1823 and 1824. They considered the heat evolved by combustion of carbon in foodstuffs as equal to that evolved by combustion of carbon when only carbon is present in the sample. Later Helmholtz corrected their error, which finally explained the discrepancies between combustion of pure carbon and hydrogen with combustion of foodstuffs in an organism.

raising or decreasing the amount of oxidation. Not chemical

combustion, but "physiological combustion". In Bernard's words:

> But with this important modification to the theory of
> Lavoisier [that combustion occurs in the tissues not in
> the lungs] ought we to say that there is a direct
> combustion in the organism and must we conclude that in
> the general capillaries for example, the oxygen brought
> there by the arterial blood directly burns the carbon
> and hydrogen of the blood or the tissues, so that
> carbonic acid and water are formed, at the same time
> producing the rise in temperature which is a result of
> this combustion?' (as quoted in [Goodfield, 1960, p.
> 131]

To make my point clear I rephrase: for Bernard foodstuffs are

degraded in the body's tissues. The process of degradation may be

part of many chains of physiological phenomena, but in any case,

as a result heat appears. Complex physiological mechanisms, well

apart from the degradation itself, preserve a constant

temperature. Thus, chemical reactions in which carbohydrates

participate are not 'mere combustion' in spite of the fact that

there is an evolution of heat.

2.3.2 HEAT MACHINES, HOT SPOTS AND CHEMICAL MACHINES

The discussion of Liebig's second category of chemical processes

-- tissue metamorphosis -- will be centered more on his treatment

of muscle contraction and ensuing developments, than on his

theory of nutrition. But, instead of chasing through the

labyrinthine debates between the sponsors of countless

hypotheses, I will examine the general way in which mechanical effects were thought to be produced in the muscle by analyzing in some detail some of the more popular models. Muscle, with its remarkable ability for macroscopic movement, is the prototype of a living machine -- machina carnis, as Dorothy Needham entitled her book [Needham, 1972]. Consequently the discussion can help us to grasp what kind of mechanisms or machinisms those researchers were inclined to accept in a living being.

During the years Liebig conceived his chemical theories, he occupied a transitional position between the caloric view of heat and the more encompassing principle of conservation of energy.[36] His intermediate position allows us to understand why Liebig is sometimes considered as a forerunner of the principle of conservation, and sometimes as the vitalist against whom Helmholtz performed his experiments on muscle. In Liebig's Animal Chemistry we can find statements like:

> The want of a just conception of force and effect, and
> of the connection of natural phenomena, has led
> chemists to attribute a part of the heat generated in
> the animal body to the action of the nervous system. If
> this view exclude chemical action, or changes in the
> arrangement of the elementary particles, as a condition
> of nervous agency, it means nothing else than to derive

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[36] It was mentioned above how the caloric theory seemed implicit in some of Liebig's assertions. But he has statements in his Animal Chemistry where he openly embraces heat as motion: "Let us remember that the most distinguished authorities in physics consider the phenomenon of heat as phenomena of motion" [Liebig, 1843, p. 32], which he then tries to prove with arguments similar to Rumford's.

the presence of motion, the manifestation of a force, from nothing. But no force, no power, come from nothing [Liebig, 1843, p. 29].

along with statements about of his idea of "living force" like this:

> The vital force in a living animal tissue appears as a cause of growth in the mass, and of resistance to those external agencies which tends to alter the form, structure and composition of the substance of the tissue in which the vital energy resides... [Liebig, 1843, p. 196].

> By means of the nerves all parts of the body, all the limbs, receive the moving force which is indispensable to their function, to change of place, to the production of mechanical effects. Where nerves are not found, motion does not occur [Liebig, 1843, p. 219].

Never is found in his book any idea that the heat evolved in combustion is the source of the "force" or "power of motion" for mechanical action in the muscle. In fact, we find again and again explicit statements distinguishing chemical processes for the sake of generating heat alone from tissue metamorphosis, the chemical process he associates with the mechanical effect in the muscles.

> The sum of the mechanical forces produced in a given time is equal to the sum of forces necessary, during the same time, to produce the voluntary and involuntary motions... The amount of azotised [nitrogen-containing] food necessary to restore the equilibrium waste and supply is directly proportional to the amount of tissue metamorphosed. <u>The amount of living matter, which in the body loses the condition of life is, at equal temperatures, directly proportional to the mechanical</u>

effects produced in a given time. The amount of tissue metamorphosed in a given time may be measured by the quantity of nitrogen in the urine" (as quoted in [Needham, 1972], p. 35; my emphasis).

During exercise the tissue is degraded. 'Burnt' would not be the appropriate word to describe what Liebig had in mind, as will be confirmed below by Liebig's further assertions about the process, but no description of any kind of machinery is present anywhere in his Animal Chemistry. Chemically, he affirms, flesh is degraded mainly into choleic acid and ammonium urate, and the presence of urea in the urine can be used as a measure of muscle degradation. To what extent in 1842 Liebig proposed an idea that muscle degradation provides 'force' for the muscle is not clear, and it is certainly not clear in what is said in the underlined portion of the quotation above.

As can be seen, it is not possible to address the problem of muscle contraction during this period without giving some consideration to the emerging concept of energy and its conservation. On the other hand, in the complex conceptual environment leading to our present view of energy the precise chemical events in muscular contraction could not be ignored. This will become even more clear with Helmholtz's work on muscle.

In 1845, Hermann von Helmholtz, who had just finished his doctorate under the prestigious physiologist Johannes Muller, published his first paper on muscle where he showed that indeed

a chemical transformation occurs upon contraction.[37] It is

important to stress here that Liebig had had no direct proof of

this; after all, he was a chemist, not a physiologist. But

Helmholtz could not deduce from his experiment either the exact

nature of the chemical change or even if a breakdown of the

muscle fiber occurs. Thus, he ended his article promising future

work which supposedly was going to include "more exact analysis

of the material extracts". This never appeared. In fact,

Helmholtz abandoned muscle research after his 1847-8 papers

described here.

In his next paper on muscle Helmholtz reported careful

measurements of temperature changes in muscle after strong

tetanic contractions.[38] Helmholtz concluded that detectable

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[37] Hehlmholtz's first article on muscle was 'Uber den Stoffverbrauch bei der Muskelaction' and was published in the *Archiv fur Anatomie und Physiologie* in 1845. The description of the experiments. as well as some quotations from the articles I have taken from Timothy Lenoir's book [Lenoir, 1982].

[38] 'Uber die Warmeentwickelung bei der Muskleaction" is Helmholtz's second article on muscle. Although published in 1848, it was presented to DuBois Raymond's newly established Physikalische Gesellschaft in Berlin the year before. Lenoir's description of the experiment reported in this article refers to careful measurements of heat production, but in that description we do not see any provisions made to perform actual measurements of heat. Also according to Lenoir, Helmholtz "had shown unequivocally that heat is generated directly in the muscle tissue itself and that its origins are due to chemical processes in the muscles" [Lenoir, 1982, p. 209]. Lenoir's evaluation is unobjectionable as far as he is meaning that some heat is produced in the muscle. But if Helmholtz's aim was to show that Liebig was wrong in the view that heat is generated mainly by oxidation processes taking place in the blood, his proof falls short of being unequivocal.

temperature changes are produced on contraction and that no
significant temperature change can be attributed to the nerve.
From this latter result he can state for sure that something is
wrong with Liebig's claim about the role of nerve action.

In the same year 1847, Helmholtz wrote his famous paper 'Uber der
Erhaltung der Kraft'. Allusion to the muscle is restricted to
some few lines in a paragraph:

> Animals... consume a certain quantity of chemical
> tensions, and generate in their place heat and
> mechanical force. As the latter compared with the
> quantity of heat represents but a small quantity of
> work, the question of the conservation of force is
> reduced to this, whether the combustion and
> metamorphosis of the substances which serve as
> nutriment generate a quantity of heat equal to that
> given out by animals" (as quoted in [Elkana, 1974])

No doubt mechanical action as a consequence of chemical changes
in the muscle was conceptually very relevant for Helmholtz's
thinking about conservation of 'force', but it is remarkable that
from the quantitative point of view the work performed by muscles
was just ignored.

To get a feeling of the further development of ideas about
muscular contraction it is necessary to keep in mind the
interconnections between four strands of research:

(1) Histological studies resulting from improvements in microscopy, which by the end of the century had produced results to allow claims, albeit disputed, about the muscle morphology in gross terms resembling accepted views today: the existence of longitudinal fibers in voluntary muscle with alternating anisotropic and isotropic bands; the existence of a functional unit of contraction, named "sarcomere" since then, a portion of fibre limited by two lines at its longitudinal ends (today's Z lines) approaching each other during contraction, with different shortenings in the A bands and I bands.

(2) Chemical research, some in the old animal chemistry style of studying chemical composition which had identified, for example, the existence of the protein myosin in the muscle tissue.[39] But more relevant were the results coming out of the new physiological chemistry, for example, Bernard's results on glycogen 'fermentation' to lactic acid in the muscles.

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[39] As remarked above, proteins were considered the chemical substances responsible for living processes, which often meant that they were thought to comprise the structure of cells. The highly 'destructive tests' proper to the techniques of animal chemistry -- "Frog muscles were freed from blood by injection of 1% salt solution, then removed and frozen; after 3 hours the mass was cut up and pounded to a snow; on thawing it gave a syrupy liquid which was filtered through a linen cloth..." [Fruton, 1972] -- amply justify Bichat's complaints about this type of investigation even at the beginning of the century: "one analyzes urine, saliva, bile, etc. taken haphazardly from this or that subject, and from their study emerges animal chemistry: so be it, but that is not physiological chemistry, it is, if I may say so. the post-mortem anatomy of fluids" (X. Bichat, as quoted in [Fruton, 1972]).

(3) Proper 'physiological' experiments with intact animals or with excised muscles subjected to never-ending variations of conditions (fixed ends, one end raising different loads while starting with different lengths, stimuli varying in duration, intensity and frequency, and so on).

(4) Advances in physical and chemical theories that provided the source of possible models, regulated by the concurrently developing thermodynamics and physical-chemistry, all in a period when explanations of chemical affinities and the structure of molecules were frequently changing and quite speculative.

The first model for the conversion of chemical energy into work formulated clearly within the context of the conservation of energy was probably J.R. Mayer's:

> Whilst the fibers bend, and the muscle, without
> suffering an alteration in volume, shortens, work is
> produced to greater or smaller degree; at the same time
> in the capillaries of the muscles an oxidation process
> takes place to which a heat production corresponds; of
> this heat with the action of the muscle a part becomes
> 'latent' or expended, and this consumption is
> proportional to the work performance... The muscle, to
> speak in familiar terminology, uses heat in status
> nascens in performing work" (Mayer, J. R., "Die
> organische Bewegung in ihren Zusammenhang mit dem
> Stoffwechsel", 1845 [Ostwalds Klassiker der exakten
> Wissenschaften 180], as quoted in [Needham, 1972, p.
> 39]).

Mayer's model for the muscle is, unquestionably, a heat machine, although imprecisely formulated: there are no considerations of

the temperatures of heat sources and sinks, no discussion about
efficiency.

The model of muscle as a heat machine enjoyed mixed acceptance
for 50 years, but was almost forgotten by the turn of the
century. Adolf Fick strongly criticized it (at first in 1882) on
the grounds of the second law of thermodynamics: if the muscle is
a heat machine, it must work between two heat reservoirs at
different temperatures, and a measured 20% efficiency was
unthinkable with temperature differences of the order of 0.001 °C
detected in the muscle. Ludimar Hermann rejected Mayer's model
"on the score that there was not a single fact to be adduced in
its support" [Macallum, 1913].[40] But, interestingly enough, even
by 1895 the heat-machine theory for muscle contraction had strong
advocates, such as Th. W. Engelmann.

Engelmann, who had published remarkable papers on microscopical
studies of muscle between 1873 and 1895, suggested in the
Croonian Lecture before the Royal Society on 1895 [Engelmann,
1895] that Mayer's proposal appropriately modified was more
probable than those hypotheses he called "chemiodynamic". These
he described as "hypotheses according to which contraction of
muscle is a <u>direct</u> manifestation of chemical attraction"

---

[40]   Ludimar   Hermann   along   with   Eduard   Pfluger   and   Max
Verworn were leading German physiologists during the last decades
of the century; all of them wrote treatises in physiology widely
used in Germany.

[Engelmann, 1895]. To dispute Fick's objection to Mayer, it was only (!) necessary to welcome the existence of very hot particles in the muscle:

> we must assume exceedingly large differences of temperature in the stimulated muscle. What holds good of the whole body holds good of the muscle also; the temperature, measured with our instruments, is but an arithmetical average, 'comprising an infinite number of different temperatures, pertaining to an infinite number of different points' (Pfluger).

> From the fact that at the contraction an infinitesimal part only of the muscular mass is chemically active, we infer that the temperature of these particles must, at the moment of combustion, be an uncommonly high one... [Engelmann, 1895].

For an efficiency of 25% he calculates that

> the temperature of the active particles would consequently exceed the average temperature of the normal muscle by 100 degrees Celsius, only.

> The objection that these high temperatures must necessarily destroy the life of the muscle... is of small value only. For it is ever an infinitesimal part only of the muscular mass that is exposed to these high temperatures. At a small distance from these furnaces of heat the temperature must have fallen so low as to be harmless. The muscle will no more be destroyed by stimulation than a steamship will be destroyed by heating the furnaces. The material of combustion only will be destroyed; the vessel as a whole remains unharmed [Engelmann, 1895].

This risky hypothesis of hot spots was supplemented by many arguments and an experimental model. Using the known fact that fibrillar connective tissue contracts when heated, he

experimented with a catgut string of a violin (other features of his model will be treated again below).

Variations of what Engelmann had named "chemiodynamical hypotheses" were the subject of many debates. In 1870 Liebig advanced a version of these:

> All parts of the animal body arise from inner alterations of protein... in which oxygen has a causal part and one can assume that, if these products of the protein are sources of energy, the movement which they produce depends, <u>not on their combustion and the transformation of heat into movement,</u> but on the tensile force (<u>Spannkraft</u>) (which was piled up in them during their formation) becoming free on their breakdown (Liebig, 1870, as quoted in [Needham, 1972], emphasis mine).

This looks more like a mechano-chemical machine -- in this case a machine whose very structure is considerably altered in the process (supposing that protein somehow gives muscle its structure). Liebig was here still sticking to the core of his basic ideas on nutrition, among them, that muscle is degraded during exercise, although this latter idea was widely questioned by then. Myosin, that protein obtained from muscle press-juice (by Kuhne, in 1859) was, according to Liebig, a product of such degradation; the <u>Spannkraft</u> was restored in the chemical process of rebuilding the living tissue, a process made possible, energetically speaking, in part because heat was absorbed.

Variations of Liebig's theory of muscular action were proposed to account for the finding that the amount of urea in the urine does not increase accordingly with exercise -- until his death in 1873 Liebig dismissed this result -- and that in consequence it is unlikely that protein is irreversibly degraded during contraction. Fick, Hermann, Pfluger and Verworn were exponents of some of these variations.

Hermann, for example, affirms in his Physiologie des Menschen that:

> The muscle contains at any moment a store of a complicated N-containing substance, dissolved in the muscle contents and plasma (which one can designate for sake of brevity the energy-generating or 'inogen' substance) which is capable of splitting with development of energy; the product of the splitting are, amongst others: CO_2, sarcolactic acid [lactic acid], perhaps glycerophosphate and a gelatinous protein body separating out and later contracting firmly (as quoted in [Needham, 1972, p. 37]).

Here muscle contraction is explained by means of the contraction of a substance that is liberated from inogen. The hypothesis proposes to account for chemical events detected in contraction: the evolution of CO_2 during contraction in excised muscles, the fact that a supply of oxygen is not needed at the moment of contraction, as well as the fact that lactic acid appears after contraction and gradually disappears. As lactic acid was known also to be a product of muscle decay in putrefaction, it was straightforward to characterize it as a waste product of the

decay of inogen. Later, during the recovery period, lactic acid

was reincorporated into the living tissue with the help of

external oxygen.

Protein degradation, or splitting, during exercise was considered

not just a process accompanying muscle contraction. In the muscle

cell and in any other cell there is continuous formation and

degradation of a labile "living proteid", and muscle would

exhibit a particular kind of this vital process. Thus, in 1875

Pfluger wrote:[41]

> The life process is the intramolecular heat of the most
> highly unstable protein molecule dissociating with
> formation of carbonic acid, water and compounds
> resembling amides; this protein molecule is formed in
> the cell substance which continually regenerates it,
> and it grows by polymerization [sic].
>
> As the intramolecular swinging [of the same molecules]
> changes the attraction atoms come into relation with
> one another which otherwise did not work on one
> another, so one understands the sudden appearance of
> strong pulling forces as these atoms attract each
> other. If such attracting parts lie in an ordered
> series and if the attraction arises at the same moment
> in the whole series, so forces can be generated in this
> way significant for the muscle twitch (as quoted in
> [Needham, 1972, p. 38]).

Contractile molecules, living-labile proteids, contractile

networks, all represent sorts of chemo-electrical models for

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[41] 'Beitrage sur Lehre von der Respiration. I. Uber die physiologische Verbrennung in den lebendigen Organismen'. Arch. f. ges. Physiol., Vol. 10, 251, 1875.

contraction strongly influenced by the concept.[42] Arguing for a

contractile protoplasmic network, Kuhne in 1888 was pleased to

remark that this hypothesis "puts back the muscle nearer to

protoplasm" (as quoted in [Needham, 1972] p. 140). Verworn, for

his part, felt some apprehension to talk about a living molecule,

so he coined the term 'biogen' -- and made quite clear the

similarity of muscle contraction with the general process of

life:

> biogen molecules have not in all cells exactly the same
> chemical composition, but ... there are various biogen
> bodies,... different in various differentiations of the
> same cell, such as exoplasm, ... contractile fibers,
> muscle fibrillae...etc. The biogens, therefore, are the
> real bearers of life. Their continual decomposition and
> reformation constitutes the life process, which is
> expressed in the manifold vital phenomena [Verworn,
> 1899].

This was the kind of chemiodynamic model critized -- not quite

conclusively, in fact -- by Engelmann in his 1895 article. He

calculated that only a minute portion of muscular substance was

chemically active during contraction, and he found inconceivable

"that a relatively infinitesimal part of the soft watery

substance of the fibre" [Engelmann, 1895, p. 415] could set in

motion the whole muscle.

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[42] Later criticism, particularly from F.G Hopkins, would
identify the concept of protoplasm as the most truly labile
thing. The new synthetic organic chemistry after Berthelot and
Kekule provided the ground to sustain the existence of such giant
molecules that physiologists had been advocating.

Engelmann's central theme was the presence of ordered
birefringent substance in the muscle ("the fibrils are
contractile because they contain doubly refractive particles"
[Engelmann, 1895, p. 417]). He knew that

> all histological elements possessing doubly-refractive
> power tend, even at an ordinary low temperature, to
> contract... when their volume is enlarged by the
> imbibition of a watery fluid [Engelmann, 1895, p. 428]

He had reported in previous papers that on contraction the
anisotropic (birefringent) bands increase in volume while the
isotropic ones decrease. Water flowing from the latter band to
the former was a plausible account for contraction.

But he himself acknowledged that the same argument he used
against the chemiodynamic model -- only a minuscule part of the
muscle is activated -- could be used against his own 'imbibition
model'. That is why he fortified the latter with the hypothesis
that active thermogenic molecules -- hot spots -- supplied the
fiber with heat to cause contraction.

Furthermore, Engelmann pointed out that lactic acid in the medium
surrounding the fibre -- in his experimental model, the
birefringent catgut fibre -- was able to alter the tension-
length properties, so he could provide a rationale for its
presence in the biological system.

Engelmann's thermogenic molecules did not receive much attention.[43] But his imbibition idea was very influential, if not exactly as he suggested, as an example of how changes of solutions could bring about mechanical changes. Probably the more important among the models inspired by Engelmann were variations of the idea that muscle contraction was caused by changes in surface tension.

A model along this line was suggested in the next Croonian Lecture dealing with muscle in 1915 by W. M. Fletcher and F. G. Hopkins [Fletcher and Hopkins, 1917]. They summarized the evidence obtained since 1898 that was eroding the experimental support for inogen: among other things, that CO_2 is not produced during contraction but during recovery and in consequence the chemical events leading to contraction are not oxidative. The idea of an oxygen-containing substance undergoing some kind of explosion and rendering CO_2, lactic acid and so on was plainly false. Lactic acid was produced, indeed, but it could not be interpreted as a waste product:

> Far from being regarded as a toxic product to be
> eliminated as rapidly as possible... lactic acid
> [appears to be] an essential agent in the machinery of
> contraction itself. The development of acid, with free
> H-ions, in the neighborhood of colloidal fibrils gives
> the condition for contraction, whether increasing the
> molecular tension along longitudinal surfaces, or

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[43] Macallum [Macallum, 1912] quotes a model advanced by N. Zunzt in 1908 requiring spots in the muscle with temperature of 6000 °C!

whether by the process of imbibition [Fletcher and
Hopkins, 1917].

It was known that the heat developed during recovery is much less

than it would be if all lactic acid produced in the contraction

were burnt, a fact that was currently interpreted -- in part

supported by the same authors in previous papers -- that this

lactic acid was inserted after oxidative recovery in a precursor.

"The lactic acid on that view would be 'part of the machinery and

not part of the fuel', to use a familiar Cambridge phrase" they

said (ibid, p. 462). Fletcher and Hopkins then changed their

view. The process of recovery must involve the removal of the H-

ions that caused the increase in tension, and this removal is a

change in a physico-chemical system whose potential energy

increases. This would account for the missing heat of combustion

of lactic acid.

2.4   DISCUSSION OF THE CHEMICAL MACHINE

The general problem of any chemical-machine model of the muscle

is, of course, that the chemical energy contained in chemical

bonds must be harnessed in some way -- this link is precisely the

problem -- to produce a macroscopic mechanical event,

contraction, or better, lifting a weight. One obvious way to

accomplish this is by burning substances to obtain heat which is

delivered to some arrangement of solid-like structures to produce

expansion. 'Obvious' because in the days of the so-called thermodynamical model this method was used extensively in technical contrivances. Electrical machines could have also been called upon, but the electrical models that were advanced were inspired more by theoretical considerations from electrostatic attractions or in theories of chemical structure relying on electrostatic attractions, than by already existing contrivances.

Liebig's original ideas on muscle showed a lack of confidence to postulate a 'something' (energy) whose fate could be used to evaluate quantitatively connections between mechanical effects and chemical changes. He only offered a vague statement about the proportionality between the amount of tissue degraded and the mechanical phenomenon, which itself he did not think of as heat-mediated probably because to him proper combustion in capillaries was the major process of heat production. His 1870 model, the tension or Spannkraft accumulated after chemical processes, was more a 'why not?' hypothesis than anything else, for there was no evident experimental model. Nor were the inogen or biogen views free from this shortcoming.

This is not the case for Engelmann's and subsequent attempts. Firstly they relied heavily on structural observations, notwithstanding how disputable the details were. Secondly, they relied also on new results in physical chemistry. Both directed Engelmann to equate birefringence with contractility. On the

other hand, Fletcher and Hopkins could count on experimental

studies on how chemical factors -- dilution of substances,

presence of charged ions and so on -- affect systems of dispersed

particles or colloids in clearly mechanical ways (such as changes

in surface tension or volume).

All these kinds of models, like heat machines, require a

macroscopic geometrical arrangement able to select particular

degrees of freedom of random-moving particles to produce a

macroscopic effect -- loosely speaking, they are machines

producing macroscopic order. Interestingly enough, none of them

proved valid.

> The tremendous effort that went into biochemical
> investigations of muscle between 1900 and 1930 produced
> very little that has since turned out to be directly
> relevant to the coupling between chemical and
> mechanical events [Huxley, 1980, Ch. 2].

Between 1953 and 1957 A. H. Huxley and H. E. Huxley obtained

results with the use of electron microscopy and x-ray diffraction

techniques that led to a quite different view of muscle

contraction: the so-called sliding-filament theory. The theory

varied greatly from previous models in the relation between

structure and function. But more important than structure and

function are the physico-chemical events required to accomplish

the sliding which showed important differences compared to the

physico-chemical events posited by models in vogue during the

first decades of the XXth century. It is these latter differences which are the more relevant to my account.

Of course, to identify the level of organization at which the contractile mechanism is located we have to go deeper than the whole organ. The muscle behavior is a sort of summation of the behavior of the muscular cells (also called 'muscular fibres'). Each fibre is, in its turn, made up of almost identical longitudinal units, the myofibrils. The myofibrils of a human adult can have a diameter of 50 microns and be as long as the muscle itself. Along its length the myofibril is made up of a repeating unit, the sarcomere, whose length is approximately 2.5 microns. Figure 1 depicts schematically the sarcomere's structure and the structural changes upon contraction. The shortening of the muscle is not produced by alteration of the length of the parts of the machine -- not by their contraction -- but by the intercrossing of finely organized systems of filaments.

On the right of Figure 1 a closer view of the filaments is also shown. The actin filament is a double helix whose threads are formed by the union of many identical globular proteins of 42kD called actin. To grasp the dimensions at stake, each small sphere in the figure will have the same mass as 42000 hydrogen atoms. So, Figure 1 is quite far from discriminating single atoms.[44]

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[44] This not the whole story of the thin filaments' composition and workings; in this and the following I restrict the description to what is considered of greater relevance for
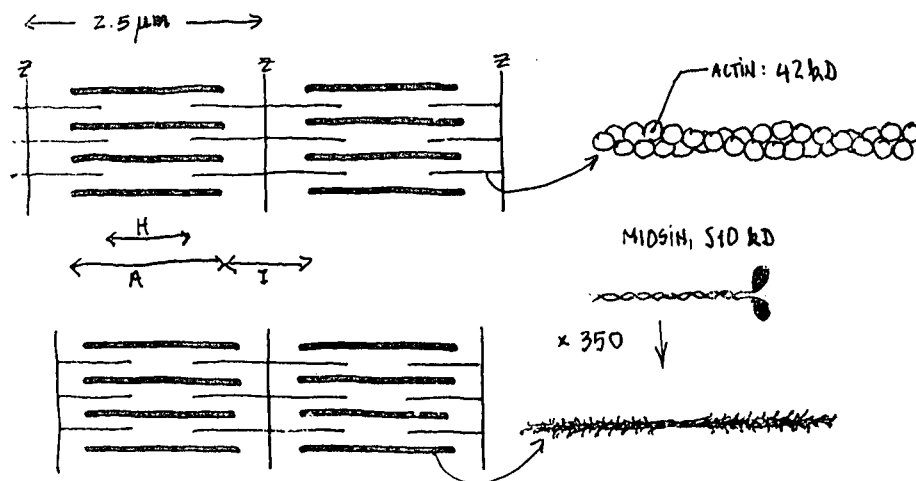
Fig. 1   Structure of the sarcomere depicting the structural changes upon contraction as well as an steric view of the thin and thick filaments.

Fig. 2   Close view at the 'powerstroke' in skeletal muscle contraction (taken from [Alberts et. al., 1989]).

the arguments here presented.

The thick filaments are made of ordered bundles of long protein molecules of 510 kD each called myosin. Myosin is a long molecule with two heads at one end. The heads show ATP-ase activity of their own: they hydrolyze ATP molecules -- the direct fuel of bioenergetic processes -- into ADP + P_i. But this enzymatic activity is greatly enhanced when the heads are allowed to bind actin.

When sliding, these heads interact with the actin monomers of the thin filaments. Figure 2 increases the details to illustrate this interaction where the chemical energy is converted into mechanical energy. The 'powerstroke' is produced by a conformational change of the myosin head which displaces the actin filament one actin-length. The new position of the head enhances the release of ADP, completing the cycle. If the other conditions for contraction are present -- for example, adequate concentration of Ca^{2+} -- the head will be ready for another actin-length slide.

Strictly speaking, the way in which chemical energy is converted to mechanical energy is not dealt with at this level of organization. Without appealing to sub-molecular events, the connection between the release of a phosphate bond and the power stroke is left as a 'why not?' hypothesis. But a level of description has been reached in which it can be assured that the macroscopic event of contraction has been reduced to the sum of

microscopical (molecular) mechanical events. These molecular events have the main macroscopic features of the machine, that is, working cycles and permanence of the participating structure.

This new account of physico-chemical events, in which the transformation of chemical energy into mechanical energy calls upon microscopic chemico-mechanical transducers, represents the other basic change brought in with the present view of muscle contraction. Changes in fiber length or fiber tension in the presence of H-ions, as Fletcher and Hopkins had suggested, are not only different models, but very different <u>kinds</u> of models.

This significant difference, however, should not lead us to ignore an interesting similarity, namely, that the machine is preserved during operation in both models. In fact, aside from the direct experimental evidence, Fletcher and Hopkins included some other considerations showing that their view was sound and coherent with other strands of research about different workings of the cell. Among these considerations, the following is quite interesting in our search for the basic machine features of the models:

> With an understanding that the relatively permanent
> physico-chemical system of the muscle can, <u>without</u>
> <u>itself undergoing chemical modification</u>, carry changes
> of potential as a result of changes in its physical
> configuration, it becomes easier for us to realize that
> the food-stuffs, or at least that sugar, may be the
> direct source of the contractile energy [Fletcher and
> Hopkins, 1917].

Contrary to the Cambridge phrase they quoted, the separation between fuel and machine is fully restored.

. . . .

In my inquiry about the features of an alleged chemical machine I have dealt with the muscle as a case study of Liebig's "metamorphosis of tissues" with the muscle the prototype of a living machine. Fletcher and Hopkins' discussion of muscle in the 1915 Croonian Lecture was also a case study for the new vision of chemical events in the cell. In a way, theirs was also the general problem of the chemical machine, "the general nature of the processes of metabolism" [Fletcher and Hopkins, 1917, p. 452], of which the muscle itself was the most striking example. The inogen hypotheses and its relatives were general views of the chemical processes inside the 'protoplasm', and although the authors' concern was the production of mechanical effects brought about by chemical changes it was also, if not mainly, the general view of chemical events inside the cell -- "We are concerned in this Lecture in the main with the respiratory oxidative phenomena..." [Fletcher & Hopkins, 1917].

This relationship between muscle contraction and the general workings of a cell was openly stated.

These conceptions of Hermann and Pfluger have had an historical importance reaching far beyond the particular enquiry into muscular energy. They summarized the only aspects of cell metabolism which had received any experimental analysis at all, and up to the end of the nineteenth century they not only represented all that was known of cell respiration and of its relations to cell energy, but they dominated also all our ideas of cell metabolism in general. It was conceived that the chemical processes of life in all cells consisted essentially in the building up of elaborate, unstable, and oxygen-charged molecules, by the processes of so-called 'anabolism', into the mystical complexes of irritable protoplasm. From protoplasm, as seen in chemical imagination, a descent by the stages of so-called 'catabolism' was conceived to follow, by which through successive splitting processes energy was discharged, and certain recognizable end-products were displayed [Fletcher and Hopkins, 1917].

Fletcher and Hopkins continue then by quoting Michael Foster, who had been the leading physiologist in England during the last decades of the XIXth century, as follows:

The oxygen taken in the muscle, whatever be its exact condition immediately upon its entrance to the muscular substance, in the phase which has been called 'intramolecular', sooner or later enters into a combination, or, perhaps we should rather say, enters into a series of combinations. We have previously urged that all living substance may be regarded as incessantly undergoing changes of a double kind, changes of building up, and changes of breaking down... We cannot as yet trace out the steps taken by the oxygen from the moment it slips from the blood into the muscular substance to the moment when it issues united with carbon as carbonic acid. The whole mystery of life lies hidden in the story of that progress, and for the present we must be content with simply knowing the beginning and the end (Textbook of Physiology, 6th edition, Book II, p.610) [Fletcher and Hopkins, 1917].

Liebig's metamorphosis of tissues was the predecessor of the chemical picture of protoplasm. The chemical machine that emerged from Hopkins school was remarkably different: a chemical structure active through its catalytic powers.

3. THE CATALYTIC MACHINES

3.1 NON-FERMENTATIVE FERMENTS

Another kind of chemical machine emerged from a chemical idea

foreseen by Jacob Berzelius. In his widely read <u>Jahresbericht</u>

(translated to the German by Friedrich Wohler, who had stayed a

couple of years at Berzelius's laboratory in Stockholm) he

reviewed some research results in inorganic chemistry in which

the presence of some bodies greatly enhanced a chemical

reaction.[45] To these phenomena Berzelius supplied a name:

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[45] Constantin Kirchhoff, in 1811, found that in low
concentrations a boiled mixture of sulfuric acid with starch
produced the change of the latter into sugar without alteration

It has been shown that many bodies ... possess the
property of exerting an influence on complex bodies...
causing the rearrangement of the constituents ...
without necessarily taking any part therein with their
own constituents... I will call it the 'catalytic
power'... (as quoted in [Dixon, 1970]).

These chemical facts of 'inorganic nature' were referred to in

the section on vegetable chemistry [Partington, 1964, p.263].

Berzelius was suggesting that catalytic susbtances might be

present in other situations.

When we turn this idea to living nature, an entirely
new light dawns for us. It gives us good cause to
suppose that in living plants and animals thousands of
catalytic processes are taking place between the
tissues and the fluids... (Berzelius, 1837, as quoted
in [Dixon, 1970]).

The notion of 'catalytic power' offered a speculative instrument

that very quickly caught the imagination of the growing circle of

chemists working in life-related phenomena. The mechanical

---

of the acid. In 1833-34 Michael Faraday published the paper 'On
the power of metals and other solids to induce the combination of
gaseous bodies', where he extended previous work by Humphry Davy
(1817), Louis Jacques Thenard (1823) and others, reporting
particularly the striking influence of different forms of
platinum -- platinum sponge, wire, foil, black -- which was known
as quite an inert element [Partington, 1964, Ch. 7].

philosophers of the XVIIth and XVIIIth centuries relied on cogs, wheels, gears, springs and the like to picture living organisms as machines. With the progress in chemical knowledge, organs could be thought of as chemically inert bags inside which the reactions of life proceeded, or they could be supposed to undergo continuous degradation -- as in Liebig's view of the muscle -- and some processes imagined to recover them. But a living organism endowed with these 'catalytic powers' would be able to take part in guiding the chemical processes necessary to sustain life in such way that after the processes the machine would remain essentially intact.

What had Berzelius in mind when he proposed to transfer the idea of catalytic power to the living realm? Fermentation processes, particularly, alcoholic fermentation.

> the conversion of sugar into carbonic acid and alcohol, as it occurs in the process of fermentation cannot be explained by a double decomposition-like chemical reaction between a sugar and so-called ferment, as we name the unsoluble substance under the influence of which the fermentation takes place. This substance may be replaced by fibrin, coagulated plant protein, cheese and similar materials, though the activities of these substances are at a lower level. However, of all the known reactions in the organic sphere, there is none to which the reaction bears a more striking resemblance than the decomposition of hydrogen peroxide under the influence of platinum, silver, or fibrin, and it would be quite natural to suppose a similar action in the case of the ferment (Berzelius, 1836, as quoted in [Fruton, 1972, p. 47]).

To understand the fate of Berzelius' proposal and the meaning of the modern 'enzyme' we have to trace the history of fermentation. The term 'fermentation' is an ancient word, a victim of many uses. By the end of the XVIIIth and during the XIXth centuries it remained equivocal, designating sometimes a broad category of processes and sometimes designating specifically some of these processes.[46] The following classification can be useful to understand the account presented in this section [Waksman, 1926]: 'digestion' referred to reactions in which organic matter was decomposed by organic juices; 'putrefaction' encompasses those process accompanied by the formation of foul smelling substances and 'fermentation' was restricted to the situations in which gas -- mainly CO_2 -- was liberated. The latter can also be divided into spirituous (wine), acid (vinegar) and putrefactive.

On 'catalytic force' in organic nature Berzelius was just a commentator, as most of his experimental work was done in inorganic chemistry. The "double decomposition-like chemical reaction" in the quotation above is an idea due to Lavoisier and Gay-Lussac, who considered fermentation as a chemical process in which a sugar molecule is split in two parts, one of each receiving oxygen from the other (in modern notation, what Gay-Lussac finally put into the equation was $C_6H_{12}O_6 \longrightarrow 2C_2H_5OH + 2CO_2$). But of course Lavoisier recognized that the ferment was

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[46] The existence of equivocal uses of the word is very far from being historically irrelevant, as will be seen later in the brief account of Pasteur's dispute with Liebig.

necesssary. According to Lavoisier, a small quantity of it

initiates a process that then runs on its own. Berzelius agreed

in the view that fermentation is a chemical process, but the fact

that to be accomplished a small quantity of something called a

ferment was needed, as well as the fact that the overall process

can be described chemically by an equation not involving the

ferment itself, was enough for him to make an analogy with

inorganic catalysts.[47] In spite of the meaningful results

reported by the advocates of fermentation as a process related to

the life of microorganisms during the years 1836-9 (for example,

Schwann, Kutzig and Cagniard-Latour), Berzelius stated in his

1839 _Jahresbericht_ that yeast is "no more to be regarded as an

organism than ... a precipitate of alumina" [Harden, 1911], a

position he maintained until 1848.

A chemical approach to fermentation was backed mainly by the more

prestigious chemists of the continent, like Liebig and Wohler,

although there were important differences in the accounts.[48]

Liebig published in 1839 a paper explaining his view. He

admitted, following Gay-Lussac, that the presence of atmospheric

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[47] There were contradictory reports about the fate of the ferment: did it grow, remain the same or disappear during the process? Thenard claimed that ferments like yeast diminished in weight with the process, loosing nitrogen and carbon and that this carbon was present in the CO_2 evolving fermentation came from the yeast.

[48] At the same time the brewery industry worked with the idea that fermentation is a life-related processes [Harden, 1911].

oxygen was crucial for the process of fermentation to go. This atmospheric oxygen entered in contact with the nitrogenous substance of the ferment and the latter became quite unstable, communicating its motion to loosely bound sugar molecules which decomposed into alcohol and carbonic acid, while the ferment itself suffered alteration. The congruity of this view with the 'metamorphosis of tissues' we described above is remarkable.

The chemical view in general, though not the particular models, relied on strong experimental facts: the discovery of soluble ferments. In 1833, Anselme Payen and Jean Persoz obtained from germinating barley a substance they called diastase that after being dried was able to convert starch into sugar. Evidently this substance was not a living organism, and although this was not the first report of this sort, it certainly marks the beginning of a period during which similar important findings of other so-called soluble ferments were announced. Schwann, following a current line of research in digestion, reported in 1836 that he had identified the active principle in gastric juices that were known to dissolve coagulated egg white and gave to it the name pepsin. He remarked on its resemblance with the agents of alcoholic fermentation, as there was "a spontaneous decomposition of organic materials, elicited by a substance acting (through contact?) in a minimal quantity" (Schwann, 1836, as quoted in [Fruton, 1972, p. 68]). In 1837 Liebig and Wohler reported about

an albuminoid material obtained from almonds -- emulsin they
called it -- capable of decomposing amygdalin.[49]

On the other hand, fermentation as a phenomenon correlative with
life received strong support with the work of Louis Pasteur. In
experiments beginning in 1857 he claimed, among other things,
that a microorganism for lactic fermentation indeed existed --
its non-existence was used as an argument by those who held the
opposite view -- and that a simple equation for alcoholic
fermentation like Gay-Lussac's could not be true because other
chemical susbtances like succinic acid and glycerine are produced
as well. Pasteur's experiments during three years culminated in
his now classic 1860 'Memoire sur la fermentation alcoholique'
where he plainly declares that the chemical act of fermentation
is essentially a phenomenon correlative with a vital act.

To circumvent the undeniable existence of soluble ferments
Pasteur affirmed that those encompassed by his theory were the
"properly so-called fermentations", and about the chemical fate
of reactions in the living organism he formulated a Newtonian
'hypothesis non fingo'.[50] Chemists, or physiological chemists,

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[49] Ferments in human saliva, pancreas and vegetable tissues
were reported one after the other. By the end of the nineteenth
century, the number of soluble ferments had grown to two dozen.
For a brief although detailed account, see [Fruton, 1972].

[50] It is remarkable that some modern historians and almost
invariably all modern authors of text books fond of making
historical remarks usually justify extreme mechanicist positions
in this period appealing to an unavoidable crusade against

were interested precisely in the chemical events inside the

microorganism. In 1858 Moritz Traube warned against stopping just

there, at the border of the organism:

> Even if all decay processes depend upon the presence of
> infusoria or fungi, a healthy natural science would not
> permit [Schwann's] hypothesis to preclude further
> investigation. It would simply conclude from these
> facts that there are present in microorganisms chemical
> susbtances which evoke the appearance of decomposition.
> It would attempt to isolate these substances and, if it
> could not do so without changing their properties, then
> it would only conclude that all means used for
> separation must have exercised a chemical influence on
> these very substances, changing them. (M. Traube:
> Theorie der Fermentwirkungen 1858, as quoted in
> [Sourkes, 1955]; my emphasis)

Soluble ferments would be the evident model to rely on when

thinking about the internal chemical machinery producing

fermentation. After all, pepsin, for example, and pancreatic

ferments, were substances excreted by organisms.

> Ferments are the causative agents of the most important
> vital-chemical processes not only in the lower, but
> also in the higher organisms" (Traube, M. Die chemische
> Theorie der Ferment wirkungen und der Chemismus der
> Respiration, Ber. dtsch. chem. Ges. 1877, Vol, 10, a
> quoted in [Fruton, 1972])

'living forces' and the like. However, Pasteur's predicament that
in fermentations and putrefactions microorganisms must be
present, for which he is charged with 'vitalism' -- 'vitalist' is
anything but a 'neutral descriptor': for a biologist "it is worst
than being blamed as communist by an FBI agent" [Szent Gyorgyi,
1962] -- is never justified recalling a necessary crusade against
would-be Paracelsian heirs not far from claiming, as Paracelsus
did, that it is possible to obtain mice from rotting organic
material inside closed bottles.

In fact, Marcelin Berthelot, who had been working in general synthesis of organic compounds with alcohols and sugars, reported in 1859 that he had obtained from yeast a soluble ferment able to invert sugar. And later in his influential <u>Chimie Organique Fondee sur la Synthese</u> published in 1860 he suggested also the all pervasive presence of fermentations:

> among the phenomena that are related to the transformations of matter in living beings, whether during the life or their death, there are few that do not involve fermentations to a greater or lesser degree (as quoted in [Fruton, 1972, p. 52]).

The idea of fermentation, the "mysterious ... change which converted the insipid juice of the grape into stimulating wine" [Waksman, 1926], was beginning to be used not just as the process producing vinegar, wine or lactic acid in milk. More than 'fermentation', Berthelot seems to be suggesting a 'fermentation-like chemical process', that is, catalysis. Thus, Anselm Payen wrote under the entry "Fermentation (chemistry)" in the <u>Encyclopedie du XIXe siecle</u>:

> One should understand by this word a spontaneous reaction, a chemical alteration excited within a mass of organic matter by the sole presence of another substance, without the latter borrowing or lending anything to the body it decomposes... (as quoted in [Laszlo, 1986, p. 430]).

In 1878 Willy Kuhne designed a term supposed to avoid equivocal arguments about the nature of fermentation processes. Instead of the ferments of fermentation (which are chemical substances, also called 'unorganized ferments') and the ferments of 'properly so-called fermentations' (which are organisms, also called 'organized ferments'), Kuhne proposed to call the unorganized ones 'enzymes' ('in zyme', that is, inside yeast). Although he insisted that the new term

> is not intended to imply any particular hypothesis, but
> it merely states that in zyme something occurs that
> exerts this or that activity, which is considered to
> belong to the class called fermentative (as quoted in
> [Fruton, 1972, p. 74]).

But his new word ended up being used to imply that this something is a 'substance', a soluble ferment. This was Felix Hoppe-Seyler's idea -- the generalization of enzymes as internal soluble ferments driving all chemical phenomena as hydration and dehydration reactions [Kohler, 1964] -- although very unlikely Kuhne's, who was one of the contributors of the protoplasm theory. Hoppe-Seyler's was in general the same idea as the one behind Traube's 'causative agents' quoted above.

The controversy on the nature of fermentation -- whose effects are still felt today -- is a well documented story and we are not going here into many of its details. Some current historiography describes it as the debate between a 'vitalist' approach

(Schwann, Pasteur) and a 'mechanist' approach (Liebig, Berthelot, Traube, Hoppe-Seyler), that is, not a debate about fermentation, but one about the scope of chemical research in organic processes. Actually, the polemic was not devoid of the common exercise of disqualifying the opponent's 'scientificity', and even included angry nationalism exacerbated by the Franco-Prussian conflict. Patriotism was brought in by Pasteur against those Frenchmen defending a "German theory". The so-called vitalists of this polemic are sometimes blamed for imagining insurmountable barriers to the true chemical approach for entering the cell and unraveling its secrets, which is supposed to be in general what Traube and Hoppe-Seyler had in mind: internal enzymes.[31] But we have to refrain from thinking that the present 'enzyme theory of life processes' was the only chemical approach that '_Homo scientificus_' could pursue.[32] For almost twenty years until Edward Buchner's surprising success in obtaining a juice from yeast capable of some alcoholic fermentation in 1897, the chemical view of the inner workings of the cell was that of the protoplasm, described in the second chapter. It was absolutely rational to deduce from the protoplasm idea that some chemical behavior was not possible when the

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[31] Pasteur did not suggest such kind of obstacle. In fact, in the 1880s he tried -- not with great enthusiasm, I guess -- to extract soluble ferments from yeast.

[32] This is what, for example, T.L. Sourkes contends: "The history of XIXth century conflict between the mechanist and vitalist outlooks in science may very appropriately be told from the standpoint of enzyme chemistry" [Sourkes, 1955].

integrity of the cell is disrupted. In addition, in spite of the subsequent successes of biochemistry, we could have foreseen some shortcomings in Traube's views about internal substances when they were suggested, aside from the fact that soluble ferments, or in the new vocabulary, internal enzymes, had not been obtained. What are the effects of considering that fermentation processes inside the cell are accomplished by "substances"? Is it possible to explain the effect of a hammer as an iron-woodish action? Would we dare to say that a mitochondrion, without whose fine organization important chemical wonders would not exist, is a 'substance'? From hindsight it might be said that it is not proper to bring in an analogy with a hammer, since it is a mechanical process very unlikely to produce the kind of chemical changes that were to be explained. But Traube's acceptance of chemical changes being produced by mechanical action shows how unstable was the terrain on which any proposal was standing:

> The pressing out of the juices is not a mere
> mechanical, but simultaneously a chemical attack upon
> the substance of the fruit. In the cells, the
> individual substances are localized near one another in
> a definite way, and their mutual action is another
> matter than in the juice where they are mixed
> indiscriminately with one another". (M.Traube: Uber das
> Verhalten der Alkoholhefe in Sauerstoffgasfrein Medien.
> Ber. dtsch. chem. Ges., 1874, Vol. 7, as quoted in
> [Sourkes, 1955]).

In this view it is more than expected that chemical phenomena in the cell depends not only on the substances, as he stated elsewhere, but in the organization as well.

Kuhne's new word was readily adopted. But the idea of extending 'enzyme' to include the inner chemical behavior of the cell turned almost inevitable after Buchner's experiment. Some years after the success was reported, Franz Hofmeister suggested openly the new tenet.

> We thus arrive at the conception that the carriers of chemical processes in the cell are colloidal catalysts, an idea that agrees perfectly with other directly demonstrated facts. For what are the ferments of biochemists but colloidal catalysts (Franz Hofmeister, Die chemische Organization der Zelle, 1901, as quoted in [Kohler, 1972]).

Berzelius's suggestion about catalysis, if not interpreted as the mere introduction of a word or as a theory about alcoholic fermentation, but rather as a novel source of models about the chemical accomplishments of an harmonious system able to preserve itself while directing continuous transformations -- a model for a chemically active machine -- was going to have immense success.

3.2 COLLOIDAL MACHINERY

In the last section I showed how it was being realized that alcoholic fermentation was a process produced by substances, that is, a process chemically definable not only in its input and output but also in its intermediate steps. We saw also the rise

of the promising idea that 'ferments' as chemical substances could provide a model for thinking about every chemical process going on inside the cell.

The meaning attached nowadays to the words enzyme, protein and such may distort our perception of the problems at stake. Schwann, for example, did not obtain the enzyme that biochemists call today pepsin. He dried a chemically undefined gastric juice showing pepsin-like activity. Zymase, what Edward Buchner obtained from yeast, was a juice extract capable of some sort of alcoholic fermentation but with remarkably lesser activity than the original yeast. Today it is recognized as a mixture of twelve enzymes and some coenzymes. In 1900 'ferment', or even 'organic catalyst', were concepts defined in terms of their actions as substances whose presence in small amounts alters the rate of a chemical process without suffering alteration themselves. So, the idea that the chemical machine acts through agents called ferments leaves still open questions like: What are the chemical compositions, structures and classification of these agents? How do they act? Can they be characterized as chemical individuals? These are the kind of questions whose answers are necessary to validate the characterization of an organism as a chemical machine -- not only input-output analysis, but also the means whereby they act.

In his first edition of <u>Animal Chemistry</u>, Liebig indeed invents chemical reactions when what he actually knows is the elementary chemical composition of reactants and alleged products. With this information, he balanced chemical reactions he had invented by adding or subtracting appropriate amounts of water, oxygen, carbonic acid and ammonia. For example, the reaction

```
      5     atoms of protein
  + 15      of starch
  + 112     of water
  + 5       of water
```

giving

```
      9     atoms of choleic acid
  + 9       of urea
  + 3       of ammonia
  + 60      of carbonic acid
```

was a possible one because the quantities of the constituent atoms, C, H, O, and N were equal on both sides.

This chemical reasoning "from the desk" (as Berzelius in a strong critique called it) could hardly replace detailed chemical research. Kohlrauch, though a mild critic of Liebig's book, pointed out that "one could reach the ridiculous conclusion that the oxidation of protein in the body produced the poison prussic acid and the explosive compound fulminic acid" (as quoted in [Holmes, 1963]). In the third edition Liebig took out the

appendix with the equations and began to inquire about the intermediate steps.

But researchers did not have to think about the more complex achievements of a living being such as protein synthesis to ask challenging questions. Compelling enough was the problem of oxidation. How could oxygen, a rather unreactive substance outside the animal body at low temperatures, becomes so fiery inside it?

In the previous chapter we saw that examples of catalytic behavior in inorganic reactions were cited by Berzelius when he proposed to extend the model of catalysis to the chemical actions of organic bodies. In many of the examples that were taken from the inorganic realm, the existence of a metallic surface was responsible for the acceleration of a chemical reaction in which atmospheric oxygen participated. These catalytic surfaces provided a theme that was not abandoned in speculations about the mechanism of oxidation -- and fermentation in general -- for many decades. J.R. Mayer, for example, after accepting the view that combustion occurred in the blood, imagined the capillaries' walls as porous surfaces able to promote oxidation.

The conception of the cell as a chemical machine whose reactions were effected by catalysts (many of them probably acting through surfaces), discoveries of the microscopists, developments in

thermodynamics, particularly what later was called physical
chemistry, blended by the turn of the century into a suggestive
idea: there is a kind of physico-chemical system whose behavior
and composition can account for processes occuring in the cell:
colloids. Colloids held out the promise of chemists,
physiologists, histologists and physicists working together in
harmony. It is useful to begin by assessing how the nowadays
almost extinct phrase 'colloidal behavior' caught the imagination
of biological thinking at the turn of the century.

3.2.1 WILLIAM B. HARDY

> [T]he unification of the biological sciences was begun
> by the recognition of the cell as the unit of all life,
> and of the glutinous sarcode as its physical basis...
> Living matter is composed of very large molecules, and
> substances so built possess certain special properties
> which mark them off from simpler substances. To them
> the name of colloids is given, after the type of the
> class the jellies...
>
> It is only in the colloidal state that we could have
> within so small a space so great a diversity of matter,
> and such differences of chemical potential as must
> exist to support the multifarious activities of the
> living cell, combined with the molecular mobility
> necessary to give chemical change free play.
>
> On [the] blending of opposites, on the curious
> combination of inertia and chemical mobility in the
> colloid state, is reared the whole fabric of the
> dynamics of living matter [Hardy, 1906, p.447].

So wrote William Bate Hardy (1864-1934) in his "The Physical
Basis of Life", a popular article published in 1906. Hardy, a

biologist by training, turned to the colloid chemistry of proteins (today we would say biophysical chemistry) during the middle of his research life and ended up doing research on lubricants. He is mostly remembered for his discovery of the influence of the acidic or basic character of a solution on the electric charge borne by proteins, a discovery leading him to develop the concept of isoelectric point of a protein.

After general statements like those quoted above on the marvels performed by the colloidal state of matter, Hardy singled out three features of life -- choice and purpose, growth, and heredity -- to show that physico-chemical systems can behave in ways perfectly resembling these. He illustrates choice and purpose with the phenomena of chemotaxis, "the influence of a chemically heterogeneous medium upon the free cells living in it" [Hardy, 1906, p. 450]. Opalina, a parasite living in the frog's intestine, does not simply respond to chemical changes in its immediate environment. It displays chemotactical behavior in the presence of concentration gradients, but its behavior also depends on the medium in which it was immersed before. The microorganism manifests a sort of memory.

> The faculty ... of storing impressions, so that the
> response to any particular stimulus is in part
> conditioned by the stimuli which have preceded it, is a
> familiar property of living matter, and also of matter
> in the colloidal state. The molecular state of a jelly
> is not fixed by the conditions of the moment. Just as a
> piece of wrought iron has properties different from
> those of cast iron, so the circumstances which attend
> the making of a jelly - temperature, concentration, and

the like confer on it an internal structure which
controls its properties for years to come. Each jelly,
therefore, has an individuality due to the record which
it bears of its past [Hardy, 1906, p.452].[53]

Regarding growth, Hardy describes experiments performed with

Paramecia in which senile decay after many generations was

reversed by "artificial rejuvenation" after immersing them in

infusions of beef extract. Many simple chemical solutions can

lead to this artificial rejuvenation: "Thirty minutes' immersion

of an individual Paramecium in very dilute solution of potassium

phosphate was found to restore vitality". The salt, so he thinks,

provides a sort of chemical shock restoring again the necessary

difference from the inactive state of equilibrium. Rejuvenation

is a puzzling phenomenon, he admits, but there is a physical

behavior resembling it. First he points out the striking

properties of surface layers, where

all physical properties become abnormal ... when the
surface energy forms a large fraction of the total
molecular energy, as in films, or fluid in fine
capillaries, ordinary chemical or physical knowledge
fails us [Hardy, 1906].

And then he continues:

---

[53] Some breath-taking generalizations are braved by Hardy
here: "The biologist is cognizant of no break in the series from
the choice of [the bacteria] Vibrio, which can be analyzed
algebraically, to the choice of a child between two toys" [Hardy,
1906, p. 451]. The relationship between 'free will' and the
automatic response of elementary organisms to external stimuli
has haunted the mind of many researchers coming from the physical
sciences. Jacques Loeb went through similar lines of arguments to
Hardy's, and many years later Max Delbruck abandoned his phages
to study chemotactical behavior.

> There is no lack of evidence to prove that the lifelike
> characteristics of colloidal matter, its capacity for
> storing impressions, the elusiveness of its chemical
> and physical states, are due to the fact that an
> exceptionally large fraction of this energy is in the
> form of surface energy [Hardy, 1906, p. 57].

Finally the physico-chemical phenomenon that could account for

rejuvenation can be brought forward:

> [I]t is just in experiments on surface energy that one
> finds a case analogous to the effect of the salt in
> bringing about rejuvenescence ...: By the use of minute
> amounts of salts one can fix in the surface layers
> certain qualities [direction] which for instance define
> the electric properties of the surface... The salt can
> be removed, the effect remains. So far as we know, in
> the absence of active chemical intervention, it will
> endure for all time, always exerting a directive
> influence upon the molecular events in its
> neighborhood. In these experiments there is, it seems
> to me, a real clue to the nature of the phenomena of
> rejuvenescence [Hardy, 1906, p. 457].

As for heredity, Hardy did not refer to colloids but relied on

microscopical observation of chromosomes to show that only

physico-chemical processes are ocurring.

In his use of the concepts of protoplasm and colloids Hardy plays

here an intermediate position. "Protoplasm" was a term, if not

invented by Thomas Huxley, surely made popular by him in his 1868

lay sermon "On the Physical Basis of Life" and "colloidal

behavior" was surely intended to replace it, as "protoplasm" was

considered too fuzzy.[34] Thus Hardy's intermediate position, and

to grasp the sort of novelty that colloidology promised to bring

in to explain the puzzling features of life, some statements from

his essay are worth quoting:

> "Proteids unquestionably are the material basis of
> life, but when isolated after the death of the cell
> they are not living. They are chemically stable
> bodies... It is therefore conjectured on experimental
> grounds that the living molecule is built up of proteid
> molecules, that it is so complex, so huge, as to
> include as units of its structure even such large
> molecules as these. But when such very large molecules
> enter into chemical combination with one another,
> whether by reason of the great magnitude of the masses
> of matter in each in relation to the magnitude of the
> directive forces, or because the molecules themselves,
> owing to their great size, to a certain extent cease to
> be molecules at all in the physical sense, and possess
> the properties of matter in mass, it is at any rate
> certain that in their chemical combinations they cease
> to follow the law of definite combining weights which
> is the basis of chemistry. The quantity of the
> substance A which will combine with a fixed quantity of
> the substance B is determined not only by the chemical
> nature of A and of B, but also by the chance conditions
> of temperature and concentration of the moment. This
> class of chemical compound is within limits
> continuously adjustable to changes in its surroundings,
> while at the same time it resists those changes by
> reason of its inertia. Here is a real adumbration in
> non-living matter of the chemical flux which is the
> abiding characteristic of the matter of life.

Hardy explains further:

----

[34] At least four rather important essays were written under
the title "The Physical Basis of Life". Aside from those of T.H.
Huxley and W.B. Hardy, E.B. Wilson published one in 1923 [Wilson,
1923] and J.D. Bernal another in 1951 [Bernal, 1951]. A sort of
general strategy exists in them: there are unanswered questions
in inorganic processes that can be as enigmatic as those in the
living realm as to invent magical virtues in the workings of the
latter ones. But some features proper to life can be imitated by
well defined physico-chemical systems.

> The biologist speaks of these molecular complexes as
> molecules, and in that he is wrong in so far as the
> word implies a defined structure, a chemical unit. The
> biogen, or chemical unit of living matter, is not a
> fixed unit like the molecule of dead proteid; it is an
> average state. That we know from the chemical phenomena
> of living matter [Hardy, 1906, p. 461].[55]

From this article we conclude without hesitation that colloids

could be taken as direct explanations of relatively complex

achievements of organisms. How did this enthusiasm about the

colloidal state of matter arise? Not very long before Hardy,

Thomas Graham had introduced the concept of colloids in his work

on diffusion.

3.2.2 THOMAS GRAHAM AND THE ORIGINS OF COLLOIDOLOGY.

In 1861 Thomas Graham published in the Philosophical Transactions

of the Royal Society an article entitled 'Liquid Diffusion

applied to Analysis' as part of his researches on diffusion

rates. There he reported a noticeable difference in some very

general physical and chemical properties between a class of

substances he called "volatiles", referring to diffusion in

liquids using an analogy with gases, and those he called "fixed".

The latter are "marked out by the absence of the power to

---

[55] Hardy clearly does not mean "molecule" in our sense of
the word. Indeed, it is only with Staudinger's idea of
"macromolecule" that the term becomes stable.

crystalize" and by their extremely slow diffusion. Examples of
these are hydrated silic acid, starch, albumen, gelatin,
vegetable and animal extractive matters, among others.

> Although often largely soluble in water, they are held
> in solution by a most feeble force. They appear
> singularly inert in the capacity of acids and bases,
> and in all the ordinary chemical relations. But, on the
> other hand, their peculiar physical aggregation with
> the chemical indifference referred to appears to be
> required in substances that can intervene in the
> organic processes of life. The plastic elements of the
> animal body are ground in this class. As gelatine
> appears to be its type, it is proposed to designate
> substances of the class as colloids, and to speak of
> their peculiar form of aggregation as the colloidal
> condition of matter [Graham, 1861, my emphasis]

Subsequently he adds a passage that has received much attention
from historians.

> Although chemically inert in the ordinary sense,
> colloids possess a compensating activity of their own
> arising out of their physical properties. While the
> rigidity of the crystalline structure shuts out
> external impressions, the softness of the gelatinous
> colloid partakes of fluidity and enables the colloid to
> become a medium for liquid diffusion like water itself.
> The same penetrability appears to take the form of
> cementation in such colloids as can exist at a high
> temperature. Hence a wide sensibility on the part of
> colloids to external agents. Another and eminently
> characteristic quality of colloids is their mutability.
> Their existence is a continued metastasis. The
> colloidal is, in fact, a dynamical state of matter; the
> crystalloidal being the statical condition. The colloid
> possesses ENERGIA. It may be looked upon as the
> probable primary source of the force appearing in the
> phenomena of vitality. To the gradual manner in which
> colloidal changes takes place (for they always demand
> time as an element), may the characteristic protraction
> of chemico-organic changes also be referred [Graham,
> 1861].

What Graham considered appropriate for carrying out organic processes was not, of course, the extremely slow rate of diffusion of these colloids of animal and vegetal origin, but their resistance to chemical changes, as well as their capacity of preserving structure and at the same time registering changes after interaction with the environment. Others (Liebig, perhaps) could have seen this sort of chemical inertia as a shortcoming, but Graham (himself not a biologist or an 'animal chemist') saw this stability as the very attribute signaling colloids as the bearers of life.

Graham characterized colloids as those substances that did not go through parchment membranes. But apart from his dialyzer, an instrument that was going to be used later as one of a set of experimental tests for colloids, he did not deal with the relationship between colloid behavior and life processes, at least not in a way that would allow anybody to suspect that 40 years later his definition was going to be considered as a breakthrough in the inquiry about the nature of life. In fact, he suggested the term 'colloid' only 8 years before his death, as part of his continued research on chemical separation by mechanical methods, first pursued with gases. As can be seen in the collection of his Chemical and Physical Researches he made only a few more experiments with inorganic colloids. Only with

hindsight could later biologists and physiologists recall

Graham's work as the origin of a school of biological thinking.

3.2.3 FROM THOMAS GRAHAM TO WOLFGANG OSTWALD.

Wolfgang Ostwald (1886-1943) is considered the most remarkable

propagandizer of colloid chemistry in its beginnings. The son of

Wilhelm Ostwald, he was a zoologist by training, and worked under

Loeb in 1904-6 in California. In 1906 the Kolloid Zeitschrift was

established in Germany, and one year later Wolfgang Ostwald was

appointed its editor. In 1909 Ostwald established the

Kolloidchemische Beihefte. After a series of lectures in the

United States Ostwald published The World of Neglected

Dimensions, whose first German edition was published in 1914 and

had undergone ten editions by 1927. In 1909 he published the

Grundriss der Kolloidchemie, translated into English as A

Handbook of Colloid Chemistry in 1915. Wo. Ostwald acknowledged

that in the study of colloids themselves no theoretical

breakthroughs had occurred from Graham's death until the

beginnings of the 1890's. In the interval, proteins had been

recognized as colloids due to the jelly-like appearance of their

solution in water and because they did not passed through most

semipermeable membranes. Proteins and inorganic colloids -- of

the latter probably the more thoroughly analyzed were colloidal

gold, arsenious sulphide and silicic acid ($SiO_2.nH2O$) -- had

other properties in common: they scattered light (Tyndall effect) and sometimes in the cone formed by the ray of light traversing the solution very small particles were seen undergoing Brownian motion. Moreover, the salting-out procedure widely used to precipitate proteins was equally effective in precipitating inorganic colloids.

The new theoretical insights came after Svante Arrhenius' theory of electrolytic dissociation. Harold Pincton (1867-1956) and Samuel Ernest Linder found that colloidal particles were electrically charged and explained the persistence of the colloidal solution by electric repulsion between the particles. The coagulation effects of the salting-out method was the result of adsorption of opposite charged ions appearing after the electrolytic dissociation of a neutral salt.

Other finer details of the behavior of colloids were also readily explained by referring to the electric charge. For example, Schultze's 'valency rule' enunciated in 1882, according to which 'tervalent metal salts' -- later under the dissociation theory known to bear three elementary charges in solution -- were more effective as coagulators than bivalent ones, and these more effective than monovalent [Partington, 1964, Ch. 23].

During the decade 1890-1900 it was also suggested that the individual particles wandering in a colloidal solution are of

mechanical aggregates of various numbers of small chemical

molecules, a view that would replace Kekule's proposal in 1877

that these aggregates really are molecules with atoms held

together by valence forces. And the newly established physical

chemistry contributed to the field not only with the formalism

developed by Williard Gibbs to tackle systems of coexisting

phases, but with effective methods to treat surface phenomena.

The range of alleged applications of colloid chemistry was

impressive: "Industries such as dyeing, cement, rubber, soaps,

photography, artificial textile fibers, starches, glass, tanning

involved colloid phenomena" [Oesper, 1945]. Although nowadays

some of these fields surely do not rely on the theoretical

grounds developed between 1900-1920 (a main concern would emerge

in polymer chemistry, built upon the concept of macromolecule)

and although probably these fields were more empirical than

theoretically based, what is seen in the early 1900's is the

institutionalization of a discipline whose practitioners promised

achievements in many fields. From Wolfgang Ostwald's handbook

[Ostwald, 1919] a reliable overview of the field, its research

program and predicted applications can be obtained.

Identification of the Colloidal State

In a chemically heterogeneous liquid we can have either a true

solution, a colloid solution or a coarse mechanical suspension.

The latter can be easily separated by filtration or using a hand centrifuge. The first is a molecular solution, and we can distinguish it from the intermediate one because the intermediate, the colloid solution, gives a positive Tyndall effect.

Once identified as a colloidal solution, two remarkably different behaviors can be observed: the suspension colloids -- called also suspensoids, lyophobic or hydrophobic, although the terms are not exactly equivalent -- will show low viscosity and small molecules will diffuse through them at rates very similar to those of a pure solvent; the emulsion colloids -- emulsoid, lyophilic or hydrophilic -- have a great viscosity noticeably affected by temperature changes.

Notwithstanding the macroscopic homogeneity of a colloidal system it has at least two different phases thermodynamically speaking, one continuous and the other disperse. Fog is a colloid in which the disperse phase is a liquid and the continuous one a gas; in a foam the disperse phase is a gas while the continuous one a liquid. We can have gas in solid (lava), solid in gas (smoke), and so on. Nevertheless, the more interesting ones involve a liquid. In all these cases the disperse phase can be in different 'degrees of dispersion', conferring different propertoes on the system.

'Equations of State' for Colloidal Systems

The state of a colloidal system depends on pressure and
temperature like any other system but is remarkably affected by
the degree of dispersion, concentration and the electrolytes in
solution. In general the degree of dispersion decreases with
increasing concentration, and different degrees of dispersion can
be obtained with the same concentration depending on the
procedures for preparation -- one of the grounds for the
statement that colloids have 'memory'-- and different degrees of
dispersion may cause, for example, different compressibilities.
In a colloidal solution there can be different particle sizes, so
the degree of dispersion can not be described by a single number.
Changes in viscosity, boiling and freezing points were commonly
analyzed and contrasted with predictions from theoretical models,
either to choose between different models or to complete
parameters inside one of them.[56]

Most substances when in the disperse phase assume an electric
charge, the sign of which was detected, for example, by examining
the migration under electric fields. In this kind of study Hardy
discovered in 1899 that in the case of proteins the sign depended

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[56] After his request for the purchase of a centrifuge from
Sweden was rejected, Staudinger engaged in a long study of the
viscosity of 'colloidal solutions' that became the grounds for
his hypothesis of 'macromolecule' to replace the concept of
aggregates.

on the degree of acidity or alkalinity of the solution. Coagulation of colloid solutions can be obtained in different ways, but the more interesting way was using the influence of electrolytes. Suspensoids, that is, hydrophobic colloids when the continuous phase is water, were coagulated by adding small quantities of neutral salts, whereas emulsoids required substantial amounts. With emulsoids it was found that coagulation was produced by lower concentrations of trivalent than bivalent and bivalent than monovalent ions, but also more effectively according to the chemical species of the ion in this order:

Cations: $Ba^{++} > Sr^{++} > Ca^{++} > Mg^{++}$

$Cs^+ > Rb^+ > K^+ > Na^+ > Li^+$

Anions: $SO_4^- > Cl^- > Br^- > NO_3^- > I^- > CNS^-$

The differences in cations were found to be less marked. The effect was claimed to be almost general, independent of the chemical features of the colloid involved. These rankings are the so-called lyotropic or Hofmeister series [Partington, 1964, Ch. 23]. Similar or related orders were observed in the influence of these ions on viscosity and osmotic pressure.

Interestingly enough, the reverse of coagulation was called

peptization, a term originally referring to the action of pepsin

(a proteolytic enzyme) on proteins.

Theoretical Framework of the Colloidal State

It was promptly realized after Graham that any crystalloid could

be prepared in the form of a colloid, the more readily the more

complex the substance. Therefore, the classification separating

crystalloids from colloids was not tenable. Instead, 'colloid'

began to refer not to a set of substances, but to a state.

> Colloid is not a chemical entity like salt, acid,
> base... but is expressive of certain physical elements
> like mechanical heterogeneity... Colloid chemistry
> deals with the relations of the surface energies to
> other kinds of energy as shown in an especially
> characteristic way in dispersed heterogeneous systems.
> Thus viewed, colloid-chemistry appears as a branch of
> physical chemistry [Ostwald, 1919, p. 112].

Three ideas formed the core of colloid-science during the years

1900-1920: the electrostatic explanations of stability and

coagulation to which we referred above; the idea that "colloid

chemistry is not the study of colloid materials but that of the

colloid state of materials" [Ostwald, 1919], a view that

identified what we call today 'macromolecule' as aggregates of

small molecules; and the relevance of surface energy, which put

colloid chemistry in the field of physical chemistry, in the

attempt to explain the behavior of substances in the colloid state.

Jacques Loeb stated quite clearly the aggregation hypothesis when he described the battlefield in the historical introduction of his influential book Proteins and the Theory of Colloidal Behavior:

> The colloidal state is defined by colloid chemists as that state of matter in which the ultimate units in solutions are no longer isolated molecules or ions, but aggregates of molecules ...[Loeb, 1924].

As for the third idea, surface energy, Wolfgang Ostwald was categorical: "A development of much surface [sic] is the fundamental property of dispersoid systems" [Ostwald, 1919, p. 66]. The extreme subdivision present in disperse systems brings about an enormous increase in surface area, but what grows even more remarkably is the ratio between the absolute surface area of the entire disperse phase to the total volume of the same, what Ostwald called 'specific surface'. Starting subdivision from a cube with edge of 1 cm (and thus 6 cm^2 of total surface area and a specific surface area of 6 cm^2) to smaller and equal cubes, Ostwald calculated that we obtain, for example, 10^{15} cubes with edges of 0.1 microns, a total area of 60 m^2 and specific surface of 6 x 10^5. Evidently, most of the behavior of a system of 10^{15} cubes will depend on what happens on the interface between the system in the dispersed phase and the continuous phase. Physical

chemistry, particularly the thermodynamics of heterogeneous

systems developed by Gibbs, offered the theoretical tool to treat

surface phenomena. Three phenomena must be considered: adsorption

of molecules on the interface, surface tension, and changes of

density.

The consequences of the fact that chemical behavior is likely to

be determined by what happens in the interface can be far

reaching.

> Since colloids belong to the heterogeneous systems, the
> general law of chemical kinetics governing such systems
> may be applied to them. This states that the amount of
> chemical change in the unit of time is proportional to
> the absolute surface [Ostwald, 1919, p. 93].

> We would expect that the phenomenon of catalysis would
> be especially marked in colloid systems. The
> distinguishing characteristic of a catalyzer resides in
> the enormous change which it is capable of bringing
> about in the velocity of a chemical reaction... [I]t
> has been shown that many catalytic effects may be
> brought about by highly dispersed surfaces of all
> kinds, and that the especially important catalytic
> reactions of the organic ferments may be closely
> imitated by various inorganic materials in the colloid
> state, such as the colloid metals (ibid., p. 94).

3.2.4 PROMISES OF COLLOIDS IN PHYSIOLOGY.

Such is a bird's eye view of the field of colloid chemistry as a

developing branch of physical chemistry around 1915. Colloids

were necessarily alluded to in physiology and physiological

chemistry because after extraction proteins behaved as colloids. 'Colloids' was a physico-chemical concept.

It was not only the radical procedures of the late XIXth century physiological chemists in their search for the chemical composition of tissues that made them attracted to colloids. Cytologists had been suggesting the thesis that apart from differences due to specialization, there is something in common inside all living cells, a 'jelly-like' substance which they ended up terming "protoplasm", and which Max Schulze in 1863 described as "the physical basis of life" [Singer, 1989, p. 342]. Since it was found that protoplasm showed a positive Tyndall effect and that the particles responsible for it wandered in Brownian motion, protoplasm was thought to be in a sort of liquid state. Carl Naegeli discovered that protoplasm contains nitrogen and so it is a proteid [Singer, 1989, p. 340]. With the use of new staining and fixation techniques, microscopists began to inquire about the structure of protoplasm, some of them claiming the existence of network structures in it, others rejecting this. In 1899 W.B. Hardy published an article in the Journal of Physiology, 'On the Structure of the Cell Protoplasm' [Hardy, 1899], describing the polemic in the following way:

> At the present moment the living cell protoplasm is
> regarded by many as being composed of two substances,
> one of which is disposed as a contractile net according
> to some, as a relatively rigid framework according to
> others, or as free filaments. Other workers again
> regard cell protoplasm as being built up of a more

solid material, and of a more fluid material which
occupies the minute spaces of vacuoles which are
hollowed out un the former. Still others view it as a
homogeneous jelly holding granules. Lastly there are
still those who deny the truth to all these views and
maintain that the living cell protoplasm is homogeneous
in so far that it does not manifest the relatively
coarse structure which these theories ascribe to it.
Its peculiar and transcendent qualities are according
to them associated with molecular and not molar
structure [Hardy, 1899, p. 249].

Hardy's article was to become a landmark in the study of cell

structure, as he showed there that:

The lack of consonance in the views held as to the
structure of the cell protoplasm is traceable in the
main to the fact that they are largely based on details
of structure visible both in fresh and fixed cells
which are the result of the physical changes which the
living substance undergoes in the act of dyeing, or at
the hand of fixatives [Hardy, 1899, p. 249].

This he showed mainly by producing in artificial colloid systems

the same structure that was claimed to exist in protoplasm:

A study of the action of reagents upon colloidal matter
shows that when an insoluble modification is formed
there is a separation of solid particles which are
large molecular aggregates, and that these become
linked together to form a comparatively course solid
framework having the form of an open net which holds
fluid in its meshes [Hardy, 1899, p. 291].

No cytologist could anymore think of the structure of protoplasm

without referring to these findings. Even though Hardy had argued

it was an artifact, the mesh-like structure did not disappear at

all from biology-related texts, in part because Hardy's results

had two faces. On the one hand, they cast doubt as to the

structure claimed to exist in cells before fixation and dyeing,

but on the other, they stressed the ability of colloids to form

structures through chemical changes, some of them simple chemical

or physical alterations. It was unavoidable but to accept that

any cell, particularly under mitosis, experienced structural

changes like those that can be made to appear in simple colloid

solutions.[37]

Along with this strand of inquiry about the structure of

protoplasm there were also grounds -- and likely stronger than

the merely chemical -- to confer upon colloids a central position

in the theory of life processes, particularly in the workings of

the cell. "Life as we know it is indeed inseparably bound up with

matter in the colloid state", wrote E.B. Wilson in the 1928

edition of his classic The Cell in Development and Heredity

---

[37] It is important to stress that colloid chemistry did not
have a unified view about the nature of the solid-like structure
appearing after the process of gelation, and so two different
theories emerged from the microscopist's results about the
physico-chemical state of the protoplasm. There was one led by
Butschli, maintaining that gelation was the formation of a
continuous solid net holding liquid in its meshes. But in the
transition from sol to gel (as this process is called) the rate
of diffusion of small molecules as well as the electrical
conductivity of the system changes gradually, a result that could
not hold after the net is formed. The other view of the process
led by Carl Naegeli held that gelation involved the growing of
'micellae', sorts of aggregates with crystalline properties,
which, by the way, were suggested by Nageli as the responsible
for the polarization of light scattered by biological tissues.
See [Bayliss, 1924].

[Wilson, 1928, p. 633], even though two pages later he gave

strong support to Loeb's findings in protein chemistry (see

below) that were to be major factors in the replacement of molar

mechanisms by molecular ones. Wilson's rationale for his colloid-

view is remarkable:

> This conception seems likely to prove as fruitful in
> cytology as it has been in physiology. More modern
> attempts [than earlier reticular theories of
> protoplasmatic structure] to consider the structure and
> transformations of protoplasm, the mechanism of
> mitosis, the nature of fertilization, the nature and
> function of the cell membrane and the physiological
> relation between nucleus and protoplasm, have for the
> most part taken the colloidal nature of protoplasm as a
> common starting point; and numerous recent observations
> on both living and fixed cells tend to demonstrate that
> we are here on the right track. On the physiological
> side of the subject this is even more obvious, and many
> striking cell-phenomena have in a measure been imitated
> in artificial colloidal systems: for instance, the
> properties of surface films or membranes, the
> antagonistic effect of inorganic salts on the nature
> and stability of the system, or the changes of
> viscosity in the living cell-substance [Wilson, 1928,
> p. 633].

Hardy's results, as referred to by Wilson, increased the degree

of apprehension about the results obtained from microscopy, but

increased also the confidence that colloids and their associated

set of concepts were the candidates to provide the explanation

for the more complex phenomena of living matter. What were, in

more detail, the alleged successes of the colloidal view?

In the preceding chapter the explanations for muscle contraction

relying on some sort of surface action -- one of the preferred

theoretical tools of colloidology -- were treated in detail.
Other avowed successes can be found in physiology textbooks or in
essays written by the propagandists of the colloidal approach.

William Maddox Bayliss (1860-1924) was one of the most
influential advocates of the primacy of the colloidal approach.
Himself an outstanding researcher in physiology, he is the author
of <u>Principles of General Physiology</u> [Bayliss, 1924], a widely
used and respected textbook on the subject.[88] In 1923 he
published <u>The Colloidal State in its Medical and Physiological
Aspects,</u> [Bayliss, 1923] apparently as an answer to Loeb's 1922
book (see below).

Referring to the permeability changes in cell membranes -- one of
the examples brought up by Wilson in the quotation above --
Bayliss states that

> two kinds of systems of two immiscible liquids are
> possible..., say, an emulsion of oil in water or of
> water in oil. If we may compare the oil to land, we may
> look upon the former system as a number of islands in a
> large lake; the latter as a number of small lakes
> surrounded by land. Fish could pass from one side to
> the other of the former system; rabbits not. The
> opposite would be the case with the lakes surrounded by
> land. A layer of the oil in water system would only
> allow to pass through it substances soluble in water,

---

[88] The fourth edition of his book was published in 1924 some
days after Bayliss's death, and was prepared by a "Committee of
Sir William Bayliss's friends", as A.V. Hill writes in the
preface, "partly in order to ensure that what we regard as the
greatest book of this kind shall continue to be available for the
service of the scientific public".

because the water is the only continuous phase. The
latter would be permeable only to substances soluble in
oil... Clowes shows also that one system can be changed
into the other by the action of certain salts, such as
those of calcium... [Bayliss, 1923].

Immediately after he warns the reader about the crudeness of the

model. In his _Principles_ he devoted a chapter to this complex

issue, stressing that no simple artificial membrane had been able

to reproduce the selective mechanism combining size and

adsorption properties of permeants. The protoplasmatic substance

of the cell, he wrote, is capable of forming a new membrane on a

fresh surface:

The substances present in the protoplasm which lower
surface energy... will be concentrated at the interface
between protoplasm and external phase... In this way
the membrane is formed [Bayliss, 1924, p. 144].

Clotting of blood is another example, according to Bayliss, of a

process that can be handled within colloidology:

It is obvious that the process is essentially a change
in the physical state of certain colloids present in
the plasma. An unnecessary degree of complexity has
been introduced into the numerous theories of clotting
by the assumption of a large variety of participants,
each supposed to be a definite chemical compound and
given a name. There is evidence, indeed, that the
investigation of the phenomena with due regard to the
colloidal factors involved will simplify the theories
[Bayliss, 1923].

Another phenomenon ascribed to colloids was artificial parthenogenesis, first obtained by J. Loeb and later pursued by his assistant Wo. Ostwald. With Martin Fischer, Ostwald published some research articles in which fertilization was considered a colloidal aggregation process.[39]

3.2.5 BIOCHEMISTRY AND COLLOIDS.

But the most fruitful field of colloidology was one whose absence in all the tributes we have gone through above is remarkable. In 'The Physical Basis of Life' Hardy states common wisdom about the role of proteins:

> The central chemical problem of living matter [is] the chemical structure of proteid [Hardy, 1906, p. 446].

In Bechhold's Colloids in Biology and Medicine we can read also, in 1919:

> [The living cell is] a city in which colloids are the houses and the crystalloids are the people who traverse the streets, disappearing into and emerging from the houses, or who are engaged in demolishing or erecting buildings. The colloids are the stable parts of the

---

[39] One phenomenon allegedly explained within colloidology was anaphylaxis, "anaphilactoid phenomena" [Bayliss, 1923] or, in general, phenomena related with what is named today "antigen-antibody" reaction. A careful analysis of the debates in favor and against colloidal interpretation of those can be found in [Mazumdar, 1974].

organism, the crystalloid the mobile part, which
penetrating everywhere may bring weal or woe (as quoted
in [Tauber, 1937]).

If the colloids are the houses and buildings, what is their

participation in the dynamics of chemical change? How are we to

interpret the absence of ferments (or enzymes) in these

formulations, after all those pronouncements about the centrality

of the 'enzyme theory' we saw in the last chapter? By today's

meanings there is no puzzle, as enzymes are presently recognized

as protein molecules, but at the root of the quandary about the

chemical nature of enzymes between 1900-1930 was the issue of how

chemical processes go on in the cell. To see this it is necessary

to look in some detail at the development of biochemistry.

Frederick Gowland Hopkins' school represents more than any other

the spirit of the emerging discipline of biochemistry during the

first 40 years of this century. Hopkins' presidential address to

the Physiological Section of the British Association for the

Advancement of Science in 1913, entitled 'The Dynamical Side of

Biochemistry' [Hopkins, 1913] is considered nowadays the

exposition of the fundamental tenets of intermediary metabolism

"It is remarkable how the development of biochemical knowledge

followed the course he had foreshadowed", his colleage Marjorie

Stephenson observed [Stephenson, 1949]. To him, the theoretical

obstacle to the advancement of knowledge on the chemical workings

of the cell was the 'biogen' concept, a view which, as we saw

above, Hopkins and Fletcher had rejected in their discussion of muscle physiology. In more general terms Hopkins stated here his rejection of 'biogen' as an "obsession" such that

> the really significant happenings in the animal body
> are concerned in the main with substances of such high
> molecular weight and consequent vagueness of molecular
> structure as to make their reaction impossible to
> study...[Hopkins, 1913].

Why 'high molecular weights' necessarily implies consequence 'vagueness of molecular structure' is so obvious for Hopkins that he does not find it necessary to explain further. Statements like this, present all along in his papers, are motivated by his unequivocal distrust of 'biogen', and are taken also to show Hopkins' rejection of proteins as macromolecules.[60] Hopkins emphasized his own approach:

> My main thesis will be that in the study of the
> intermediate processes of metabolism we have to deal
> not with complex substances, which elude ordinary
> chemical methods, but with simple substances undergoing
> comprehensive reactions [Hopkins, 1913].

---

[60] Hopkins apparently did not participate in the sometimes bitter debate on the nature of proteins and enzymatic mechanisms, either the aggregate theory (the properly colloidal theory) or the macromolecule one, although evidently he disliked the concept of 'huge molecules'. Pirie has an anecdote about it: The large size of molecules resulting from Svedberg's centrifuge "caused Hopkins considerable distress, for he feared the reappearance of the vague concepts he abhorred. I well remember his consternation when I pointed out... that there was not enough matter in the universe... to make simultaneously one molecule of each of the isomers of a protein with 200 amino acids in it" [Pirie, 1962].

The research of Hopkins and his colleages went almost unaffected by this misconception because the 'small molecules' he is referring to are substrates. In this address he describes in a general way the experimental methods of intermediary metabolism: structural considerations allow hypotheses about what the intermediary products are. Then, an animal is fed or inoculated one of these. If it is completely metabolized, then, very likely it is an intermediate step. Or, taking advantage of the "eclecticism of the body" (his words), they give the biological specimen molecules not exactly the same as the normal ones, and draw conclusions from the chemical results. Their technical problem was not, then, the chemical handling of huge molecules, but the separation and detection of small molecules that as intermediates do not accumulate, but exist in low concentrations.

But how do the reactions occur?

> For the dynamic chemical events which happen within the cell, these colloid complexes yield a special milieu ... but in the cell itself, I believe, simple molecules undergo reactions of the kind we have been considering. These reactions, being catalyzed by colloidal enzymes, do not occur in a strictly homogeneous medium...[Hopkins,1913].

Then he continues with one of his more widely repeated statements on the cell:

>   The life [of the cell] is the expression of a
>   particular dynamic equilibrium which obtains in a
>   polyphasic system [Hopkins, 1913, p. 220].

As for his rejection of associating the life of the cell with one

particular big molecule called biogen, the statement is clear.

But it is not clear at all about the nature of enzymes and

enzymatic action. "[E]ach chemical reaction within the cell is

directed and controlled by a specific catalyst" (Ibid, p. 221),

and these enzymes are of a colloidal nature -- which means, given

his rejection of big molecules, that they are aggregates.

Finally, the colloids of the cell offer a special milieu for

chemical changes to occur, chemical changes that very likely are

catalyzed by surfaces, and the whole cell is a polyphasic system.

What enzymes are, then, and how they act, is left rather obscure.

Presiding at one of the sessions in the meeting about "Colloid

Science Applied to Biology", Hopkins repeated his views:

>   With the birth of modern physical chemistry there
>   arose, I think, in many minds the belief that it was
>   destined to provide in itself an adequate approach and
>   a short cut to a real understanding of the nature of
>   living systems. Its data are, indeed, essential to any
>   such understanding.
>
>   But those dynamic events and the diverse chemical
>   reactions which, within the living cell, provide energy
>   and specific chemical synthesis, are as much part of
>   the essence of life as the behavior of the colloidal
>   apparatus in which they occur. Without them no
>   colloidal system whatever can display, save in some
>   accidental and unreal aspects (of which the importance
>   is often exaggerated), the attributes of life. We have
>   come to believe that the living cell, considered from

its most general aspects, is a system in which surface
catalysis controls many and diverse chemical events,
while the high degree of coordination and organization
to which these events attain may be due in some way to
the nature and architecture of the colloidal apparatus
in which they progress... [Hopkins, 1930, p. 770].

3.2.6 ENZYMES AS COLLOIDAL CATALYSTS

When the measurement of reaction rates involving enzymes started

it was soon realized that the law of mass action did not hold.

The rate of sugar inverted by acid is proportional to the

concentration of sugar at any moment:

$$-dC/dt = kC$$

as in the reaction

$$C_{12}H_{22}O_{11} + H_2O \longrightarrow 2C_6H_{12}O_6$$

while the concentration of water remains to a very good

approximation constant. This is what is expected from the law of

mass action for this reaction. Then, the rate of reaction

diminishes with time. But in the presence of invertase, k is not

a constant, but increases with time and more generally in most

enzymatic reactions it diminishes. On the other hand, it was

found that when enzymes are present in low concentrations, during

the initial stages the reaction rate remains constant.

These results, which are just some examples of the failure of the mass-action law does to hold, were explained from the very beginning with the hypothesis of the formation of enzyme-product compounds as intermediates to the formation of products. The velocity of the formation of products would depend then on the concentration of these compounds, and a big theoretical issue was the nature of these intermediary compounds.

As part of the series 'Monographs on Biochemistry' whose editors were R.H.A. Plimmer and Hopkins himself, William M. Bayliss published in 1908 the book The Nature of Enzyme Action, a book that by 1925 was in its fifth edition. Although there was not a uniform position on the mechanism of enzyme action, Bayliss' was one of the more popular ones in the 1910's. At the beginning of his book Bayliss singles out the main theme of the relations between colloids and enzymes:

> It would be unfruitful, in the present state of
> knowledge, to discuss in further detail the various
> hypotheses put forward to explain catalysis. One of
> these, however, is of importance in connection with
> colloidal catalysis, such as enzymes are, namely,
> surface-condensation of the reacting bodies, in which
> case the accelerated rate of change is, in all
> probability, due to increase of concentration [Bayliss,
> 1908, p. 5].
>
> As colloids, enzymes will be particularly prone to
> form what we have called 'adsorption compounds...
>
> [C]olloids take up by adsorption various other bodies,
> and especially colloids... These 'adsorption
> compounds', or colloidal complexes as they are called

by some when constituents are colloids, play a very
important part in enzyme action... (ibid, p. 16).

Being colloids, enzymes are capable of surface action; adsorption

on their surfaces will increase concentration, and in consequence

the increased concentration would play an important role in rate

enhancement.

Bayliss makes clear what is for him the nature of the

intermediate substrate-enzyme compound: it is an "adsorption

compound". Enzyme action will be in good part a surface effect.

This fact will have important consequences for the stoichiometry

of the first step of the reactions catalyzed by enzymes:

> It is very important to bear in mind that all these
> colloidal reactions have both a physical and chemical
> aspect. Certain colloids, have a special adsorptive
> affinity for one another, which is not purely chemical,
> since it follows the law of adsorption and not those of
> constant combining proportion. This fact is of great
> importance with regard to enzymes...
>
> It must be clearly understood that it is only the
> preliminary combination of enzyme and substrate that
> follows the law of adsorption. After close association
> has taken place, the proper chemical actions, due to
> the agency of the enzyme, begin to make their
> appearance [Bayliss, 1908].

Particularly referring to his experimental model, the hydrolysis

of proteins by trypsin, Bayliss found that the formation of the

enzyme-substrate compound as a colloidal complex would readily

explain the kinetical behavior: the specific activity, that is,

the ratio between mean velocity and concentration, is greater for

lower concentrations of trypsin.

> If we make the reasonable assumption that the rate of
> change is in proportion to the amount of "compound" of
> enzyme and substrate in existence at the time, it will
> be seen that the result is what would be expected if
> this combination were of the nature of an adsorption
> compound, since more trypsin will be in association
> with the substrate in proportion to the concentration
> of the enzyme when the latter is lower [Bayliss, 1908].

One of the arguments he uses to support his theory of the nature

of the enzyme-substrate compound is its resemblance with

inorganic colloid catalysts:

> That this state of affairs is due to the colloidal
> nature of enzymes, and therefore an adsorption
> phenomenon, is indicated by the fact... that in the
> catalysis of hydrogen peroxide by colloidal metals the
> same kind of law holds, contrary to what obtains in the
> inversion of cane sugar by hydrion, where the law of
> proportionality holds [Bayliss, 1908, p. 60].

Bayliss is well aware that he has to account for the high

specificity involved in enzyme action, as suggested by Emil

Fischer with the key-lock simile in 1898 when he summarized his

long work on enzyme action on sugars. The chemical nature of the

surface or its molecular geometry can, wrote Bayliss, perfectly

explain it.

The effect of electrolytes and neutral salts on enzymatic

reactions seemed suitable to be approached with the same kind of

arguments used to explain other features of the general behavior of colloids: the formation of the enzyme-substrate compound required a favorable relation of electrostatic charges, and the adsorption of free electrolytes in solution on the surface of the enzyme (and of the substrate, if it is a colloid itself, as in the case of proteolytic enzymes) could alter that relation.[81]

Bayliss's stance changed very little in his 1923 book. As for the mechanism of rate enhancement he added the fact that adsorbed particles on the surface of a colloid aggregate are spatially oriented, which may render these particles more suitable for a specific chemical reaction. On the other hand, he insists on the central theme of colloid-chemistry, surface action:

> It is now generally recognized that the enzymes which play so important a part in the speeding up of chemical reactions in living organisms are a particular class of heterogeneous catalysts. In other words, they are colloids, and the reactions which they accelerate occur in the surface of the dispersed phase... In the first place, [there is] the effect of degree of dispersion on the activity of the enzyme. The greater the number of particles into which a given mass of agent is subdivided, the greater is the surface of activity [Bayliss, 1923].

---

[81] Other views on the nature of the enzyme-substrate compound were suggested, and Bayliss himself cites V. Henri's assumption in 1903 of a stoichiometric one-to-one compound. L. Michaelis's work during the 1910's, using the hypothesis of a stoichiometric compound and monitoring pH carefully in getting the data became important only by the end of the 1920's, after Sumner and Northrop succeeded in crystallizing complex proteins and afer the publication of J. B. S. Haldane's book The Enzymes.

3.2.7 THE FADING OF BIOCOLLOIDOLOGY

In the minds of the students of the phenomena of life during this period, the chemical machine was unravelling its secrets: it was a colloidal machine. Colloids provided the buildings of the factories inside the cell, buildings conceived as an apparati able to provide a high degree of coordination and organization, while the chemical processes themselves were effected by the surfaces of colloidal catalysts, perhaps the walls of the same buildings. This looks like a polyphasic system complex enough to allow a high number of correlated events in an overall pursuit towards equilibrium. The celebrated biological order was at hand!

But it did not work out. During the 20's the magic of colloids began to disappear. More than 20 years after his 'The physical basis of life', Hardy himself observed:

> The mystery of life is as great as it was [40 years ago]... Nothing is to be gained claiming living matter as colloidal.. At present the colloidal kingdom seems to be an Alsatia wherein difficult states of matter find refuge from a too exacting enquiry [Hardy, 1928, p. 744].

By then A.V. Hill had shown that the muscle could not be a surface machine by calculating that there could not be enough surface area for the required energy; the adsorption-compound as a first step in the process of enzymatic action was extensively

rejected but, most especially, no clear breakthrough was obtained with the use of the tools offered by colloidologists. Meanwhile, another pattern of explanation was emerging with new tools, new concepts, and new sources of models to imagine the unknown: the explanation through macromolecules.[62]

The theoretical change that overthrew colloidology can be looked from two points of view. The first addresses the change brought about by the set of new experimental results and new physico-chemical interpretations that shook the support of the typical colloidal explanation. Colloidal chemistry, as we saw, appealed to the idea of 'aggregates' when referring to 'colloidal particles', like proteins, and considered many physiological events such as enzyme action to be surface phenomena. With respect to this, I will discuss briefly the work of Jacques Loeb on the chemical behavior of proteins, Richard Willstatter on the purification of enzymes, James B. Sumner and J.H. Northrop on

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[62] Of, course, there were still strong advocates of the colloidal approach, among them, Ross Aiken Gortner in the United States. His Outlines of Biochemistry, [Gortner, 1929], was an extensive treatise on colloids. Almost 300 pages out of 750 are 'pure colloidology', and in the scarce 30 pages devoted to enzymes, statements like the following can be read: "According to the older viewpoint the catalyst was looked upon as a mysterious chemical compound which in some way speeded up a reaction. According to the newer viewpoint a catalyst is looked upon as a source of surface energy, the chemical nature of the catalyst being relatively unimportant providing that the space configuration of the atoms in the surface of the catalyst are such as to cause certain oriented adsorption relationships and the surface of the catalyst is in such a state as to contribute a given quantity of surface energy to the system [Gortner, 1929, p. 708].

crystallization of enzymes and Theodor Svedberg with the ultracentrifuge. The second point of view deals with the new sources of models for the machine view of living organisms which I will discuss in the next section.

In 1922 Jacques Loeb, at that time working in The Rockefeller Institute for Medical Research in New York, published the book Proteins and the Theory of Colloidal Behavior. Here he contended that the aggregate view of proteins - and in consequence its associated explanations - is wrong. If enough care is devoted to measure and maintain pH values during the experiments, he argued, proteins will behave in solution just as individual chemical entities. Electrolytes are not 'adsorbed' at the surface of proteins, but they form valence bonds in a stoichiometric way. That is, these products are not colloidal complexes. They are molecules.

> When the hydrogen ion concentrations are duly measured
> and considered, it is found that proteins combine with
> acids and alkalies according to the stoichiometrical
> laws of classical chemistry and that the chemistry of
> proteins does not differ from the chemistry of
> crystalloid [Loeb, 1924].

A protein molecule would remain in solution if the forces between it and the molecules of solvent are strong enough. Otherwise, the protein molecules coalesce, forming small solid aggregates which will remain in suspension if electrostatic charges allow the formation of Helmholtz's double electrical layer.

Experimental results of undeniable relevance against the
aggregation view of proteins were obtained by Theodor Svedberg
(1884-1971) using his ultracentrifugation technique. Svedberg
developed the technique and the associated theoretical tools as
part of his long study of the fundamental properties of colloidal
systems, especially the use of differential sedimentation to
assess the size of aggregates. After some improvements of his
first ultracentrifuge he decided to measure the degree of
dispersion of some proteins, hemoglobin being his first success.
But, contrary to his own expectations, he reported in 1926 that
the solution of hemoglobin was monodisperse and that the latter's
molecular weight was quite large: approximately 68000 D. His most
surprising result was finding that some proteins (hemocyanins)
could have sharply defined molecular weights of the order of
millions of daltons.

Loeb's and Svedberg's researches were about the nature of
proteins, but the idea that enzymes are proteins was only
entertained for a short time at the beginning of the century and
was abandoned when attempts at purification and isolation proved
to be extremely difficult. As pointed out at the beginning of
this section, 'enzyme' was a term defined operationally by the
chemical effects brought about by preparations of usually unknown
chemical composition. 'Something' was supposed to be 'in there',
and this 'something' was responsible for catalyzing chemical

changes. Finding what that 'something' is proved a difficult

endeavour. By 1909 the English physiologist W. Halliburton in the

Annual Report of the Progress of Chemistry felt the necessity of

warning about the increasing use of the 'ferment-in-there' idea:

> We must take care in the twentieth century that the
> adoption of a new phrase, "ferment action", is not
> considered in itself to be a final solution of vital
> problems. To label any particular change as due to
> enzyme activity should be rather a signal for the
> commencement of renewed research in attempts to
> understand it still further (as quoted in [Kohler,
> 1964]).

Bayliss himself, acknowledging that no great progress had been

made after Buchner's report of the zymase extract to identify its

exact chemical nature, gave some support to an hypothesis

formulated even before Buchner's announcement:

> When we consider the way in which definite chemical
> properties diminish more and more as the preparations
> are purified, we see a certain degree of justification
> for the view expressed by De Jagger and Arthus [in 1890
> and 1896, respectively], that enzymes are not chemical
> individuals, but that various kinds of bodies may have
> conferred upon them properties which cause them to
> behave like enzymes; so we have to deal with properties
> rather than substances [Bayliss, 1908, p. 20].

A view like this was actively sponsored in 1922 by A. Fodor, who

supported the view that "enzymes are not to be regarded as

special chemical individuals of peculiar chemical structure, but

as known constituents of protoplasm, merely having a special

degree of colloidal dispersity" [Waldschmidt-Leitz, 1929]. As

late as 1932, at the meeting 'On Recent Advances in the Study of
Enzymes and their Action', Richard Willstatter was still far from
considering that the quandary was solved:

> Enzymes in most cases are only characterized, at the
> start and for a long period [by their activity], ... as
> long as nothing can be said concerning their chemical
> composition. It is to be remembered that the
> constitution of an enzyme cannot be determined in the
> same way as the structure of simpler substances such as
> hormones and vitamins... [Willstatter, 1932]

The school more thoroughly committed to the search for the
chemical nature of enzymes during the 1910's and 20's was that of
Willstatter and his associates (mainly Ernst Waldschmidt-Leitz)
in Munich and later in Zurich. Their main endeavour was the
purification of enzymes as the only evident way to assess their
specificity and chemical nature. To accomplish this, Willstatter
devised the method of looking for specific adsorbants to which an
enzyme preparation was exposed; afterwards, the system was washed
with mild chemical methods to free the adsorbed substance from
the adsorbant and the procedure repeated again and again.

A summary of Willstatter's school's findings can be read in
Enzyme Action and Properties by E. Waldschmidt Leitz, published
in 1929. Claims that enzymatic reactions do not comply with the
law of mass action are found but with no experimental evidence;
the interaction is stoichiometrical instead of adsorption-like,
but a small dependence on the degree of dispersion induced

Willstatter to adopt a sort of intermediate position between the purely chemical and the purely colloidal approach:

> Willstatter considers ... that the enzymes are composed
> of a colloidal bearer and a specific, active group,
> which enables them to be bound to the substrate, and
> the composition of which at the same time conditions
> the colloidal nature of the entire complex. Such a
> concept gives equal value to the physico-chemical and
> to the structural chemical behavior of the enzymes.
> [Waldschmisdt-Leitz, 1929].

In 1926 J.B. Sumner working in the US reported he had crystallized the enzyme urease taken from jack beans. Sumner's preparation was highly active, which meant a high degree of purity, and gave positive results to tests for protein. Willstatter did not agree that this was a proof that enzymes are proteins. Other enzymes, he claimed, did not give such positive results. In addition, what Sumner had obtained is an active preparation of the enzyme that includes its protein carrier. Sounding a little sarcastic, Willstatter pointed out at the meeting of the Royal Society on enzyme action quoted above:

> While the Munich laboratory endeavoured to purify
> enzymes so that they should be more and more free from
> protein, Sumner and Northrop, by contrast, have
> employed the methods for the crystallization of
> proteins to produce enzymatically active preparations
> in the form of proteins [Willstatter, 1932].

But other enzymes were soon crystallized, and it was shown that some tests used to detect the presence of proteins in some

preparations were not sensitive enough, which explained other
negative results [Tauber, 1937]. By the middle of the 1930's all
enzymes were known to be proteins, all of them also molecules of
rather high molecular weight. The last, and weak, stronghold of
the colloid movement seemed to be surrendering.

3.3 THE AGE OF COLLOIDOLOGY

Between the years 1900 and 1920 the term colloid and its
associated concepts were invoked if not to explain at least to
point the way to an explanation for events occurring in the cell,
be they particular, such as cell contractility, or of a general
kind, such as enzymatic catalysis. The pervasive presence of the
colloidologist's baggage allows us to dub the period 'the age of
colloidology'.[63]

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[63] Part of the prestige of colloidal science in physiology
could have been borrowed incidentally from unrelated achievements
in other realms. The so-called first experimental evidence of the
existence of atoms came from Perrin's measurements of and the
application of Einstein's theory to Brownian motion, a colloid
phenomenon. Millikan's experiment was performed also in a colloid
system, a dispersion of liquid drops in gas. Colloidologists
seemed to be aware of this transferred prestige. When an
itinerant cycle of lectures was organized in the United States
during 1925 and 1926, Robert Millikan was in charge of the first
talk, 'Principles underlying colloid chemistry', which, despite
the title, he devoted entirely to the existence of the electron
and to his method of altering the charge of the colloidal oil
droplets.

One can finish reading a modern biochemistry textbook without seeing the word "colloid" even once. The book Proteins, Amino Acids and Peptides as Ions and Dipolar Ions, a landmark in the physico-chemical study of proteins, written by Edwin J. Cohn and John T. Edsall and published in 1943 [Cohn, 1943], does not have the word colloid in its analytical index (and very likely not anywhere in its more than 400 pages).[84] In 1948 J.D. Bernal decided that his turn had come to write his own essay on The Physical Basis of Life [Bernal, 1951]. There he recalled the term colloid in the following way:

> Until the advent of the electron microscope, a great blank existed between the knowledge of atomic combinations provided by chemistry and that of histological structures observable with the microscope. This gap was filled with the mystic word "colloid", which served to explain the very real but very obscure properties depending on the existence of structures of magnitudes between ten and ten thousand Angstroms. Now the colloid world is open for inspection, and the term itself will probably vanish or acquire precise and limited meaning [Bernal, 1951].

Marcel Florkin, co-editor for many years of the huge collection Comprehensive Biochemistry and himself a historian of biochemistry, labeled the period "the dark age of biocolloidology" [Florkin, 1972]. The crystallographer John C. Kendrew blamed the colloidologists for lack of faith:

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[84] The book is dedicated, among others, to Hardy and Loeb, as pioneers in the physico-chemical study of living matter.

> The concept of structure itself became ascribed to biological molecules only at a fairly recent date. The really important biological molecules, such as the nucleic acids and the proteins, are difficult to handle by classical chemical methods; and their old classification, as colloids, was a confession of ignorance and at the same time of lack of faith [Kendrew, 1969].

With similar arguments Kendrew could blame for lack of faith those researchers still finding micelle-like structures in solutions of soap in water. Colloidology was in itself a sound field of research, as can be inferred from the account given in this chapter, and sound also were the claims about the appropriateness of its tools to deal with phenomena inside the cell. Its use as a speculative tool to explore behavior not completely understood is not at all different from the contemporary speculative appeal to huge molecules suggested in order to explain not completely clear physiological events by means of their imagined capacity simply to be able to do it.

To this speculative role of concepts I want to refer now. Biocolloidology was not just a set of concepts to deal with physical and chemical changes in protein solutions of relatively simple composition caused by the addition of some electrolytes. Colloidal behavior represented also a particular conception of what a chemical machine may be like so it can account for life processes as well as being consistent with current theoretical tools. To detect what characterizes colloidal models as different

from those molecular models that were going to replace them, an

argument commonly used by Bayliss may be recalled here:

> It might, perhaps, be supposed that if the process of
> subdivision were carried farther and farther until
> molecular dimensions were reached, the phenomena due to
> surface would be more and more manifest. In point of
> fact, however, this is not the case; although we know
> nothing of what the molecular state essentially is, we
> do know that bodies in this condition do not show the
> properties of matter in mass, _i.e._, bounded by surfaces
> [Bayliss, 1908, pp. 13-14]

The physical discontinuity that Bayliss points out here implies a

choice in the theoretical tools you count on to tackle a problem.

For a given question will you have to be a physicist or a

chemist? There is implied also a preference in the kind of

mechanisms that are going to be proclaimed as those producing the

multifarious events of the cell as a 'chemical machine'. In the

section on muscle models in the last chapter I referred to the

general differences between the surface models -- which in fact,

were colloidal -- and the presently accepted ones, relying on

solid-like molecules. The former ones are 'molar' mechanisms, for

which descriptions in terms of bulk properties are used. When

surface effects are considered as the main issue in catalytic

activity, and the account of rate enhancement is regarded largely

to be a consequence of increased concentration at surfaces, molar

mechanisms are being invoked. But when enzyme action is changed

from a surface phenomenon to a molecular interaction the

mechanism of enzyme action will be looked as a mechanical

'alternative' way for two molecules to react. If enzymes are considered as colloidal aggregates and enzyme action as some kind of surface action, molar mechanisms are associated with enzymatic catalysis. They were replaced by another way of thinking about physiological matters: molecular mechanisms. As the aggregate view of the "world of neglected dimensions" was replaced with the macromolecular view, the physiological models of the cell's marvels were replaced by the alleged behavior of macromolecules.

Since the working of a machine requires solid-like features, it was inevitable that the new kinds of models were preceded by the general acceptance of the existence of huge molecules in the cell, as was described in the end of the last section. In fact, the ups and downs of the modern belief in big biological molecules coincides remarkably well with the ups and downs of the place of the macromolecule concept in organic chemistry. Zandvort [Zandvort, 1988] divides the latter in three periods. From 1860 to 1900 a structuralist, chemical view was held by the majority of chemists, following ideas mainly originating in Kekule's model of valence which recognized no limit to the size of a molecule. Then, between 1900 and 1925 a physical view, that of aggregates, was dominant and it was common for chemists to say that the investigation of these substances should be left to physicists. Finally, from 1925 on, especially after 1935, the chemical view, whose great advocate was the German chemist Hermann Staudinger, definitely overthrew the aggregation view.

Staudinger's macromolecule was not, however, the same big molecule as that of the biochemist. According to what they then called the chemical view, natural and artificial polymers behave in solution as independent molecules, separated by molecules of the solvent. But the polymers have neither a precise molecular weight nor a defined structure. What the crystallization of proteins showed, and later x-ray diffraction results confirmed, is the aperiodic crystal nature of most biological macromolecules.

The historian of science Robert C. Olby has suggested the inclusion of the notion of macromolecule in the history of molecular biology [Olby, 1979]. We have seen that the adversaries of the 'biogen', 'inogen' and similar concepts during the first decades of this century generally did not address the question of the existence of big molecules. To them, a big molecule was synonymous with lack of structure. On the other hand, when Zandvort traced the history of the notion of macromolecule, the only reference he made to studies in biological fields is to Olby's article. The idea that big molecules do not exist, or are so indistinct as not to deserve the name molecule, apparently was so widespread that it was not even worth mentioning. The obvious relevance of well defined macromolecules to sustain a properly-called machine of molecular dimensions strongly backs Olby's contention. I would dare to suggest that the existence of the

aperiodic solid is the main breakthrough leading to molecular biology in its broad sense. Curiously enough, this was the view adopted by Schrodinger in his immensely popular (and misread) book <u>What is Life?</u>.

As we saw in the second chapter, the mechanists of the XVIIth century, particularly Boyle, appealed to molecular operations similar to those operations occurring in the macroscopic world. The suggestion rendered poor results, as can be seen from the fact that chemistry developed following quite different lines. But although chemistry and physics finally arrived at a point where they can say that Newton's program of action at a distance is the triumphant one, biochemical models of physiological workings look in some way similar to what Boyle envisioned.

We are returning to Boyle's models, but this time Newton would not say that hooked atoms do not explain anything. Hooks indeed can be found with x-rays or electron microscopy techniques, 'Van der Waals radii' replaced contact repulsive forces and affinities replaced molecular wedges. The dynamics of the system is now the integrated operation of myriads of minuscule machines. The analogy between the dynamics of the macroscopic world and the cell is established through the operation of molecular machines.

4. MOLECULAR MACHINERY

'Molecular machinery' has become a catchy phrase. Nowadays saying
that the cell is a chemical machine falls too short as a
recapitulation of the most fashionable view of the workings of
the unit of life. As usually happens with these brief
metaphorical expressions, its power as a speculative instrument
resides in its two-fold feature of leaving a good range of
unprecisely specified analogies and disanalogies to work on and
at the same time summarizing in an image many debates and results
in the history of ideas about the subject in which it is embedded
and about its relations with related disciplines and associated
worldviews.

To begin to see what is implied by the metaphor of a molecular
machine, some examples are worth exploring. A striking one is the
fatty acid synthetase complex which synthesizes palmitic acid (a
saturated fatty acid having 16 carbons) in higher animals.

After 'activating' the first two contributing molecules -- acetyl
CoA and malonyl CoA, itself a modification of acetyl CoA -- the
synthetase complex proceeds with an enzymatic reaction (a
condensation step) at the end of which four of the future 16
carbons form a small chain at the tail end of a moeity attached
to a protein that makes up part of the complex. Three successive
enzymatic reactions will arrange carbons and hydrogen into the
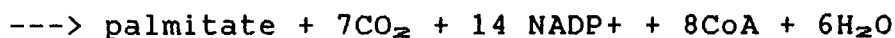form

$$CH_3 - CH_2 - CH_2 - C \ldots$$
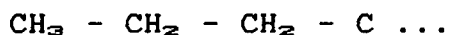
A new step of condensation comes next, another molecule of
malonyl CoA serving as the donor of two more carbon atoms, and
the condensation step is followed again by the same reactions
that occurred in the first cycle. At the end of this second cycle
six of the future 16 carbon atoms are in place with their
respective hydrogens. The cycle repeats again and again until the
hydrocarbon chain is completed, and finally another enzymatic
reaction releases the fatty acid from the complex.

Six enzymes act orderly in seven cycles to produce one molecule
of palmitic acid. In higher animals the six enzymes are assembled
in this synthetase complex. In the middle of the complex is
placed another protein provided with a 'movable arm'. Thermal
fluctuations move this arm which holds the growing fatty acid

molecule so it can go orderly from the active site of one enzyme to the active site of the next, to have the respective work done on it (see figure 3, taken from [Fox, 1982]).

Fig. 3. The fatty acid synthetase complex, after having finished the first cycle (taken from [Fox, 1982]).

By a sort of metaphor whose literal realm is the macroscopic contrivance this supermolecule is assimilated to a machine: movement of solid-like parts are arranged in a specific way to produce a coherent and cyclic behavior.[65]

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[65] The chemical reactions are very nearly the same in E. coli, but here the enzymes are not arranged in this sort of complex and in consequence the process is not as efficient as in higher animals. However, we can say that these kinds of coordinated reactions are conceived from the beginning with machine-like features in mind.

The overall reaction is described as follows:

Acetyl CoA + 7 malonyl CoA + 14 NADPH + 7H+ --->

---> palmitate + $7CO_2$ + 14 NADP+ + 8CoA + $6H_2O$

but considering the reactions rendering malonyl CoA from acetyl CoA, CO_2 and ATP, it can be rewritten:

8 Acetyl CoA + 7 ATP + 14 NADPH --->

---> palmitate + 14 NADP+ + 8CoA + $6H_2O$ + 7ADP + $7P_i$
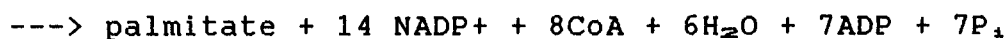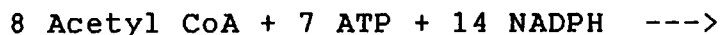
Written in this way with the participation of ATP, it can easily be calculated that the reaction has a total negative change in free energy, and will be said to be 'thermodynamically possible'. The previous description of the complex renders a sketch of how the reaction takes place, but, apart from other features, it leaves aside one crucial point: how is energy harnessed to overcome the energetically unfavorable steps?

The evident first way of building a tolerable explanation of how processes in an organism can go 'uphill' was the one used, for example, in Liebig's late model of the muscle. After an input-output evaluation it is said that the energy provided by the foodstuffs will account for the energy necessary for muscle

contraction. As for 'coupling', phenomena similar to those occurring in heat machines were recalled: in the case of Liebig's Spannkraft, a big specialized molecule is presumed to receive energy from its surroundings, accumulating it in the form of contractile or expansive power. Later the mechanical energy so stored is released and macroscopic work is performed.

To understand the central issues of processes like this it is necessary to look in some detail into the operation of a heat machine. Heat can come either from the surroundings or, as in an internal combustion engine, it may appear as the result of the fuel's transformation into more stable substances. In the latter situation, energy stored in the configurational degrees of freedom of molecules is transferred to thermal degrees of freedom. The heat machine, an appropriate arrangement of solids (considering the times and temperatures involved), is designed in a way that allows it to take small bits of energy from the thermal degrees of freedom and to store them in a change of configuration of a 'mechanical reservoir', for example, by lifting a weight in a gravitational field, or compressing a spring. To produce the mechanical effect, then, in an internal combustion machine chemical energy is converted into heat energy, and the subsequent drop in the latter accounts directly for the appearance of energy accumulated in mechanical degrees of freedom (in this instance, of course, macroscopic degrees of freedom).

The argument shows what is brought from heat machines when models like Liebig's _Spannkraft_ for conversion of chemical energy into energy stored in macroscopic mechanical degrees of freedom are suggested. During the years of biocolloidology 'thermodynamical models' were also suggested for processes of chemical synthesis in the organism. It was known that in humans ingested proteins are degraded completely into amino acids before any process of synthesis begins.[66] Protein synthesis was an almost intractable problem, but there was the suggestion that since enzyme catalyzed reactions are reversible, a high concentration of amino acids could drive the reaction toward synthesis. It was proven so _in vitro_, but it was recognized at the same time that high concentrations of amino acids are not detected in the tissues. Ross Aiken Gortner struggled, nevertheless, to keep alive the plausibility of the thermodynamical model of protein synthesis:

> It seems highly probable that the synthesis within the
> tissues may be brought about by a similar mechanism [to
> _in vitro_ synthesis with proteolytic enzymes] and that
> an effective high concentration of amino acids may
> result from the 'binding' of a large part of the water
> within the cell, thus effectively concentrating the
> amino acid to a point where synthesis in the presence
> of proteolytic enzymes takes place [Gortner, 1929, p.
> 433].

There is one contrivance whose arrangement supposedly permits a chemical reaction to go 'uphill' using directly the chemical

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[66] A "discovery of a peculiarity in metabolism which to the biochemist represents a very fortunate aspect of affairs", said Hopkins in a memorable address in 1916 [Hopkins, 1916].

energy stored in other part of the system. Two electrochemical
cells can be arranged in series in such a way that the electrical
current generated in one of them is used to produce a chemical
reaction in the other.[87] Two metal electrodes (for simplicity we
can consider the same metal) are immersed in two separate and
different concentrations of a salt of the metal. The two
solutions are connected, as usual, through a salt bridge. The
different concentrations will generate a potential difference
between the electrodes, and equilibrium is reached between each
electrode and its solution when the exchange of ions between them
is balanced. A chemical process starts after connecting the two
electrodes through an external circuit containing another
chemical cell, for example, an electrolyzer, in which water is
separated into hydrogen and oxygen. The flow of electrons into
one of the electrodes lowers the potential barrier obstructing
the metal ions' adsorption on the electrode, and now slower ions
would be able to reach the metal. Something similar occurs on the
other metal electrode. Heat rushes into the solutions from the
thermal reservoir (the atmosphere in this case), keeping the
temperature constant. It is this energy that is being used to
produce the electrolysis! In spite of the apparent differences

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[87] This situation was discussed by C.W.F. McClare [McClare,
1971 and 1974] and later in more detail by L. Blumenfeld. McClare
(who died in 1977) was probably the first one to begin a thorough
discussion about the implication of treating molecules as
machines. Here I am following Blumenfeld's argumentation
[Blumenfeld, 1983 and 1981], but he himself follows McClare's
conclusions.

from a heat machine, in this situation again chemical changes in

the electrolyzer are produced by thermal energy.

Before giving more detailed examples to grasp the differences

between macroscopic machines and molecular machines found or

suggested in living tissues, it is convenient to adopt the

terminology commonly used in the literature. In a one-phase

system a thermodynamic potential, the Gibbs free energy, has the

property that in a process where p and T are held constant (as in

most chemical reactions in solution),

$$dG = -dW_o$$

where dW_o indicates work different from pV, that is, different

from work of expansion. It is important to remark that

thermodynamics is not a theory that can provide expressions for

dW_o by deduction from its principles. These arise either from

theoretical considerations -- conceivable systems or models -- or

must be induced from the experimental results. Thus, we know that

springs (or rubber) would be able to perform work due to

elasticity, and the expression for infinitesimal work in the case

of a spring ('an elastic system') will be fdL. The creation of a

surface is a process needing expenditure of energy, or

theoretically we can suppose that molecules on the surface are in

different conditions than molecules in bulk, define a coefficient

to account for the difference, and then match experimental results with the new term gdS.

In a physicochemical system having only one phase and one chemical species, then, we have

$$G = G(p, T, X_1, X_2, \ldots)$$

where the variables X_1, X_2 are extensive variables appropriate for the system according to observation, and then

$$dG = -dX_1 (\partial G/\partial X_1) - \ldots$$

where $(\partial G/\partial X_1)\ldots$ are intensive variables related to the respective work-yielding event. Each expression for infinitesimal work, then, can be written as the product of change of an intensive factor $(\partial G/\partial X_1 \ldots)$ and a differential expressing an infinitesimal <u>change of configuration</u>:

$$dW_o = - fdL - gdS - vdQ$$

where dL is a change in the length of a linear elastic system, dS a change of surface area, dQ a change in the amount of charge accumulated in a place were the electric potential is v. If the system comprises different chemical species and different phases, the Gibbs free energy will be a function of

$$G = G(p, T, X_1, X_2, \ldots, N_1, N_2, \ldots)$$

with N_1, N_2, ... denoting the number of moles of different chemical species in specified phases, the change of free energy during a process with T and p constant will be expressed as:

$$dG = -dX_1 \ (\partial G/\partial X_1) - \ldots - \mu_1 dn_1 - \mu_2 dn2 - \ldots$$

where each μ_i -- the so called chemical potential -- is equal to $\partial G/\partial n_i$. These additional differentials are expressions of what is called chemical work, and they describe changes due to chemical reactions or movement of chemical species from one phase to another.

For chemical processes going on in solution, like those in a living organism, description of changes in terms of changes in free energy instead of changes in internal energy is usually adopted. If after some process the energy accumulated in one of the possible ways to describe the configuration increases while another one decreases it is said that a free energy transduction has occurred. If the exchange in forms of energy storage is caused by the operation of a particular piece of the cell's machinery, the latter is described as a 'free energy transductor'.

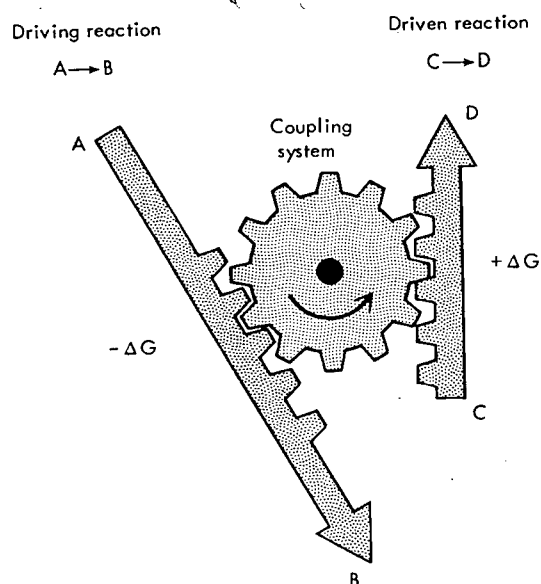The drawing in figure 4 (taken from [Peusner, 1974]) illustrates the idea of free energy transduction.

Fig. 4. Metaphorical picture of a transduction process (from [Peusner, 1974]).

A process thermodynamically able to occur by itself drives another process that alone cannot happen. The drawing depicts a transductor, in this case a gearing, which is a typical solid device characterized by

input work = output work

Do devices like these occur in living organisms? Can they be molecules? What kind of processes are used to drive and what kind of processes are driven? These are the sorts of questions we must answer when the existence of molecular machines is postulated.

Suppose there is a membrane separating two compartments. In the left compartment two neutral non-reacting molecular species are in a higher concentration than in the right compartment. The diffusion of any or both species will lower the free energy of the system, and they will migrate if the membrane separating both phases is permeable to them. Now, given some concentration, the free energy change due to the diffusion of one of the species could be used, in principle, to carry molecules of the other species against its concentration gradient, if the combined processes give a total negative free energy change.

Again, it is important to look a little closer at this process. The macroscopic result, changes in concentration in both phases, is due to a net result of molecules spontaneously migrating from each side to the other. Two molecules of the same species that are close to the membrane but in different compartments will have the same probability, independent of concentration, of crossing the membrane to the other compartment.

This kind of transduction process is quite common in cells. For example, non equilibrium concentrations of Na^+ are thought to drive glucose across the plasma membrane against the latter's concentration gradient. But although the process is thermodynamically feasible by itself, it involves the participation of separate molecular devices -- free-energy molecular transducers -- called 'glucose pumps' [Alberts et. al., 1988, pg 310]. The phrase 'separate molecular devices' here implies that the macroscopic process resulting in a measurable flux of chemical species is the sum of individual exchange processes accomplished by molecular devices. 'Molecular devices' here means more than just 'mechanisms of molecular dimensions'; it means that the devices are molecules, in the same sense that enzymes are molecules.

In her account of the debate about anaphylactic reaction Pauline Mazumdar [Mazumdar, 1974] says about Loeb's 1922 book -- in which Loeb argued that proteins are molecules -- that

> Loeb managed to destroy with [his arguments] not only
> the application of colloidal analogies to the antigen-
> antibody reaction, but the entire assumption that
> proteins needed a special set of laws to account for
> their reaction... Curiously, Loeb had produced in 1921
> a very passionate declaration in favor of a mechanistic
> conception of life with examples drawn from plant
> tropisms and from parthenogenesis in eggs induced by
> inorganic means, but none of his examples, then, were
> as good an argument against vitalism as this one turned
> out to be [my emphasis].

Loeb's position turned out to be that in the physiological realm, 'hammers are molecules'. 'Physiological hammers' -- an expression I use to denote those devices responsible for most microphysiological process -- turned out to react with acids and bases just as any other simple substance. They are just molecules, an amazing result, in fact, as can be made clear rephrasing it with the aid of an example: the 'two-potassium-three-sodium-ions-ATP-splitter-translocator' turns out to be a substance, that is, it comes in molecules.[68] Why Mazumdar denounced as vitalists those researchers thinking otherwise -- for instance, that surfaces are responsible for these processes -- is not clear at all.

If we compare the heat machine and the electrolyzer in series with a galvanic cell, on the one hand, with the coupling of flows existing in biological membranes on the other, we find that in both the overall macroscopic event is the outcome of elementary acts which are 'bits' of the process. The upward movement of a piston is caused by elementary acts of collision between a microscopic body and a macroscopic one, each elementary collision yielding a 'bit of expansion'. The coupled flow of chemical species in the example of the membrane is also the outcome of elementary acts, small 'bits' of translocation. But in the latter situation, the macroscopic phenomenon is seen to involve the

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[68] The example refers to the sodium-potassium ATP-ase pump, which is discussed below.

participation of 'third entities' that after the elementary act return to their initial conditions to accomplish a new elementary act. Each microscopic 'bit' is the result of a complete cycle of operation of one of these 'third entities'. This feature is even displayed by those simple enzymatic reactions where the catalyzer enhances the velocity of a chemical process with total negative free energy change, no coupling being necessary. The reaction is accomplished with the participation of a molecular machine providing the elementary acts of chemical transformation, a machine that operates repeatedly going through almost the same set of configurations.

The molecular devices responsible for the free-energy transduction between Na^+ and glucose gradients are not the most interesting ones from the point of view of what a molecular device is thought to be able to perform. If a transduction process like this exchange of small molecules is to occur continuously, the non-equilibrium concentrations of the 'driving' chemical species must be restored. To do this, a number of separate molecules called Na^+-K^+ pumps move Na^+ out of the cell against its electrochemical potential gradient and at the same time move K^+ into the cell, also against its electrochemical potential gradient.[69] A 'coupling' must exist with other process

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[69]   This is quite far from being an irrelevant example. Today it is considered that one third of the ATP consumed by a resting animal is spent in this pumping that maintains the cell out of equilibrium [Stryer, 1988, p. 950]. When a muscle is contracting it becomes indeed a large consumer of metabolic

that guarantee a total negative free-energy change. Here another

sort of free energy transduction is displayed: part of the Na^+-

K^+ pump is a Na^+-K^+ ATP-ase. One molecule of ATP is split into

ADP and P_i, and the excess free energy of this reaction is used

to translocate three sodium ions and two potassium ions against

their thermodynamic tendency.

Chemical energy stored in the internal conformational degrees of

freedom of one molecule, ATP -- mostly, though not only, in the

bond between the last phosphate and the rest of the molecule --

is used in each act of translocation. However, this is anything

but a small heat machine.[70] Part of the chemical energy of the

one-molecule system ATP is stored by the molecular machine -- I

repeat: a substance! -- the 'Na^+-K^+ pump' which uses it then for

the translocation process. A transduction process similar to

this, in the sense that chemical energy taken from one molecule

is "stored" in a larger one so that the latter can do work, takes

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energy, but the fact that for many decades muscles were conceived
as the user of metabolic energy par excellence shows that the
animal machine was considered as existing mostly at equilibrium.

[70] The most popular model for the process of oxidative
phosphorylation -- the chemiosmotic theory -- shows, interes-
tingly, central features of a heat machine. Small 'bits' of
energy given by H^+ ions moving 'downhill' are relatively slowly
accumulated until enough energy is available to establish the
high energy bond of ATP.

place in each elementary act of muscle contraction, as was

described in the previous chapter.[71]

However small, the tiny devices are allegedly able to perform

coherent changes of configuration, a characteristic which

immediately brings to mind that they necessarily have a solid-

like structure. In phase space, the machine -- a protein --

undergoing conformational transitions traverses a fairly constant

path again and again. This is entirely conceivable in macroscopic

devices where fluctuations affect the operation in a minimal way,

but it is surprising in molecular devices, even in biological

macromolecules, especially in coupling, when the machine is

thought to 'store' energy and to deliver it, thus doing work. The

protein-machines have movements resembling the macroscopic motion

of everyday machines. And when they store energy in specific

degrees of freedom they must be able to prevent them from

exchanging with thermal degrees of freedom.

McClare calls such processes "mechanical" : "A mechanical process

is either one in which heat is not exchanged, so that the only

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[71] "Stored" is the word commonly used, but I put it in quotation marks because it can be another extension of the machine metaphor. It is loosely used to designate something that must happen -- some chemical facts and the conservation of energy force the conclusion that energy must come from, stay or go somewhere -- but how it happens is less known. In the animal body energy can be "stored" in ATP as gas is stored in an automobile. But, how is the energy originally contained in individual molecules used to drive a change that otherwise would mean the increase in total free energy?

flow of energy is between forms that remain stored" [McClare, 1971]. These mechanical ones are clockwork-like mechanisms, and in part that is why I stated at the end of the last chapter that Boyle's idea has been revived.

. . . .

The age of biocolloidology, with its models obtained from a physical chemistry dominated by thermodynamics, represents the historical pinnacle of the idea that small macroscopic systems describable by thermodynamics could be able to explain microphysiological events.

The ups and downs of the molecular devices -- the machine metaphor taken to the molecular realm -- that became the favorite speculative instrument of biochemistry and molecular biology have not been thoroughly analyzed. Definite landmarks are Lipmann's suggestion that ATP is the 'combustible' for chemical changes going uphill, the discovery of the structure of DNA with the mechanism for biological replication springing naturally from it, as the separation of the strands and the synthesis of a complementary thread in each strand. Finally, I will mention the Singer and Nicholson fluid mosaic model. Certain microphysiological events, for which a protein layer on the surface of the cell was considered responsible, according to the model of Dawson and Danielli, were after the acceptance of the

Singer and Nicholson model considered to be caused by individual protein molecules now floating _in_ the membrane of the cell like icebergs in the ocean. These model making activities are all connected. The success of the DNA molecular machinery encouraged the idea that other molecular machines exist.

The success of the hypothesis that proteins are molecules -- and the other hypothesis that enzymes are proteins -- gave birth to an appreciation that most microphysiological processes are due to the existence of molecular machines operating in living things.

5. EPILOGUE

History of ideas seems nowadays a discredited approach for
writing history of science. Dr. X. made this experiment or
observation, obtained these results, induced this theory,
published these books and articles, rejected or accepted those
results and theories on such and such grounds, and so on. If the
account is directed to justify the most recent fashionable
theory, it is called Whiggish history. If it is too faithful to
the multitude of hypotheses and researchers it becomes a
meaningless account.

The history of 'molecular biology', in the broad sense, as a
history of ideas has preferred to whirl around theoretical and
experimental breakthroughs: the consolidation of the idea that
DNA is the molecular species responsible for hereditary
characters, the unraveling of its structure, the discovery of
RNA. In the approach I have pursued in this essay I have tried to
follow historically the way in which the machine metaphor,

sometimes hidden, sometimes openly debated, was present as a
constraint and as a guide -- as if the models themselves were
trying to find actualization as viable machines -- in exploring
hypotheses about the workings of the biological individual. Kant
suggested that nature is necessarily categorized by man under his
a priori concepts of space and time. Canguilhem insinuated that
"a certain technological and pragmatic structure of human
perception in the matter of organic objects showed up the
condition of man [as] an organism [and] maker of machines"
[Canguilhem, 1961].

Today more than ever man regulates his life in order to feed and
to take care of the machines he has built as extensions of his
body and capabilities. And now, more than ever, he is eager to
understand himself as a being similar to what he has been able to
build.

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