IS IT POSSIBLE TO RECONSTRUCT THE RESEARCH PROCESS?: SOCIOLOGY OF A BRAIN PEPTIDE

B. LATOUR
STS, CNAM Paris

When social scientists started studying the details of the scientific research process, they first tried to phrase their observations in the then traditional framework provided by sociologists and historians of science, i.e. how internal and external factors contributed to the production of science. The term 'external' refers to concepts invented by social scientists and economists such as 'group', 'profession', 'institution', 'culture', 'influence' and so on. Terms considered 'internal' were folk terms used by scientists and some philosophers such as 'coherence', 'logics', 'problems', 'objectivity', 'rules of method' and so on. A few concepts also had to be invented such as 'paradigm', 'themata' or 'episteme' in order to account for observations that did not fit inside the internal/external frame of reference.

Soon, however, it was evident that most of the terms employed in order to describe 'internal' factors, were actually amenable to sociological analysis and accounted by concepts so far used to describe 'external' factors. The notion of replication of an experiment was reduced by H. Collins (1) to the sociology of controversies; the writing of an article was explained by Latour (2) and Knorr (3) in rhetoric or semiotic terms; the notion of 'proof' had been further reduced to social factors by Pinch (this volume) and Harvey (this volume). Even the small word 'problem' had been made amenable to sociological explanation by Callon (4) (this volume). Indeed, the whole process of fact construction has been shown to be accountable inside a sociological framework.

No matter what one could think of this wealth of new studies dealing with the research process, it is clear that they cannot be located within the internal/external frame of reference, since all the so-called 'internal' concepts have now been re-explained in sociological terms. Although it is not yet clear

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what new framework will replace the obsolete internal/external one, it is possible to survey briefly the terms that have been found most useful to account for the details of the research process. In this article I present these various concepts in action, so to speak, by using them in accounting for the devising of analogs of a brain peptide named 'somatostatin'.

Presentation of the Case Study

For several years, a large laboratory of neuroendocrinology described at length in another study (5) had looked for a hormone coming from the brain that would trigger the release of another hormone responsible for the regulation of the body growth. This Growth Hormone Releasing Hormone (GHRH), was demonstrated in various cell assays. But in 1971, two young physiologists started stumbling on contradictory results. Instead of increasing the release of growth hormone in their assays when injecting their precious samples of purified brain extracts, they got instead a decrease of growth hormone. Their results were dismissed as mere artefacts by the head of the group. However, the two physiologists soon gathered enough data to make it impossible for the head of the laboratory to doubt their results. This was made easier, because the neuroendocrinology paradigm could accommodate an inhibiting hormone as well as a releasing hormone. After a few more months, they purified a substance they called 'somatostatin' because, they believed, it blocks the release of growth hormone.

A neurohormone can be compared to a one sentence order the brain conveys to a group of cells. To understand the meaning of this order, one has first to isolate it out of the background (this is called purification), then to decipher which letters are used in the sentence (the letters are made of aminoacids and this is called aminoacid analysis), and eventually in which order the letters (or aminoacids) of the sentence are assembled (this is called sequencing). After much debate, the laboratory decided to chose one sequence of aminoacids as being the natural sequence of somatostatin; in the aminoacid transcription the somatostatin sentence reads;

H–Ala–Gly–Cys–Lys–Asn–Phe–Phe–Trp–Lys–Thr–Phe–
1 2 3 4 5 6 7 8 9 10 11
Thr–Ser–Cys–OH
12 13 14

Each letter symbol stands for one of the 20 aminoacids that make up all proteins of the body. The meaning of this specific short protein – called peptide – was said to be: "Stop releasing growth hormone". The publication of this sequence was deemed a major achievement inside the neuroendocrinology profession (7).

In this article I will take for granted the production of all the facts dealing with somatostatin itself, and focus only on the modifications of the original sequence. Once a sequence is decided, it is possible to synthesize it from commercially available aminoacids, but it is also possible to *alter* the original sequence and to modify one, or two or all the aminoacids. These synonyms, homonyms, or antonyms, are all called *analogs* and their fabrication is one of the major tasks of the laboratory I studied. Each analog gives the cells a different order, and by studying the different responses of the cells, one can study the exact content of the message as well as the behaviour of the cells. In this article I will talk only about one aspect of the analog production: the number of *possible* analogs of this 14 aminoacid sequence is 2.6×10^{22}. The synthesis of each microgram of analog costs anywhere between $ 100 and $ 500 and several days of work for two to three researchers putting to use a two million dollar technical lay out. Since all the analogs could not possibly be tried, *what process led* the laboratory workers to choose the few hundred modifications they eventually produced? This is the case study I will use to reconstruct the characteristics of the research process.

Methods

From the protocol books used by the chemists, a chart was set up of all the analogs devised between 1971 and 1976. At this date, only 286 analogs had been made, which is a tiny portion of all the possible analogs but a major effort for the laboratory. Chemists were then asked to write down the reasons they had to devise this or that specific analog. All the articles reporting analogs, were gathered and studied according to methods developed earlier (8). Of the 286 analogs only 70 were reported in the literature. Whenever possible, patent applications were added to the corpus of papers. Earlier drafts of the present paper were written in collaboration with *JR*, the peptide chemist in charge of the analog programme. Reactions to earlier drafts by other members of the group were used as another source of material.

The Research Process is Contextual

It is an old scientific saying that a statement holds true only in the conditions set up for the experiment. Contextual means more: a statement draws its meaning from where, when and by whom it is uttered. Scientific statements have been shown to be as contextual – or as indexcal (9) – as any other statement. This is particularly clear in the case of somatostatin analogs. In the first laboratory the 14 aminoacid structure meant an order from the brain to stop releasing growth hormone. However, by sending samples of this substance all over the world to other investigators in different contexts, a vast array of new unexpected meanings started to be generated for the same substance. If you test somatostatin not only for its action on growth hormone, but also for its action on thyrotropin releasing hormone, the meaning is modified and reads now: "stop releasing growth hormone, trigger thyrotropin releasing hormone". In 1974, for instance, a new group of investigators started testing somatostatin inside their own local layout and linked it to their own personal interests, obsessions, drives and equipment. Somatostatin comes from the brain, they tried it in pancreas cells; it was supposed to stop growth hormone, they tried to show that it inhibited insulin and glucagon as well.

This change of context dramatically modified the very nature of somatostatin. Blocking growth hormones is not very useful in medical terms, (except to make dwarfs!) or more usefully, to cure some forms of acromegaly. However, affecting glucagon and insulin, is affecting a multi-million dollar business: diabetes research. Immediately, an enormous pressure was exerted back on the original laboratory; the initial interest in growth hormones became secondary, and the name 'somatostatin' made arbitrary. What now counted was to devise an analog that would block glucagon – dangerous for diabetic patients – but not insulin which was already deficient. Of all possible analogs, the ones that have to be devised in priority are the ones able to mean: "block glucagon, release insulin", because each of them is worth millions of dollars if it could be of some help in treating diabestes. Each analog was patented and the research followed month after month by the biggest pharmaceutical companies.

Everytime a new investigator uses somatostatin within a new research programme, that is within a new material lay out, the meaning of the original molecule, and then the very nature of this molecule, is modified and recreated.

There is no way to stabilise this change of meanings except by stopping the research and making routine the use of that substance inside a few networks.

The Research Process is Heterogeneous

The genesis of a scientific statement may be purified afterwards but it is never pure; many factors, coming from many parts of the social world, contribute to the production. This is what is meant by heterogeneous; no matter how close one tries to be from the research process, no homogeneous set of factors, that could be called 'internal' or 'purely internal', is visible. This multiplicity of factors is obvious when one looks at the interviews of *JR*:

All the Alanine modifications had been done . . . From the literature it is known that Tryptophane is important biologically . . . There is also a gut feeling . . . I just had received some D-Trp (dextrorotatory form) for LRF (another substance studied in the laboratory) . . . I tried the first D-modification (instead of the levoratatory form only existing in nature. It turned out that I hit right in the bull's eye.

Or, in this other case, where micropower structures are used to make sense of the making of another analog:

There were tensions in the laboratory . . . also I had trouble to cyclize somatostatin . . . something seemed to be missing. Then I supposed that the structure of natural somatostatin was not the published one and that homocysteine was necessary; the synthesis would have been made easier and I would have proven that *X* (his chemist competitor in the lab.) was wrong . . .

The multiplicity of factors is visible in the interviews by the constant jumps from one line of reasoning to another (jumps marked here by blank, silence, or copula), but is made still more visible by the *differences* between one scientist's accounts. When *W* read the account given above in the first excerpt by *JR* he was incensed:

It is not by chance at all! *N* came with a model of the molecule; he gave a seminar or something; his molecule was folded at the eight position; *I* immediately suggested to put a D-Trp at this position; that was the only way of reinforcing the molecule, probably, *N*'s model was wrong, we know that now . . . Anyway, we would have done it sooner or later. That was systematic. But we saved, maybe a year by doing it in the first place.

This is not only to show that the process of analog making is heterogeneous,

but also to show that the origin is always lost in a swarm of contradictory accounts. *JR* said it was chance; *W* that it was logical; *JR* said it was his idea, *W* that it was his; *JR* points out the availability of a component, gut feeling, habits of work, *W* points out a friend's model, the occasion of a seminar, a system and so on. When you get closer to the research process, the multiplicity and the chaos increase.

It is an apparent paradox that the inner core of the research process is full of so called 'external' factors, but this is not surprising when you realize the number of outside professional groups that impose constraints on the devising of these analogs. Physiologists need a molecule that can be radioactively labelled for their radioimmunoassay, the radio labelling is convenient only on the aminoacid named tyrosine. Since there is no tyrosine on the newly discovered somatostatin, *JR* is asked to devise analogs with a tyrosine somewhere. Investigators all over the world need more somatostatin, so that *JR* has to devise new ways of synthesizing more of the native substance and more analogs. It is known by neuroendocrinologists that some analogs can be made from the former peptides by more potent and longer acting than the native molecule. It is known that deletion of one aminoacid, or addition of an alanine, or the substitution of an alanine to each aminoacid, might increase the action or the potency. Lawyers are also asking for more specific analogs in order to protect further important analogs through patents (10). Chemists in other, more basic, departments, are interested not only in the primary structure (already known), but also in how it is folded in three-dimensional space, or how it binds with other molecules; to know that, they need specific analogs with modifications they ask *JR* to tailor. *JR* and his colleagues, have to integrate all these heterogeneous demands coming from many professions, demands that are weak or strong, that are changing almost constantly in time.

There is no better way to show the heterogeneous character of the research process, than to read one page of the chart (see Figure 1). As in the interviews, the lines of reasoning are interrupted so many times that no clear cut pattern emerges. Modification 167 combines two former successful modifications des-Asn^5 and D-Trp^8 (11). Then the alanine series is resumed – as it is constant throughout the years – positions 11 and 9, but then is interrupted: "because the chemical company mis-labelled the aminoacid threonine used at position 12, and so the batch had to be discarded". Since a few days later, a paper is

		Ala 1	Gly 2	Cys 3	Lys 4	Asn 5	Phe 6	Phe 7	Trp 8	Lys 9	Thr 10	Phe 11	Thr 12	Ser 13	Cys 14
Modification															
No. 167						Delete			D-form						
No. 168												Ala			
No. 169										Ala					
No. 170					D-form										
No. 171	Add 3	Gly						D-form							
No. 172		Tyr						D-form							
No. 173	Add 3	Gly			Delete			D-form							
No. 174			NEW SAMPLES OF SOMATOSTATIN												
No. 175										Ala					
No. 176					D-form										
No. 177						D-form									
No. 178					Ala										
No. 179													Delete		
No. 180											Delete				
No. 181	Add 3	Gly													
No. 182												Ala			
No. 183							Delete	Delete							
No. 184					Delete										

Fig. 1. The 14-aminoacid structure of somatostatin is written at the top of the figure. The modifications are inscribed in the columns beneath each aminoacid. This figure allows the sociologist to see at once which position is modified and what are the analogs invented (each analog is designated by a number coming from *JR*'s protocol books. For instance the analog No. 168 is the original somatostatin except for its 11th position that is now an Ala instead of a Phe.

published which proposes to extend the native molecule by three glycine residues, *JR* immediately manufactures these analogs. He tries them three times (modification 171, 173 and 181) and combines them with his pet analog (D-Trp^8); in his later papers, these three analogs are said to have been a dead alley: "they have not been found to be active in our hands". Then three different programmes are mixed: the deletion one, the alanine series, and the replacement of a levorotatory form by a dextrorotatory form. Each programme interrupts the other, or suddenly they coalesce as in modification 173.

JR and his colleagues get by through this turbulent context of heterogeneous pressures and demands; the process is less and less pure, less and less 'internal', and, once again, could not be purified or stabilised except by stopping it entirely or making it a routine.

The Research Process is Opportunistic

To cope with this turbulent context of heterogeneous demands, is neither a fully orderly, nor a disorderly process; it is an opportunistic one. If you listen to the scientists the first time you meet them, they will claim that the whole process is the strict unfolding of a reasoning out of a few premisses. *W* for instance, told me:

If you give me a peptide, I could devise several hundreds of analogs, just from what is already known in the literature: the D-series, the Alanine series, the replacement by Gly; the deletion series; all that is known, it is logical.

But then he adds:

When intuition arrives, it is for new combinations; OK, for choosing what to do, I mean in which order . . . that's where guess, logics, intuition come into the picture that's not systematic.

The same rupture appears in *JR*'s first presentation of the analog making. He first presents the different rules of transformation summarised by *W*, and then adds:

But see you have to be systematic *and* opportunistic this little word 'and', is the reason why *JR* so much despises 'industrial scientists':

They do everything systematically; they screen everything; just screen; it's not science; it's just a computer job.

To understand the research process one has to look exactly in the *middle* of order and disorder. There are rules – borrowed from previous experience – but they are followed *or not* according to the circumstances. In this case they cannot be followed since the number of possible analogs is too high. On the other hand, it is wrong to think like Feyerabend that 'anything goes'. The choice of the 286 analogs is not made at random. If opportunism means that one reacts to circumstances and timing, what *W* and *JR* do is to create local circumstances in which small chains of reasoning lead from one analog to the next, and invent precarious and provisional rules of transformation to sustain the reasoning for a while.

Let us look again at the page of the chart shown in Figure 1. For instance, modification 167 combines two modifications invented earlier. One of the rules is to delete one after the other each aminoacid and see what happens. One of the other programmes is to replace the levorotatory form that exists in nature, with a dextrorotatory form. From these two rules however, you cannot *deduce* modification 167, because they cannot be obtained through systematic screening except by manufacturing thousands of analogs. The modification 167 is not a chance encounter though. In the interview excerpted on page 57, I showed why *JR* and *W* were interested in the modification called D-Trp^8, it increased enormously the potency of the molecule. On page 56, I showed why the new context created for somatostatin pushed *JR* to devise analogs that inhibit glucagon but not insulin. Deleting asparagine at the fifth position, creates, they had found earlier in their work, a dissociative activity; the pancreas cells 'understand' the altered version of the molecule as meaning "release insulin, block glucagon". *JR* makes up a small rule: "combine successful modification"; and then follow another explicit constraint: "go to the analogs that are the most helpful for diabetes – and so justify our one million dollar grant". So, they devise des-Asn^5 D-Trp^8 that is understood by the cells as a 'strong' injunction to stop glucagon and release insulin and is immediately patented by the lawyers of the non-profit institute in which *JR* works.

The modification 167 cannot be deduced systematically from previous ones, but is not random either. Locally it makes sense given the time, the circumstances, and the modifications already made. 'Anything goes' but only inside local contexts and not everything is kept. What is kept however, you can push as hard as you want and combine as much as you can with the few

other successful modifications you already have, but push it only in the directions that are 'the order of the day'. This 'obstinate opportunism' so to speak is well marked in the four other modifications of the same page. 168 resumes a programme that is acting throughout the corpus; replacing each analog by an alanine and seeing what happens; 169 goes on but skips one position – the tenth – and so cannot be deduced from the former at the eleventh position. The modification 170 shifts abruptly to another programme and applies it at position 4. Then, as we explained earlier, a paper appears that proposed adding three glycine to the native molecule. Again, *JR* suddenly changes direction, jumps on that new modification and tries it. The modification 173 is particularly interesting. *JR* goes on in his makeshift rule that advises him to "combine all successful modifications" and fabricates a monstrous analog with the three glycines learned from the newly published paper, the deleted asparagine at position 4 and the dextro form at position 8. Since this analog is inactive, *JR* shifts again and invents a new locally consistent rule to get as much as he can of his few hundreds of analogs.

There is no one rule that could explain all the analogs that the laboratory devised; but the process is not without reason, or more exactly, it is not without heterogeneous, short lived, circumstantial reasons. The research process cannot be described as a game – since there is no rule – but cannot be described as a chaos of random moves and lucky guesses. It is a game 'à la' Humpty-Dumpty: make up the rules by closely following the unfolding of the previous moves, and try to persuade yourself – as well as the other partners – that you have not made up the rules but observed or followed them. It is a very soft rule indeed, but that explains why, like in a game of Go (12) from a random point of departure a coherent and logical process can be obtained. This process is not without similarity with 'bricolage' or tinkering (13). Tinkering is always opposed to 'rational' or 'scientific' reasoning, although it best approximates the way scientists work, and, according to Jacob (14), the way life itself functions.

The Research Process is Idiosyncratic

Tinkering opportunistically amidst a turbulent heterogeneous context is a process that makes sense only if one looks at the local place of work, that is the laboratory. If the history of the production of a scientific statement is

told, only dismembered and contradictory accounts can be found. What leads these accounts from one to the next is a set of material and local circumstances, most of them tacit, that Knorr described as 'idiosyncratic' (15). The chart that summarises all the analogs is a mixture of chaotic moves interrupted by short lived systematic chains that are in turn slashed by contradictory lines of reasoning. What holds these analogs together, and makes them something more than random, is the material life of this specific laboratory.

JR is able to manufacture analogs, and even to think about the possibility of manufacturing them, because a few years earlier the laboratory adopted the controversial solid phase synthetic method, invented by Merrifield (16). This method is still despised as a dirty, impure, "unscientific" method by the partisans of the liquid phase synthesis. The main advantage of the Merrifield method, however, is to be fast and entirely automated in one small piece of furniture: the Automatic Peptide Synthetizer (17). The major shortcomings of this method is that the degree of purity of the final product is not guaranteed. But, in this specific laboratory, *JR* can draw on *X*'s instruments of analytical chemistry which, at the time, are said to be the best in the country. By using these heavy and very sensitive tools, *JR* can check that each product of the synthesis is pure enough, checks that no other laboratory can afford to get. With pure, easy to produce analogs, *JR* can swamp the physiologists with many samples to test. Here again, the local conditions are crucial. The very existence of these substances – that is their detection and meaning – is based on their action in fragile biological systems. Each system – called assay – is an idiosyncratic construction that cannot be replicated anywhere else. A 'good' laboratory in this field, is essentially a laboratory that is known for its 'highly sensitive' bioassays. Without them you cannot even detect that a sample of brain extract decreases growth hormone, or you cannot observe the difference between an analog that delete the fifth aminoacid and the native molecule. In this specific laboratory, subtle differences between analogs can be detected; elsewhere, they would be different or invisible. To say that the process is idiosyncratic, is to say that the analogs exist at the *intersection* of these local lay out – synthetic chemistry, analytical chemistry, physiology – and cannot escape from it.

Idiosyncrasy not only points out the local conditions for the definition of an analog, it also points out the material existence of a laboratory. Devising

an analog is an intellectual activity only for an outsider; inside the laboratory, it is the black art of chemistry, the cooking of substances, the manipulation of instruments, the reading of literature, the discussions with grant agencies or lawyers, the constant phone calls, the injection of diluted substances, the bleeding of white rats . . . The links between analogs that appear on the chart as meaningless or absurd can be made by the proximity in a cupboard of two vials of different aminoacids; or by the use of a tacit rule known and practised only inside the group; or because a lecturer just happened to suggest that people in Switzerland had tried this modification on another substance. If you tear apart the circumstances, most of the steps leading from one analog to the next seem as many *non sequiturs*. If you re-introduce them, one step follows the other, through a long detour that cuts across the whole material life of a laboratory.

Opportunism and idiosyncrasy best designate these turbulent mechanisms that end up with only 236 analogs out of billions. There is some coherence between the few hundred modifications, a weak kind of coherence that is understandable given the specific group and the specific pressures exerted upon this group by other actors. Like a *culture* the group produced only a few artefacts that are linked only if one looks closely enough to the local setting and becomes familiar enough with its peculiar material conditions.

The Research Process is a Fiction-building

The research process never appears as I have described it so far. The tinkering through changing conditions in order to locally create some provisional pockets of meaning, is constantly re-created and re-ordered by many writing activities. Everytime *JR* or *W* writes an article or answers an interview or discusses with one of their colleagues, creditors or competitors, they build up a new version of how the analogs are linked to one another. It is clear that the process of devising the analogs is neither logical nor rational, but it is also clear that it is constantly *made* logical and made rational.

One easy way to show this re-ordering process is to look at the many interpolations as shown in Figure 2. On the right of this diagram I inscribed the analogs the way *JR* neatly arrayed them in one review paper; in the middle I listed the analog according to the date at which they were fabricated; on the left, I grouped them according to the most 'logical' programme they were

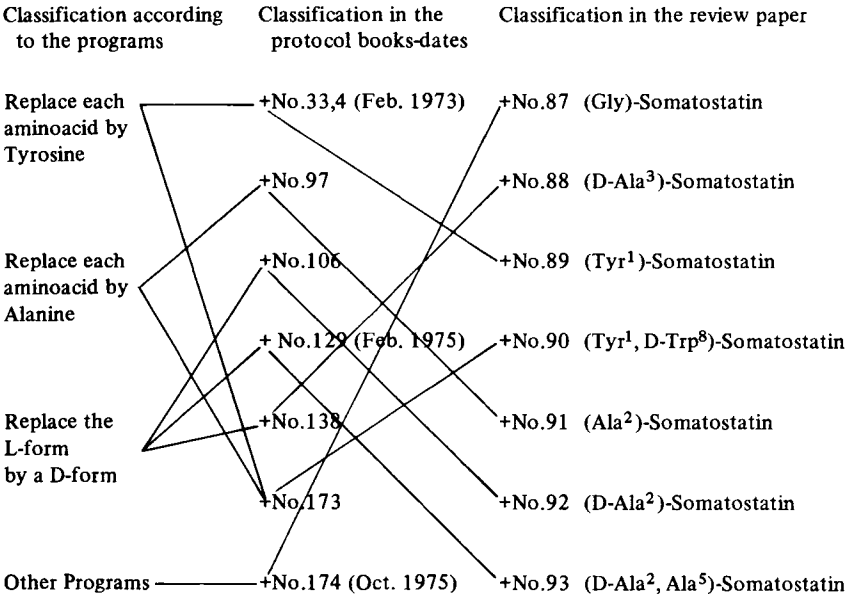

Fig. 2. The analogs number 87 to 93 in a review paper are written on the right side; then in the middle column is recorded the date of their fabrication and the number in the protocol book. In the left column analogs are grouped according to the program that best describe them. Lines linking the same analogs help visualizing the interpolations from one classification to the other.

supposed to follow (see excerpts page 60). The arrows linking the analogs allow the reader to easily follow the interpolations from one type of order to the next. Modification 174, made in 1975 appears first in the classification; however it was made a few days after another one 173, that is 'caused' by an entirely different programme which started two years earlier and 'caused', among others, modification 33 that is classified two steps below the first one. Each order mobilizes the others according to the new rule of classification that is for the time being the most useful.

This is not to say, however, that the rule is followed in any strict and straightforward manner. If you now read the drafts where *JR* wrote the classification that is shown on the right hand column of Figure 2, you find that no specific rule is applied consistently. The starting rule was to list all the modifications at the first position, then all the modifications at the second

and so on. The draft, however, is covered with corrections and small packages of analogs that are added or deleted. One is added because, said *JR*: "I wanted to draw attention to this one", but it could fit in many other places; three other analogs are eventually crossed out because: "I think that these three analogs published by . . . (a competitor) are really bad and I don't want to embarrass him". Another analog has been shifted from position 10: "Yes, I inverted this analog, and put it at the end because it seemed more logical". The path linking the analogs, even in this *post hoc* review is far from straight; it is a crooked one that follows the seams of many preoccupations (journal policy, competitor's claims, patent lawyers, aesthetic). 'Qualitative logics' should be the expression that designates this process that arrays in a plausible reasoning analogs that are made for many heterogeneous reasons.

The process, as I said earlier, is neither orderly nor disorderly, neither logical or illogical, it is an opportunistic tinkering through rapidly changing conditions. If logic was taken cut of the laudative meaning that it has since Aristotle and was understood as logos or path, then, we could say that the research process is to build paths or, to use another source of metaphor, to tell plausible stories. If one reads the article written by *JR* to present his analogs, it will be clear: (a) that his reconstruction has no relation whatsoever with the various orders followed in making them in the laboratory (18); (b) that his reconstruction is deeply different from the ones provided in other papers written by him or his colleagues; (c) that his formulation of the logics in the making of analogs is no more straightforward than any of the others. I reproduce in Figure 3 one paragraph of this review paper. If the reader disregards the 'technical' terms and concentrates on the argumentation only, the story-telling character of this paragraph will immediately appear (19).

Temporal markers invent a temporal framework which is as realistic as that of the fairy tales; it is not written: 'once upon a time', but "the early observations" (. . .) "we then looked", (. . .) "we knew that from then on", etc. As in any other fiction, actors are made up that undergo transformations or are supposed to be the authors of various actions; this making up is achieved by using words like 'we', 'one', or impersonal actors like 'the Ala^1 Gly^2 chain' or 'the early observations'. Then causes are fabricated that link transformations with one another; "the early observations *lead* us" (. . .) "*to* test this hypothesis, we synthesised" (. . .) "*to* account for . . . one might consider", etc. Writing devices are used to dramatise the text; "it was therefore a surprise

The early observation that *dihydrosomatostatin, i.e. the linear reduced form of somatostatin (has)* had *full biological activity* let us to **speculate** about *the* relative *importance of the disulfide bridge* which **would be expected to** *stabilize the tertiary structure of somatostatin* **unless** *strong interactions, such as ionic, hydrophobic, dipolar, etc., within the molecule (are)* **were** *already maintaining the molecule in a shape readily recognizable by the receptor.* To test this hypothesis, we synthesized 81–83. Their *low but significant activity (in vitro as well as in vivo)* **would suggest that** only *a small portion of these analogs exist in a conformation favorable for receptor recognition* hence *the disulfide bridge is important for activity.* But since *these molecules differ from somatostatin in additional respects other than being unable to cyclize*, alternative explanations **cannot be ruled out.** To account for *the high activity of H2 SS*, one **might** consider the **possibility** that *SS is the most potent form of the peptide* and that *H2SS is rapidly oxidized under the conditions of the bioassays./* We then looked for what **could be** *the smallest biologically active fragment of SS.* We knew that *for LRF, any deletion from either the N- or C-termini (alters)* will considerably alter *the relative potency of these new analogs.* It was therefore a surprise to find out that *the* $Ala^1 - Gly^2$ *side chain did not add much to the potency of the ring itself* and that even *des amino* Cys^3 *(has)* had *almost full potency.* Hence *the 38-membered ring of SS contains all the information necessary for recognition and binding by the pancreatotropic and pituitary receptors.* From then on, we therefore assumed that *the side chain* **could be** manipulated to yield tailored *molecules./* As a matter of fact, one approach to longer acting molecules is to render them more hydrophobic so that they **could be** slowly released from depot (whatever it may be)./ *Acylation by several organic, aromatic, bulky or aliphatic acids of the cysteine 3 residue (yields)* yielded *compounds with full biological activity in vitro and in acute in vivo studies.*

Fig. 3. This paragraph of a review paper has been treated to separate the modalities (**bold** letters) and the assertions of fact (*italics*). In parentheses are the verbs and the tense that would be required if the sentence were not modalized.

to find out", and many modalities to qualify statements and make the story still less rigid. The writing process puts to use elementary logical devices like a simple table of presence and absence (lines 5–10), a classic analogical step (line 19), but in mobilising analogs, logical tools, rhetorical devices, fictional tricks, it eventually builds up a whole world. In this specific paragraph, *JR* invents a history – a micro one of course – and epistemology (observations

lead people; steps are taken to verify hypothesis), a representation of the research process (people do things to check out alternative hypothesis; there are scientists led by observations) and also a plausible story to link analogs within an acceptable logic.

The fictional character of this specific reconstruction – and indeed of every scientific account – is immediately visible if the different articles are taken into account in which *JR* presents his analogs. Fourteen articles – including 5 abstracts – have been written in the chosen period – that use analogs to make points in the literature (20). According to which article you consider, different analogs are mobilised as arguments to make various points and the reasons to make them will be modified accordingly. First of all, in several articles, *JR* is not even allowed to write any reason for making them. The same analog can be a chemist's story – and then physiologists are used in the technical part of the text to state the potency of the analog – or a physiologist's story ... and then chemists are allowed only two lines in the technical part to state how they made the analogs. One paper for instance (number 168) was written by *JR* in collaboration with a young physiologist post doctorate: "I wrote the article very fast and before *B* – the physiologist – had done anything; so I included all the physiology in the technical section; he is still a freshman, he co-signed the article, but he could have made it a physiological paper". Having an author writing his own reconstruction of the research process is not a given; it is already the result of a fierce struggle to define *who* will make up the fictional account.

If I limit myself to the articles in which *JR* succeeded in being the first author, many more interpolations can be seen. For instance the story about des-Ala^1 Gly^2 being a surprise (Figure 3, line 21), appears only in this paragraph. In paper 339 it is presented only as a way to understand the role of the disulfide bridge. In still another paper (367), the same analog is used not to show the small role of the N-ter-minus, but to explain why a longer acting somatostatin is possible. For other arguments, on the contrary, the same sentence is repeated over and over again through all the papers and only the modalities (or the style) are adapted. Of course, there are many good rhetorical reasons for these modifications. For instance, an analog taken as a systematic one in several chemistry papers is suddenly dramatised in a new paper written, this time, for clinicians: "in view of the considerable hindrance that represents this character in the prospective clinical uses of somatostatin"

and then follows an analog 'caused' by this tactical clinical reason. In the various papers analogs are grouped, eliminated, clumped again not according to any *one* rule, but much like troops and tanks in a battlefield: for tactical reasons wherever someone thinks they could be used to make a point stronger.

The various writings when compared do not offer a quieter or more rational picture of the research process than the observation of this process or the interviews of the scientists engaged in it. Each interview, each manipulation of analog, each writing is, in a way, a reconstruction. This does not mean that there is something 'wrong' or 'dishonest' with this process, because there is nowhere any account of the research that could be something more than a fiction. We constantly make sense of the world and build paths leading points to one another and convince people that a particular path is more straightforward than any other. It is useless to say that the accounts provided in this volume, and the present account, obey the same mechanisms (21).

A New Conception of Order

I chose the example of these analogs of somatostatin only because it was the dullest, most mechanical, most systematic and most straightforward process I could observe in the laboratory I studied. If such a straightforward process can be shown to be so chaotic, illogical, opportunistic, contextual and constantly reconstructed, the reader can get a vague idea of what the research process can be when one studies more interesting, more original and less routinely made pieces of a science. If a dull piece of puzzle-solving science is made through such noise and disorder, one can imagine the 'story full of noise and furore' that is heard when one listens to a paradigm shift. Actually, everyone *knows* this noise; it is the noise of *history*. By an old privilege, science was supposed to be less disorderly, less noisy, less fictional than the rest of history. The new wealth of studies on the research process have one main consequence; they put an end to this age old (actually Greek-old) privilege. The research process is nothing *more* and nothing *less* than the rest of our daily world and daily stories of fictions and disorder (22).

The strings of words that have been chosen to describe the research process (from 'contextual' to 'fiction') all aim to end the privilege of science by using precisely the words that ought to be eliminated when passing from 'history' to 'science'. These words, however, have been chosen haphazardly

for most of them and with polemical or negative connotations. There is not yet any coherent framework – but is this possible or desirable – that would describe the research process without maintaining the former privilege. The only attempt has not been made by sociologists of science, but by isolated scientists dealing with information, or with turbulent phenomena. The works of Brillouin (23) and the recent book of Prigogine and Stengers (24) together with the philosophy developed in France by Michel Serres (25), convinced me that a new framework is already at hand to understand and rephrase our observations on the way science is made. In the old framework, disorder, turbulence, agitation, circumstances, were to be *eliminated* for a world of order, logics and rationality to appear and be maintained. In the new framework, order is nothing but local circumstances obtained from, maintained by, dissolved from time to time in *disorder*; if you eliminate the opportunism, the context, the fiction building, the agitation, the reconstruction, the rationalisation you get *nothing* at all; if you introduce them you understand how the scientific facts, discoveries and theories emerge and are maintained. More importantly, in the old framework, since disorder was to be eliminated, the factors dug out by historians, sociologists and psychologists, always appeared as 'external' to the main process of science, and hence the sterile but convenient paradigm that phrased the research process within 'internal' and 'external' factors. In the new framework, since disorder is the main component and, so to speak, the *substance* of the final orderly product, the factors dug out by historians and sociologists are not 'external' anymore. They are, to use a religious term, consubstantial to the science produced. In consequence, it is now possible to account for the very content and nature of the objects produced by scientists (26). As important is the methodological consequence that should be drawn when working in this new framework. As I have shown elsewhere (27) since disorder is the substance of science the factors and events we reveal to the scientists are not threatening to them; sociologists and scientists both feed on fiction, disorder, circumstances and, from time to time, logical stories. In the old framework, we had to observe scientists from the outside, to threaten them, or worse, to give up studying and pass inside their fortress to worship them or become their servants. Now that we are all equally inside the heterogeneous opportunistic, fictional science that is built, new alliances are possible that are much more interesting than the boring 'tête à tête' of scientists and their observer.

I am not able to fully describe this new framework, and have only shown (28) how it works when one accounts for the research process in laboratories. One thing is clear however; although we all haphazardly invented words to describe this process, they all seem to fit if we modify the conception of order we used to have. Immediately, words like circumstances, random, opportunism, fiction, idiosyncrasy, rationalisation stop being a derogatory criticism of science and rationality or a claim for relativism. If we modify the conception of order these same words start expressing the very nature of the scientific objects. The interest of micro-studies of the research process in science, is to provide the best possible ground to test this 'new alliance' that Prigogine and Stengers are advocating, and to help in what they call 'metamorphosis of science' (29).

Notes and References

1. H. M. Collins, 'The seven sexes: a study in the sociology of a phenomenon' *Sociology* 9 (2), 205–224 (1975).
2. B. Latour, 'Including citations counting in the systems of actions of a scientific text', First Four-S Meeting, Cornell, Ithaca, 1976.
3. K. Knorr, 'From scenes to scripts: on the relationship between research and publication in science', Institute for Advanced Studies, Vienna, 1978 and *Social Studies of Science*, (forthcoming).
4. M. Callon, 'De problèmes en problèmes: itinéraire d'un laboratoire universitaire saisi par l'aventure technologique', 1978 Cordes, Paris.
5. B. Latour and S. Woolgar, *Laboratory Life: The Social Construction of Scientific Facts*, Sage, 1979.
6. *Ibid.*
7. P. Brazeau, W. Vale, R. Burgus, N. Ling, J. Rivier and R. Guillemin, 'Hypothalamic Peptides that inhibit the Secretion of Immunoreative Pituitary Growth Hormone', *Science* 170, 77–79; J. Rivier *et al.*, 'Review on the Design of Synthetic Analogs', in *Peptides 1976*, Editions de l'Universite de Bruxelles, 1977 Bruxelles, pp. 427–452.
8. Latour, *op. cit.*, Note 2; Latour and Woolgar, *op. cit.* Note 5, Chapter 11; B. Latour and P. Fabbri, 'Pouvoir et Devoir dans un article de Sciences Exactes', *Actes de la Recherche*, Février 1977, pp. 81–95.
9. B. Barnes and J. Law, 'Whatever should be done with indexical expressions', *Theory and Society* 3 (2), 223–237 (1976).
10. The only analog that was invented in my presence was the result of a lawyer coming into the laboratory with the draft of a patent application. The other analogs were devised through a sort of quantic process that I was never able to document directly. I was always one day, one hour or one minute too late to add my own observations to the stories fed to me by the scientists. It is why I do not use my observer's note in this paper like I did in the other cases I could follow continuously.

11. "Des" means that the aminoacid has been deleted; the small figure indicates which position in the 14 aminoacid structure is modified. "D" means that the levorotory form that is the only form existing in nature, has been replaced by its mirror image, the dextrorotatory form that is created artificially. When a substitution is made the new aminoacid is indicated as follows: the Thr^8 Somatostatin, which means that the naive analog Cys at the third position has been replaced by the analog Thr. Of course, no knowledge of peptide chemistry is necessary to understand the paper; except for these few writing conventions, the analogs can and should be taken by the reader like the proper names in novels. What they really mean is uninteresting and no more effort is required than recognising Russian names in a Dostoievsky's novel.
12. Latour and Woolgar, *op. cit.*, 1979, Note 5, page 246. The game of Go is certainly the best model to test the various components of the research process especially because the basic rules are so few and the complexity at mid-game is so baffling.
13. Levi-Strauss, *La Pensée Sauvage* Plon, Paris, 1962.
14. F. Jacob, 'Evolution and Tinkering', *Science* **196** (4295), 1161–1166 (1977).
15. K. Knorr, 'The research process: Tinkering toward success: Prelude to a Theory of Scientific Practice', *Theory and Society* 8, 347–376 (1979).
16. R. B. Merrifield, 'The automatic Synthesis of Proteins', *Scientific American* **218**, 56–71 March (1968).
17. The instrument manufactured by Beckmann has been studied in a one-month side project of the main field study. For presentation of the importance of the instruments, see Latour and Woolgar, 1979 *op. cit.*, Note 5.
18. This is not surprising since the aim of a scientific paper is not to reproduce reports on what happened in the laboratory but to act on the literature; see Latour *op. cit.* 1976. Note 2: Knorr *op. cit.* p. 197, Note 3, and P. Medawar: 'Is the scientific paper fraudulent?' *Saturday Review*, August 1964, pp. 42–43.
19. The analysis is very crude indeed. For a full semiotic treatment of a scientific text, see F. Bastide; 'Le foie lavé. Approche semiotique d'une texte de sciences expérimentales', *Documents* No. 7 1979 EHESS-CNRS Paris.
20. For the review paper, see J. Rivier *et al. op. cit.*, 1976, Note 7. For specific examples with JR as first author, see J. Rivier, 'Somatostatin Analogs. Relative Importance of the Disulfide Bridge for biological activity', *Journal of Medicinal Chemistry* **18**, 123–124 (1975); or J. Rivier *et al.*, '$D\text{-}Trp^8$ an analog of somatostatin more potent than the native molecule', *BBRC* 6, 746–748 (1975).
21. There is nothing self destructive in this obvious consequence. 'Fiction' is not taken as synonym of 'empty', 'false' or 'fraudulent'. It is the word that describes the construction of paths and plausible stories; what count are the *effects* of the story on the readers. One of these many effects is that the story 'is true'. This effect can be studied and deconstructed – or contructed – like any other.
22. The work inspired by ethnomethodology tries to reach the same conclusions through very different techniques, see Woolgar (this volume).
23. L. Brillouin, *Scientific Uncertainty and Information*, Academic Press, New York, 1964. See also H. Atlan, *L'organisation biologique et la Theorie de l'Information*, Paris 1972, Hermann.
24. I. Prigogine and I. Stengers, *La Nouvelle Alliance*: *Metamorphose de la Science* Paris Gallimard, 1979.

25. M. Serres, *La Naissance de la Physique dans le Texte de Lucrece: Fleuves et Turbulences* Paris. Editions de Minuit, 1977. I cannot even summarise the arguments of Serres in this article.
26. This is why the major objections of microsociologists to the former brands of sociology of science was their disregard for the contents of the sciences they studied. They talked about external factors and really thought – like some scientists – that these factors were indeed external. The new framework helps to seize a new idea: these factors are the essence of the produced science and then a full study of the scientific facts is possible.
27. B. Latour, 'Who is agnostic or what could it mean to study science'. In H. Kuclick (ed.), *Sociology of Knowledge Science and Art*, 1980.
28. For a still shy and awkward tentative, see B. Latour 1979, *op. cit.*, Note 5, Chapter VI, especially the middle part.
29. Prigogine and Stengers, 1979, *op. cit.*, Note 24.

THE SOCIAL PROCESS OF SCIENTIFIC INVESTIGATION

Edited by

KARIN D. KNORR

University of Pennsylvania, U.S.A.

ROGER KROHN

McGill University, Canada

and

RICHARD WHITLEY

Manchester Business School, University of Manchester, England

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